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1 | Update on General Medicine

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2024–2025
BCSC®
Basic and Clinical Science Course™

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1 Update on General Medicine

Last major revision 2023–2024

2024–2025
BCSC
Basic and Clinical
Science Course™

Published after collaborative
review with the European Board
of Ophthalmology subcommittee

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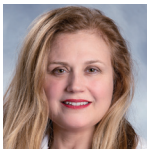

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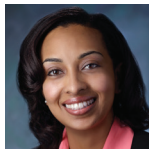

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In addition, the Academy acknowledges the following consultants for their important work on Chapter 1: Angela R. Elam, MD, and Kristen Nwanyanwu, MD, MHS.

Finally, the Academy acknowledges Linda Gadioli and Hussein Huraibi, MD, for their contributions to the development of Chapter 17.

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Contents

Introduction to the BCSC

The Basic and Clinical Science Course (BCSC) is designed to meet the needs of residents and practitioners for a comprehensive yet concise curriculum of the field of ophthalmology. The BCSC has developed from its original brief outline format, which relied heavily on outside readings, to a more convenient and educationally useful self-contained text. The Academy updates and revises the course annually, with the goals of integrating the basic science and clinical practice of ophthalmology and of keeping ophthalmologists current with new developments in the various subspecialties.

The BCSC incorporates the effort and expertise of more than 100 ophthalmologists, organized into 13 Section faculties, working with Academy editorial staff. In addition, the course continues to benefit from many lasting contributions made by the faculties of previous editions. Members of the Academy Practicing Ophthalmologists Advisory Committee for Education, Committee on Aging, and Vision Rehabilitation Committee review every volume before major revisions, as does a group of select residents and fellows. Members of the European Board of Ophthalmology, organized into Section faculties, also review volumes before major revisions, focusing primarily on differences between American and European ophthalmology practice.

Organization of the Course

The Basic and Clinical Science Course comprises 13 volumes, incorporating fundamental ophthalmic knowledge, subspecialty areas, and special topics:

1 Update on General Medicine
2 Fundamentals and Principles of Ophthalmology
3 Clinical Optics and Vision Rehabilitation
4 Ophthalmic Pathology and Intraocular Tumors
5 Neuro-Ophthalmology
6 Pediatric Ophthalmology and Strabismus
7 Oculofacial Plastic and Orbital Surgery
8 External Disease and Cornea
9 Uveitis and Ocular Inflammation
10 Glaucoma
11 Lens and Cataract
12 Retina and Vitreous
13 Refractive Surgery

References

Readers who wish to explore specific topics in greater detail may consult the references cited within each chapter and listed in the Additional Materials and Resources section at the back of the book. These references are intended to be selective rather than exhaustive,

chosen by the BCSC faculty as being important, current, and readily available to residents and practitioners.

Multimedia

This edition of Section 1, *Update on General Medicine,* includes videos related to topics covered in the book. The videos are available to readers of the print and electronic versions of Section 1 (www.aao.org/bcscvideo_section01). Mobile-device users can scan the QR code below (a QR-code reader may need to be installed on the device) to access the video content.

Self-Assessment and CME Credit

Each volume of the BCSC is designed as an independent study activity for ophthalmology residents and practitioners. The learning objectives for this volume are given on page 1. The text, illustrations, and references provide the information necessary to achieve the objectives; the study questions allow readers to test their understanding of the material and their mastery of the objectives. Physicians who wish to claim CME credit for this educational activity may do so online by following the instructions at the end of the book.*

Conclusion

The Basic and Clinical Science Course has expanded greatly over the years, with the addition of much new text, numerous illustrations, and video content. Recent editions have sought to place greater emphasis on clinical applicability while maintaining a solid foundation in basic science. As with any educational program, it reflects the experience of its authors. As its faculties change and medicine progresses, new viewpoints emerge on controversial subjects and techniques. Not all alternate approaches can be included in this series; as with any educational endeavor, the learner should seek additional sources, including Academy Preferred Practice Pattern Guidelines.

The BCSC faculty and staff continually strive to improve the educational usefulness of the course; you, the reader, can contribute to this ongoing process. If you have any suggestions or questions about the series, please do not hesitate to contact the faculty or the editors.

The authors, editors, and reviewers hope that your study of the BCSC will be of lasting value and that each Section will serve as a practical resource for quality patient care.

* There is no formal American Board of Ophthalmology (ABO) approval process for self-assessment activities. Any CME activity that qualifies for ABO Continuing Certification credit may also be counted as "self-assessment" as long as it provides a mechanism for individual learners to review their own performance, knowledge base, or skill set in a defined area of practice. For instance, grand rounds, medical conferences, or journal activities for CME credit that involve a form of individualized self-assessment may count as a self-assessment activity.

Objectives

Upon completion of BCSC Section 1, *Update on General Medicine,* the reader should be able to

- discuss the impact of social determinants of health on patient wellness
- describe the various factors to consider in critically reviewing clinical research
- explain the importance of the randomized controlled clinical study in evaluating the effects of new treatments
- describe the classification, pathophysiology, and presentation of diabetes, as well as the diagnostic criteria for this disease
- describe the various therapeutic approaches for diabetes
- classify the levels of hypertension based on blood pressure measurements
- list the major classes of antihypertensive medications, their characteristics, and their adverse effects
- discuss the indications for dietary and pharmacologic treatment of hyperlipidemia
- describe the various diagnostic procedures used in the evaluation of patients with coronary heart disease
- state the current treatment options for ischemic heart disease, heart failure, and cardiac arrhythmias
- list the common causes of stroke
- distinguish between obstructive and restrictive, reversible and irreversible, pulmonary diseases, and give examples of each type
- list some of the factors associated with a patient's adherence or nonadherence to medical regimens

- discuss the major disease processes affecting most of the adult population, and briefly explain how preventive measures may reduce the morbidity and mortality that these diseases cause
- discuss the major behavioral disorders and possible therapeutic modalities for these conditions (including the ocular adverse effects of psychotropic medications)
- explain the rationale for and value of screening programs for various systemic diseases
- list the most prevalent types of cancer for men and for women, as well as the appropriate screening methods for detecting them
- describe current concepts about the etiologies of most malignancies
- describe traditional as well as more novel approaches to the treatment of various types of cancer
- list the most common human pathogens and the typical manifestations of the infectious diseases they cause
- discuss the epidemiology, clinical features, and treatment of HIV infection
- list the newer antiviral, antifungal, and antibacterial agents and their benefits and adverse effects
- describe the ophthalmic manifestations of the major systemic diseases covered in this volume
- describe the early manifestations and treatment of malignant hyperthermia
- describe the current American Heart Association guidelines for performing cardiopulmonary resuscitation

CHAPTER 1

Social Determinants of Health

Highlights

- Social determinants of health (SDOH) are major drivers of health disparities.
- Addressing SDOH is essential to "create social, physical, and economic environments that promote attaining the full potential for health and well-being for all" (Healthy People 2030).
- Disparities in access and outcomes are pervasive in ophthalmology.
- Lower educational level, lower income, being from an underrepresented racial or ethnic group, and being uninsured or having nonprivate insurance have been shown to be associated with higher rates of self-reported visual impairment and decreased access to care in the United States.
- Ophthalmologists should assess the impact of SDOH in the diagnosis and treatment of patients as part of every clinical encounter.

Introduction

Health is not the absence of disease but the presence of wellness. As illustrated in Figure 1-1, health is the result of the complex interplay of individual (eg, genetics, behaviors, demographics) and population-level factors (health care systems and policies). *Social determinants of health (SDOH),* also known as social and physical determinants of health, are conditions in the environment in which people grow, live, learn, work, and age that affect health outcomes. Over the past few decades, increasing evidence has suggested that complex social, physical, and economic conditions have a greater impact than medical care on health outcomes and life expectancy. In a 2008 report, the World Health Organization (WHO) stated that "social justice is a matter of life and death. It affects the way people live, their consequent chance of illness, and their risk of premature death." The report calls for organized global action to address SDOH in order to achieve *health equity,* defined as the achievement of the highest level of health for all people regardless of socially determined circumstances.

Health inequities are avoidable, unjust, systematic differences in health status between different population groups that result in *health disparities*. Healthy People 2030, an initiative by the US Department of Health and Human Services, defines health disparities as "a particular type of health difference that is closely linked with economic, social, or environmental disadvantage. Health disparities adversely affect groups of people who have systematically

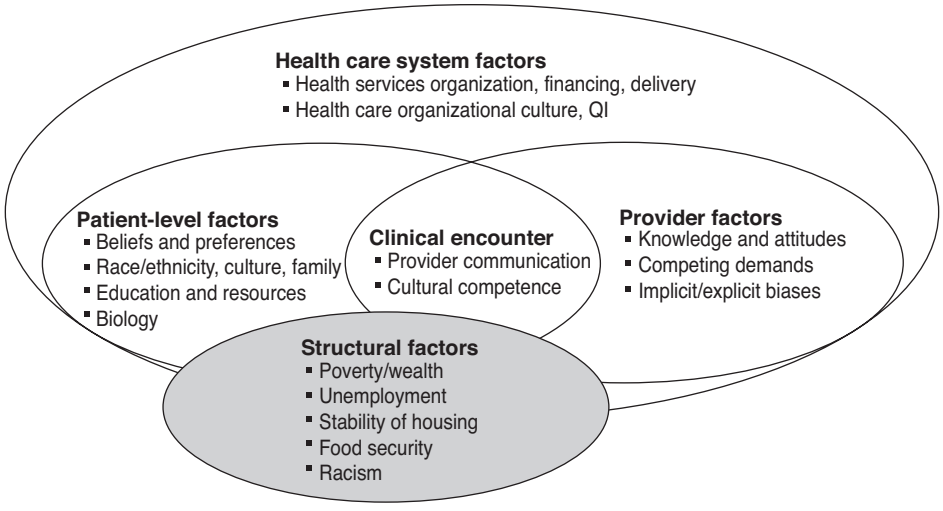

Figure 1-1 Key potential determinants of health and health care disparities. QI = quality improvement. *(From Bryant A. Racial and ethnic disparities in obstetric and gynecologic care and role of implicit biases. In:* UpToDate. *October 29, 2020. Used with permission from Kilbourne AM, Switzer G, Hyman K, Crowley-Matoka M, Fine MJ. Advancing health disparities research within the health care system: a conceptual framework.* Am J Public Health. *2006;96(12):2116. Copyright © 2006 American Public Health Association.)*

experienced greater social or economic obstacles to health based on their racial or ethnic group, religion, socioeconomic status, gender, age, or mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion."

The pursuit of health equity requires a concerted societal effort to remove barriers such as discrimination and poverty and their many consequences. One of the 5 overarching goals of Healthy People 2030 relates specifically to SDOH, with the objective to "create social, physical, and economic environments that promote attaining the full potential for health and well-being for all." In 2020, the American Academy of Ophthalmology created the Taskforce on Disparities in Eye Care to address issues related to health inequity, including access to care, health literacy, and workforce diversity. The papers produced by this group are published in the October 2022 issue of *Ophthalmology* (full-length articles appear online, while the related commentaries appear in print and online). These articles cover and expand on many of the issues discussed in this chapter.

Elam AR, Tseng VL, Rodriguez TM, Mike EV, Warren AK, Coleman AL; for the American Academy of Ophthalmology Taskforce on Disparities in Eye Care. Disparities in vision health and eye care. *Ophthalmology.* 2022;129(10):e89–e113. https://doi.org/10.1016/j.ophtha.2022.07.010

Healthy People 2030. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Accessed May 19, 2022. https://health.gov/healthypeople/priority-areas/social-determinants-health

World Health Organization. Commission on Social Determinants of Health. *Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health. Final Report.* World Health Organization; 2008.

Categories of Social Determinants of Health

Recognizing the social, economic, and physical conditions that different populations experience because of their environments is fundamental to understanding and addressing SDOH, which can be grouped into various domains (Fig 1-2):

- health care system (eg, health insurance coverage, access to primary care)
- economic stability (eg, stable housing and employment)
- education (eg, access to high-quality education, language skills, health literacy)
- neighborhood and physical environment (eg, access to transportation, walkability, neighborhood safety, access to clean water and nonpolluted air)
- food (eg, food security, access to healthy options)
- community and social context (eg, community engagement, incarceration rates, discrimination)

Although discrimination can be classified in the SDOH domain of community and social context, there is a complex relationship between discrimination and all SDOH domains, as discussed in the section Discrimination and Social Determinants of Health.

Health Care System

There are significant barriers to accessing health care and receiving high-quality care in the United States. First, although the rates of uninsured Americans have decreased under the Affordable Care Act, approximately 10% of people in the United States remain uninsured. Vulnerable populations, such as underrepresented racial and ethnic groups and low-income individuals, are at highest risk of being uninsured. Second, inadequate health

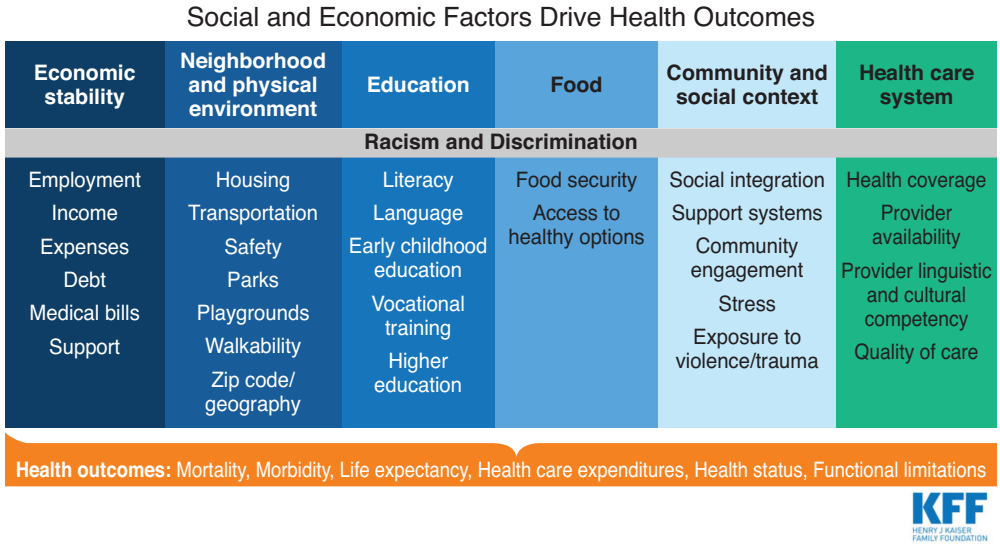

Figure 1-2 Social determinants of health. *(Reproduced with permission from Artiga S. Health disparities are a symptom of broader social and economic inequities. KFF. June 1, 2020. Accessed April 21, 2022. https://www.kff.org/policy-watch/health-disparities-symptom-broader-social-economic-inequities/)*

insurance coverage resulting in high out-of-pocket costs continues to be one of the largest barriers to health care access.

Geographic disparities in severe vision loss in the United States have also been well documented. Medically Underserved Areas and Health Professional Shortage Areas are geographic areas, populations, or facilities that have been designated by the federal government as having shortages in primary medical care, dental, or mental health services. Other barriers include poor access to transportation, limited health care resources, and poor physician-patient communication. Poor communication can be caused by several factors, including patient fear or lack of trust, lack of time, cultural and language barriers, and lower literacy levels. These social complexity risk factors have been associated with poorer outcomes with respect to preventive health care and management of chronic diseases.

Ophthalmic considerations Medicaid patients with a new diagnosis of primary open-angle glaucoma (POAG) receive substantially less glaucoma testing in the 15 months following initial diagnosis compared with patients who have commercial health insurance. This disparity is most striking in Black patients with Medicaid insurance, who have a 291% increased odds of not undergoing glaucoma testing compared with Black patients with commercial health insurance. Further, Black patients are more likely than White patients to go blind from POAG, highlighting the importance of efforts to improve the quality of glaucoma care for Medicaid recipients and underrepresented racial and ethnic groups.

Elam AR, Andrews C, Musch DC, Lee PP, Stein JD. Large disparities in receipt of glaucoma care between enrollees in Medicaid and those with commercial health insurance. *Ophthalmology.* 2017;124(10):1442–1448.

Priorities for addressing disparities in this domain include the following:

- expanding access to appropriate insurance coverage and to primary care and other health professionals
- focusing on preventive health care
- improving health communication between physicians and patients through training in cultural competency and by ensuring the availability of patient education material in various languages and at the appropriate educational level
- offering telehealth to improve services and expand access
- providing vision services in community health centers and vision outreach in underserved areas
- optimizing the electronic health records for screening and patient communication

Elam AR, Lee PP. High-risk populations for vision loss and eye care underutilization: a review of the literature and ideas on moving forward. *Surv Ophthalmol.* 2013;58(4):348–358.

Kirtland KA, Saaddine JB, Geiss LS, Thompson TJ, Cotch MF, Lee PP; Centers for Disease Control and Prevention (CDC). Geographic disparity of severe vision loss—United States, 2009–2013. *MMWR Morb Mortal Wkly Rep.* 2015;64(19):513–517.

Economic Stability

A substantial body of research has demonstrated the detrimental effects of low socioeconomic status and poverty on health outcomes. Economic stability is one of the most important SDOH, as it affects all other domains. Without stable employment, an individual may not be able to access health insurance and may also experience food insecurity, housing instability, and poor work environments, all of which have complex effects on many aspects of health. Among the goals of Healthy People 2030 is helping more people achieve economic stability through employment programs, career counseling, and provision of high-quality child care options, as well as through policies to assist individuals in securing quality food, stable housing, and access to health care and education.

Ophthalmic considerations Sociodemographic disparities are known to exist for ocular diseases such as refractive error, cataract, glaucoma, and diabetic retinopathy. In their analysis of disparity in visual impairment among adults in the United States based on race and socioeconomic status, Uhr and colleagues found that lower educational level, lower income, being a patient of color, and being uninsured or having nonprivate insurance were associated with higher rates of self-reported visual impairment and decreased access to care.

Uhr JH, Chawla H, Williams BK Jr, Cavuoto KM, Sridhar J. Racial and socioeconomic disparities in visual impairment in the United States. *Ophthalmology*. 2021;128(7):1102–1104.

Education

Higher educational level is strongly associated with improved health outcomes, positive health behaviors, and increased life expectancy. Early childhood education and primary and secondary education are key determinants of future health; therefore, addressing disparities in educational access and quality as early as possible in life is critical.

Poor health literacy is associated with poor medical adherence, decreased utilization of preventive services, and increased mortality. Educational material provided to patients should be tailored to the health literacy level of the target population.

Ophthalmic considerations In medically underserved urban communities, patients with a high school education or less are significantly less likely to have had a recent eye examination than those with greater than a high school education. The former are also more likely to report difficulties with insurance, transportation, and lack of knowledge as barriers to eye care.

Goyal A, Richards C, Patel V, et al. The Vision Detroit project: visual burden, barriers, and access to eye care in an urban setting. *Ophthalmic Epidemiol.* 2022;29(1):13–24.

Neighborhood and Physical Environment

The neighborhood and physical or built environment in which individuals live, learn, work, and play have a direct impact on health and well-being. High rates of crime and violence; unsafe air or water; poor walkability; and limited access to healthful food options, parks, playgrounds, healthy work environments, or transportation are some of the numerous factors that can negatively affect health outcomes. The Area Deprivation Index (ADI) is a metric derived from 17 US census variables calculated based on zip code—including educational level, employment, income, household characteristics, and housing—to assess the level of socioeconomic disadvantage by neighborhood.

Ophthalmic considerations Living in more socioeconomically disadvantaged neighborhoods, as measured by the ADI, is associated with nonadherence to first-time ophthalmology referrals for diabetic retinopathy screenings.

Yusuf R, Chen EM, Nwanyanwu K, Richards B. Neighborhood deprivation and adherence to initial diabetic retinopathy screening. *Ophthalmol Retina.* 2020;4(5): 550–552.

Food

Access to food, especially nutritious food, is a key SDOH that directly affects an individual's health. *Food insecurity,* defined as a lack of consistent access to enough food for an active, healthy lifestyle, affects 10.5% of American households. Food insecurity and poor nutrition are known to be risk factors for chronic illnesses such as obesity, diabetes, hypertension, and cancer.

Accessibility and availability of nutritious food choices are influenced by other SDOH such as economic stability, neighborhood and physical environment, and education.

Community and Social Context

Social, family, and community networks serve as important support systems for individuals and thus can significantly affect health outcomes. Factors such as civic participation, social cohesion, and community engagement can have positive health effects by reducing stress. Community engagement by health care providers may improve patient-provider relationships and build trust among patients. Research has shown that physician-patient concordance in gender, race and ethnicity, language, and culture is correlated with increased patient satisfaction and adherence.

Discrimination and Social Determinants of Health

Discrimination is a socially structured action resulting in the unfair treatment of individuals or groups based on their race or ethnicity, sex, gender identity, sexual orientation, age, disability, religion, socioeconomic status, or other factors and can significantly affect the health of vulnerable populations.

Race and Ethnicity

Racism, a type of discrimination based on race or ethnicity, results in significant disparities in health outcomes for patients of color. Racism exists in different forms (eg, internalized, interpersonal, systemic), can manifest in various ways (eg, stereotypes, beliefs), and can be intentional or unintentional. The US Census Bureau projects that underrepresented racial and ethnic groups will account for over half of the US population by 2045. In 2020, the American Medical Association adopted a policy that recognizes racism as a public health threat, and the organization made a commitment to work actively to dismantle racist policies and practices across all of health care.

The effects of racial and ethnic discrimination on SDOH are complex, multidimensional, and interrelated. For example, in the United States, communities of color are disproportionately affected by poverty. Individuals affected by poverty are more likely to have lower levels of education. They are also more likely to live in neighborhoods with high rates of crime and poor access to resources such as nutritious foods, safe outdoor spaces for exercise, and clean water. All of these factors adversely affect health, quality of life, and health outcomes.

O'Reilly KB. AMA: Racism is a threat to public health. American Medical Association. November 16, 2020. Accessed August 27, 2022. https://www.ama-assn.org/delivering-care/health-equity/ama-racism-threat-public-health

Ophthalmic considerations Compared with White patients, Black and Latino patients and other patients of color have higher rates of refractive error, diabetic retinopathy, cataract, and POAG. Despite being at higher risk for visual impairment and blindness, Black and Latino patients are less likely than White patients to be seen by an ophthalmologist or to receive a dilated examination.

Sex and Gender

It is important to define the difference between sex and gender in the context of discussing health care disparities. The WHO defines *sex* as the different biological and physiological characteristics of individuals that are defined by chromosomal composition and reproductive organs; sex is typically assigned at birth (male, female, or intersex). In contrast, *gender* is a social construct that refers to the roles and expectations attributed to men and women in society and evolves with time. The WHO recognizes that gender is an important factor affecting SDOH, as gender inequality leads to health risks for women globally, and unbalanced power relations between men and women affect health-seeking behavior and health outcomes.

Ophthalmic considerations A study investigating sex differences in the repair of retinal detachments in the United States found that women have a 34% reduced odds of receiving surgery for a retinal detachment diagnosis, and their detachments are repaired with different types of surgery. Future studies

are warranted to better understand the role of sex and gender disparities in ophthalmic care.

Callaway NF, Vail D, Al-Moujahed A, et al. Sex differences in the repair of retinal detachments in the United States. *Am J Ophthalmol.* 2020;219:284–294.

Sexual Orientation and Gender Identity

Gender identity is defined as an individual's personal sense of gender and includes male, female, transgender, and nonbinary classifications. Research has demonstrated that individuals who identify as lesbian, gay, bisexual, transgender, queer and/or questioning, and other sexual identities (LGBTQ+), experience health care disparities and have higher rates of mental illness and substance abuse disorder beginning in adolescence. Factors such as societal stigma and harassment, lack of cultural competency among health care providers, and low rates of insurance coverage contribute to the overall health burden in this population. LGBTQ+ individuals who are members of communities of color face even greater health disparities.

Age and Disability

Older adults and individuals with disabilities are particularly vulnerable to discrimination and its consequences. Older adults are more susceptible to illness and chronic disease with aging, and many face considerable barriers, such as limited income and physical and cognitive limitations in addition to discrimination. *Ageism* refers to stereotypes, prejudice, and discrimination against older adults and has been shown to lead to worse health outcomes. Adults with disabilities are more likely than those without disabilities to report their health to be fair or poor and to report higher rates of obesity, lack of physical activity, and smoking. Bias of health care professionals against individuals with disabilities may be a contributing factor to disparities in care.

Chang ES, Kannoth S, Levy S, Wang SY, Lee JE, Levy BR. Global reach of ageism on older persons' health: a systematic review. *PLoS One.* 2020;15(1):e0220857. doi:10.1371/journal.pone.0220857

Approaches to Addressing Social Determinants of Health

Ophthalmologists can play an important role in addressing SDOH in vulnerable patient populations. Various strategies can be used:

- *Assess the impact of SDOH on patients' lives as part of every patient encounter*. Similar to the way that the history of the present illness, medical/ocular history, and other types of patient information are obtained, ophthalmologists and their health care teams can assess the role of SDOH in the lives of their patients, how SDOH might affect patient health, and how health care can be provided more effectively. A suggested screening tool, provided by the American Academy of Family Physicians, is available (https://www.aafp.org/content/dam/AAFP/documents/patient_care/everyone_project/hops19-physician-form-sdoh.pdf).

- *Address biases in your practice.* How are people of a lower socioeconomic status or lower educational or literacy level viewed? By acknowledging potential biases, ophthalmologists and their staff members can work to mitigate the effects they may have on patient care. Consider taking an Implicit Association Test (implicit.harvard.edu) to illuminate your own unconscious biases and mandating implicit bias training for all office staff.
- *Provide patient-centered care based on the principles of empathy, curiosity, and respect.* Consider the patient's cultural values, beliefs, and family dynamics and decision making; traditions, customs, and spirituality; possible mistrust; preferred communication styles; and sociodemographic factors.
- *Integrate patient social support structures into your practice.* Empower other members of your team to identify and address SDOH. Provide support such as parking or transportation vouchers.
- *Improve access to care and quality of care.* This includes strategies such as improving patient-physician communication and patient health literacy and reducing cultural and linguistic barriers (see the section Health Care System). It may be helpful to do a quality assurance assessment of your practice to identify any disparities in the care being provided to patients.

CHAPTER 2

Using Research to Improve Clinical Practice

Highlights

- A basic knowledge of research and statistical methodology is an important part of understanding biomedical literature, applying that knowledge to practice, and being able to design a study to answer clinical questions.
- Research can help answer important clinical questions such as the utility of diagnostic and screening tests or the benefits, risks, probabilities, and expected outcomes of surgeries.
- It is important for clinicians to understand how to measure and compare the results of their clinical practice and to present data to demonstrate improved clinical practice.
- Ophthalmologists use clinical research to establish best practices for patient care; this chapter will help the clinician to critically review research and apply the results to the practice of ophthalmology.

Researching Answers to Clinical Questions

Formulating the research question is the first step in resolving a diagnostic or management issue. The question may be derived from a clinical observation, or it may be a question that remains unanswered after literature research. Examples of clinical questions in ophthalmology include the following: What are the results of minimally invasive glaucoma surgery in patients with normal-tension glaucoma versus higher-pressure glaucoma? Do racial and ethnic minority populations have a higher risk of proliferative vitreoretinopathy after pars plana vitrectomy? What is the expected survival of an endothelial graft in a patient with Fuchs dystrophy?

Sources of Information

Clinicians can use various sources of information to find answers to such questions. Resources include the following:

- general textbooks on ophthalmology
- review journals that are devoted to specific subjects (eg, *Survey of Ophthalmology* [www.surveyophthalmol.com])

- Ophthalmic News and Education (ONE) Network of the American Academy of Ophthalmology (www.aao.org/education/clinical-education) for Preferred Practice Pattern guidelines, educational materials ranging across the ophthalmic subspecialties, and multimedia resources
- Cochrane Library (www.cochranelibrary.com) for high-quality meta-analyses of the efficacy of specific management issues (eg, surgery for nonarteritic ischemic optic neuropathy, intervention for involutional lower eyelid ectropion)
- PubMed (https://pubmed.ncbi.nlm.nih.gov) for wide-ranging coverage of primary sources in biomedical literature, as well as various tools and filters to enable clinicians to narrow the search to fit the specific research question and find the most relevant articles

Data Fundamentals

In order to critically assess a study and evaluate the validity of comparisons, it is important for the clinician to understand the various types and uses of data. *Data* is defined as a collection of individual pieces of information recorded for the purpose of answering a research question by statistical methods. These individual pieces of information are called *data items* or, more commonly, *variables*.

Variables fall into 2 categories: independent and dependent. An *independent variable,* sometimes referred to as a *predictor,* or *experimental variable,* is one that stands alone and is not changed by the other variables being manipulated and measured in an experiment to observe the effect on a dependent variable. A *dependent variable* is the variable that is measured or tested by a researcher and "depends" on other variables; it is also known as an *outcome*.

Two main types of variables are measured: categorical and continuous. *Categorical variables* are those that have discrete categories or levels. Categorical variables can be further defined as nominal, dichotomous, or ordinal. *Nominal variables* describe categories that do not have a specific ranking order, such as ethnicity or gender. *Dichotomous variables* are categorical variables with 2 levels. These could include yes/no, high/low, or male/female. *Ordinal variables* have 2 or more categories that can be ordered or ranked. For example, a variable with response data ranging from "strongly agree" to "strongly disagree" would be considered ordinal. Categorical variables are described by frequencies and percentages.

Continuous variables are measured numerically and have an infinite number of possible values. The data values can be arranged from least to greatest to show their distribution. If the distribution of values is symmetrical—that is, with a center point and 2 sides that appear similar (a bell-shaped curve)—the data are said to be *parametric,* or *normally distributed*. In this case, the researcher would report the mean and standard deviation. If the data are *skewed (nonparametric)* or there are some clear outliers, then reporting the median with the 25th and 75th percentile *(interquartile range)* is appropriate.

In addition, data as a whole can be seen as independent or dependent. Data are independent if the values in one sample reveal no information about those of the other sample. If the values in one sample affect the values in the other sample, then the samples are dependent. In reviewing an article, the clinician should note whether the data are independent

or dependent. In certain situations, data on eyes can be seen as dependent because the data from the left eye and the right eye may be correlated.

Armstrong RA. Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic Physiol Opt.* 2013;33(1):7–14.

Critical Reading of Studies

Before committing time to reading a published study, the clinician should review its abstract to ascertain whether the study addresses the question of interest. If the abstract appears relevant, the clinician should then read the rest of the study critically to determine its validity and applicability to the clinical question. Relevant characteristics to consider include the study population, recruitment strategy, sample size, intervention, outcomes of interest, and statistical methods used.

Are the study population and recruitment strategy applicable to my patients?

Understanding a study's population and its recruitment strategy is key to understanding the setting of the study. Was the trial clinic based, multicenter, or community based? In therapeutic trials, the inclusion and exclusion criteria describe the characteristics of those who were or were not treated with an intervention. Specific patient groups might have been excluded because they were considered a vulnerable population. For example, most trials of ocular hypotensive drugs exclude children and pregnant women. Thus, if a clinician wants to do research before deciding whether to use a specific ocular hypotensive agent in a pregnant woman or in a child, most of the data will be found only in individual case reports or retrospective case series.

The next step in evaluating a study is exploring whether its process of assigning participants to the intervention resulted in selection bias. Was the intervention randomly assigned? Was the treatment group comparable to the control group? The purpose of randomization is to minimize bias on the part of the investigators and the participants. For example, an investigator might create selection bias by inadvertently assigning less-complex patients to a new surgery, potentially biasing their outcomes toward better results.

If the assignment process was appropriately randomized, the participants in each study group should be similar in the characteristics that can affect the outcome of interest. For example, in evaluating a study comparing the effect of laser treatment versus anti–vascular endothelial growth factor treatment on diabetic retinopathy, the clinician should note whether participants' hemoglobin A_{1c} levels, blood pressure, and severity of disease are similar between study groups because these factors can alter the progression of retinopathy. Use of a control group is also important; it indicates whether the results of the intervention are above and beyond the beneficial effects of participants' enrollment in a trial, which usually includes selected, motivated patients.

Clinical trials may study a narrow subset of a disease, making the results applicable and generalizable only to similar patients. A common error is extrapolating such data to apply to all patients or different degrees of disease severity. For example, if a treatment is successful only in patients with mild glaucomatous damage who underwent trabeculectomy but not in those with advanced glaucomatous damage, the study results should be applied only to similar patients—in this case, patients with mild glaucomatous damage.

Was the sample large enough to detect a difference?

Sample size, effect size, and power are interrelated. Together, they are used to test whether the null hypothesis can be rejected in favor of the alternative hypothesis.

The *null hypothesis* states that there is no difference in the outcome of interest between the group that received the intervention and the group that did not receive the intervention, while the *alternative hypothesis* states that a true difference exists between the groups. The *sample size* is the number of participants needed in order to reject the null hypothesis, given a predetermined effect size and power. *Power* is the probability of making a correct decision (to reject the null hypothesis) when the null hypothesis is false. Power depends on the sample size, the expected difference in the outcome of interest in the intervention group compared with the control group (eg, improvement in visual acuity, resolution of macular edema), and the variability (eg, standard deviation) of the outcome of interest. When determining the sample size needed for a study, the power should be at least 80%. *Effect size* is a number measuring the strength of the relationship between 2 variables in a population or in a sample-based estimate of that quantity.

In general, an intervention with a larger treatment effect and smaller variability can be tested with a smaller sample size. Thus, if the sample size calculation yields a large sample, the sample size can be reduced by increasing the effect size or changing the outcome variable type from categorical to continuous. The information utilized to calculate sample size (power, effect size, type of test, and alpha [ie, threshold of significance]) should be reported in the Methods section of the study.

Are the treatments and outcomes clinically relevant?

The clinician should ascertain whether the study's results can be applied to his or her patients. Questions to consider include the following:

- Is the intervention available and applicable to the current practice environment?
- Are the outcomes clinically important?
- Are all clinically important outcomes evaluated?
- Is the treatment difference clinically significant?

It is important to consider whether the intervention is useful in practice. It may be too expensive, too difficult to perform, or no longer in general use. If so, the study findings may provide little advantage over current clinical care.

Is the intervention reproducible?

The study should describe the intervention in enough detail to allow the experiment to be replicated. For example, a surgical study should explain all the steps of the procedure so that different surgeons are able to perform the procedure in the same manner in each case. Did all surgeons involved in the study perform it similarly, and were their results similar? Did the study include a training session before the start of the study, monitor specific aspects of the surgical procedure, and standardize postoperative care? In general, a study should avoid differences in study procedures except for the intervention of interest. In addition, to decrease the risk of investigator bias, the study should try to mask the observer to the intervention. *Investigator bias* may occur when the investigator expects a different

result in the intervention group and adjusts his or her measurement of the outcome of interest to satisfy this expectation.

Is the outcome clearly defined and reliable?

The study should clearly state the primary and secondary outcomes of interest as well as the expected change for these outcomes. For example, if the primary outcome is improvement in visual acuity, the study should specify the logMAR value that represents improvement, the range, the distribution of results (eg, normal, skewed to the right or left), and the variability. These statements allow the reader to determine whether the study was able to prove or disprove the null hypothesis.

Many outcomes (eg, visual acuity, intraocular pressure [IOP], macular thickness as measured with optical coherence tomography [OCT]) will have measurement error. Such measurement error will increase the variability of the outcome of interest or create a difference in results when no true difference in outcomes exists. Therefore, a study should standardize measurement of the outcome of interest for all investigators. For example, the Ocular Hypertension Treatment Study established a standardized method for checking IOP to decrease variability and error in IOP measurement. The study protocol included using a masked recorder and observer and repeating the testing.

Were all participants included in the analysis, and was the follow-up period sufficient?

The validity of a study is anchored on follow-up of all participants and adequate duration of follow-up. Thus, in evaluating a study, the clinician should look for how many of the participants completed follow-up. In order to reduce bias, results should be reported for all participants, regardless of their study group assignment or their completion status. This approach is called an *intention-to-treat analysis*. The study should state the reasons for loss to follow-up as well as any differences between the groups in their reasons for lack of completion. For example, participants in the intervention group of a drug trial may be more likely to drop out than those in the placebo group if they experience ocular adverse effects from the drug, such as burning or stinging.

The length of the follow-up period is also an important factor and should be determined based on the rate of disease progression or response to treatment. For example, in a study assessing the use of atropine eyedrops versus patching for treatment of amblyopia, a follow-up of 3–6 months may suffice; similar follow-up periods may be appropriate for monitoring visual acuity improvement after cataract extraction. In contrast, glaucoma progresses over long periods; therefore, trials assessing visual field loss in glaucoma call for a longer follow-up period, such as 5 years.

Is the analysis appropriate for the outcome?

Statistical tests depend on the type of data used to determine the difference between 2 treatment groups (see the earlier section Data Fundamentals). Table 2-1 shows appropriate statistical tests for different types of data. All of these tests provide a *P* value, a metric that indicates the likelihood that a difference between the 2 groups is due to chance alone. For example, a *P* value of <.05 suggests that the likelihood that the difference between the 2 groups is due to chance alone is less than 5%. The lower the *P* value, the less likely it is that the difference is due to chance and the more likely it is to be a true difference.

Table 2-1 Appropriate Statistical Test by Variable Type

Type of Independent Variable (predictor)	Type of Dependent Variable (outcome)	Statistical Test
Dichotomous	Continuous, parametric	Two-sample *t* test
Dichotomous	Continuous, nonparametric	Mann-Whitney *U* test, Wilcoxon signed rank test
Nominal or ordinal	Continuous	Analysis of variance (ANOVA)
Continuous	Continuous	Linear regression, Pearson correlation
Continuous or categorical	Dichotomous	Logistic regression (binary)
Continuous or categorical	Ordinal	Ordinal logistic regression
Categorical	Categorical	Chi-square test, Fisher exact test

Is the difference between the groups clinically significant?

Even though a statistical test may suggest a statistically significant difference in the results between 2 groups, the clinician should consider whether the magnitude and nature of the difference are clinically meaningful. For example, a difference in 2 letters of visual acuity on a Snellen chart may be statistically significant, but this difference may not be clinically noticeable to patients and may be within the margin of measurement error for visual acuity. In addition to evaluating primary outcome variables, the study should evaluate secondary clinically important variables related to the safety of the intervention. These variables include dropout rates, pain, and allergic reactions.

In some instances, a *P* value that is not considered significant but is <.10 may still be relevant; the difference might not have reached statistical significance because the sample size was not large enough. Moreover, the confidence interval of the data may provide more insight than the *P* value derived from a hypothesis test. Intervals that are very wide indicate that the results describing the effect lack precision and that further information is needed.

Is there any bias or confounding that should be considered?

While the results of an epidemiologic study may reflect the true effect of an exposure on the development of the outcome under investigation, the clinician should keep in mind that there could be an alternative explanation. For example, the effects of chance *(random error),* bias, or confounding could produce spurious results and lead to erroneous conclusions regarding the presence or absence of a statistical association.

Bias may be defined as any systematic error in an epidemiologic study that results in an incorrect estimate of the true effect of an exposure on the outcome of interest. More than 50 types of bias have been identified in epidemiologic studies, but for the sake of simplicity, they can be broadly grouped into 2 categories: information bias and selection bias. *Information bias* results from systematic differences in the way data on exposure or

outcome are obtained from the various study groups. *Selection bias* occurs when there is a systematic difference between either

- those who participate in the study and those who do not (affecting generalizability) *or*
- those in the treatment arm of a study and those in the control group (affecting comparability between groups)

That is, there are differences in the characteristics between study groups, and those characteristics are related either to the exposure or to the outcome under investigation. Selection bias can occur for a number of reasons.

Confounding provides another alternative explanation for an association between an exposure (X) and an outcome. It occurs when an observed association is in fact distorted because the exposure is also correlated with another risk factor (Y). Although this risk factor Y is also associated with the outcome, it is independent of the exposure under investigation, X. As a consequence, the estimated association is not the same as the true effect of exposure X on the outcome. Confounding factors, if not controlled for, cause bias in the estimate of the impact of the exposure being studied. It is important for researchers to consider the potential bias and confounding variables in the study design phase. Not doing so will require additional adjustments in the analysis phase or create a potential limitation.

Are there conflicts of interest?

A *conflict of interest (COI)* occurs when a person or organization receives financial or other interests in an entity (eg, a device company) that could consciously or unconsciously motivate them to make decisions that benefit the entity. For example, a COI would be present if a person who was a paid speaker for a company wrote and published a paper describing that company's new device and its benefits. Because of the relationship between the author and the entity, there is a risk that the COI could influence the author's evaluation in the entity's favor. Further, if the author biases the study results to ascribe large benefits to the device with minimal risk, the author may secondarily benefit by receiving more paid speaking engagements from the entity.

Although the existence of a relationship between an author and an entity does not necessarily represent an impropriety, the potential for such an impropriety is one reason that medical journals require authors and other decision makers to disclose any COIs. Even more important, medical journals also require the author and other individuals with COIs to present an *accurate* and *balanced* assessment of the benefits and *all of the risks* of the drug or new device. Direct financial benefit is not the only type of COI. All authors are motivated to publish their findings in research journals, for reasons that may include academic promotion, future research grants, and their national reputation; and studies with positive results are more likely to be published than those with negative findings. Overall, any research should include an accurate and balanced assessment of the results regardless of whether the authors have COIs, and readers should use their best judgment about whether the research includes a balanced presentation of the results.

Hennekens CH, Buring JE. *Epidemiology in Medicine.* Lippincott Williams & Wilkins; 1987.

Understanding Study Design

Clinical research uses a wide array of study designs. In *observational studies,* also known as *nonexperimental studies,* investigators evaluate characteristics, behaviors, and exposures in participants with a particular disease, condition, or complication. An observational study reports only the characteristics of the study population; it does not directly manipulate behaviors (eg, cigarette smoking) or exposures (eg, use of a medication or laser treatment). In *experimental studies,* typically clinical trials, subjects are assigned to a particular treatment, such as a prescribed behavior (eg, eating a diet high in antioxidant foods) or a therapeutic or preventive intervention (eg, use of an oral neuroprotective agent for patients with glaucoma or antioxidant vitamin supplementation for patients with early age-related macular degeneration [AMD]). In addition to these types of studies, *real-world data* contribute to our understanding of treatment effectiveness in everyday clinical practice (see the section Real-World Studies).

When conducted and interpreted appropriately, each type of study design can provide valuable information. Researchers employ observational studies to describe the presentation and progression of disease, generate hypotheses for further study, and efficiently assess data that may already exist for testing a hypothesis about an intervention. Examples of observational studies include case reports, case series, case-control studies, cross-sectional studies, and cohort studies. In contrast, prospective randomized controlled trials provide the best evidence regarding the effects of an intervention. Finally, meta-analyses provide a methodology to summarize the results of multiple clinical trials addressing similar research questions. Meta-analyses and controlled trials offer the highest levels of evidence. See Figure 2-1 for an algorithm for classification of clinical research and Table 2-2 for an overview of each of the study designs discussed in this section.

Case Reports

A *case report* describes a finding in a single patient to alert readers to a rare condition or an unusual treatment result. Case reports cannot provide information on treatment efficacy or determine whether a disease is caused by an exposure. At most, they can suggest a previously unsuspected finding or mechanism of disease and be a source for generation of a hypothesis to test in a larger prospective study.

Case Series

Case series investigate the presentation, history, and/or follow-up of a group of patients and provide valuable information on the natural history or prognosis of a disease. Case series may differ from clinical trials in regard to patient selection, patient characteristics, and length and completeness of follow-up; these characteristics may establish the quality and applicability of a case series. The case series provides preliminary information for a larger study with a comparison group.

Case series can be biased if they include only patients with severe disease from tertiary referral centers such as university-based clinics or patients with only mild cases of a disease. Moreover, the collection of patient information, measurements, tests, and other evaluations might not be standardized in case series.

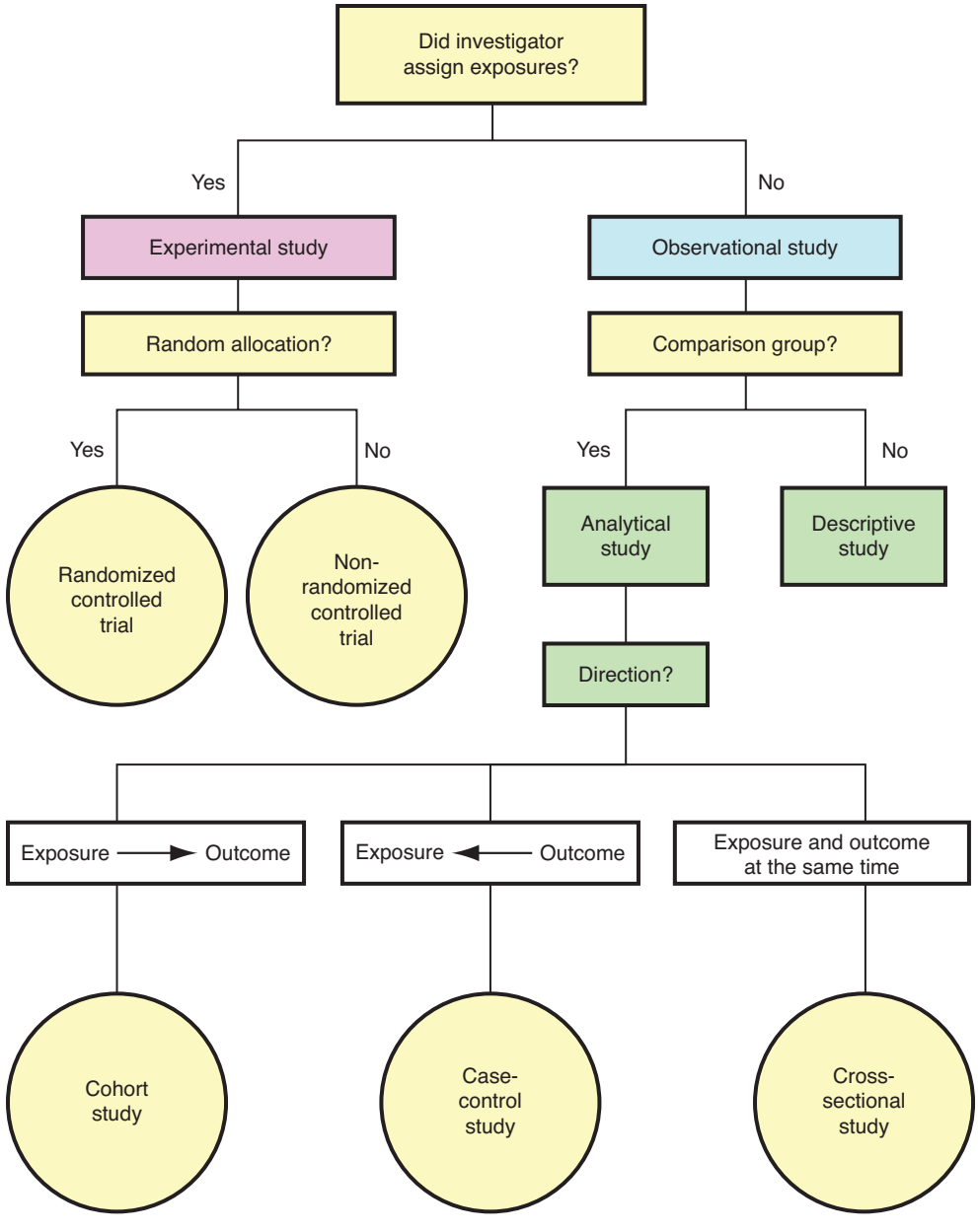

Figure 2-1 Algorithm for classification of types of clinical research. *(Modified with permission from Grimes DA, Schulz KF. An overview of clinical research: the lay of the land.* Lancet. *2002;359(9300):57–61. https://doi.org/10.1016/S0140-6736(02)07283-5)*

Length of follow-up intervals may vary within a single case series. If there are differences in the duration of follow-up, the study should report the specific follow-up period, such as 1, 2, and 3 years after the initiation of treatment. When the outcome being measured is an

Table 2-2 Advantages and Disadvantages of Study Designs

Type of Study Design	Description	Advantages	Disadvantages
Case report or series	An observation of an event that occurred in a single patient (or a small collection of patients).	• Informs patients and physicians about natural history and prognostic factors • Easy and inexpensive to do in health care settings • Helpful in hypothesis formation for a future prospective study	• Cases may not be representative • Outcome may be a chance finding, not characteristic of disease • Cannot easily examine disease etiology • Exposure reflects the underlying population, not the outcome • Begs the question "Compared to what?"
Case-control studies	Patients with a certain outcome or disease and an appropriate group of controls without the outcome or disease are selected, and information is then obtained on whether the subjects have been exposed to the factor under investigation.	• Quick and inexpensive • Only feasible method for very rare disorders or those with long lag between exposure and outcome • Fewer subjects needed than for cross-sectional studies	• Reliance on recall or records to determine exposure status • Confounders: ▪ Selection of control groups is difficult ▪ Potential for recall bias and selection bias
Cross-sectional studies	A study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. Best for quantifying the prevalence of a disease or risk factor and for quantifying the accuracy of a diagnostic test.	• Inexpensive and simple	• At best, establishes association, not causality • Susceptible to recall bias • Confounders may be unequally distributed • Neyman bias (where the very sick or very well or both are erroneously excluded from a study) • Group sizes may be unequal

Type of Study Design	Description	Advantages	Disadvantages
Cohort study	Data are obtained from groups who have been exposed, or not exposed, to the technology or factor of interest. Best to study the effect of predictive risk factors on an outcome.	• Subjects can be matched • Can establish timing and directionality of events • Eligibility criteria and outcome assessments can be standardized • Administratively easier and less costly than randomized control trial	• Controls may be difficult to identify • Exposure may be linked to a hidden confounder • Masking is difficult • Randomization not present • For rare disease, large sample sizes or long follow-up necessary
Clinical trial	An experimental comparison study in which participants are allocated to a treatment/intervention group or a control/placebo group using a random mechanism. Best for studying the effect of an intervention.	• Unbiased distribution of confounders • Masking more likely • Randomization facilitates statistical analysis	• Costs in time and money • Volunteer (ie, selection) bias possible • Ethically problematic at times
Systematic reviews and meta-analyses of clinical trials	A form of analysis that synthesizes all the available evidence on a particular question, such as how effective a drug is; a meta-analysis is a type of systematic review that looks at numerous studies for the answer.	• Systematic method for selecting studies for the review reduces bias • More reliable and useful than any single study • Information for evidence-based practice and decision making • Comprehensive	• Often more time-consuming than other types of review • Can quickly become outdated • May not be enough research in the literature to analyze • Quality depends on what has been published in the literature

event, such as corneal graft failure, a *survival analysis* can account for the varying lengths of follow-up. If the study does not follow all of its participants for the full length of the possible follow-up period, these losses to follow-up can create bias in the reported outcomes for the case series. Overall, if a large percentage of patients do not return for complete follow-up, the study results may not be valid; the remaining subjects might have had an unusually good or unusually bad course compared with the subjects lost to follow-up.

Case-Control Studies

A *case-control study* investigates a hypothesis about an association between exposures or potential risk factors (eg, smoking, medical conditions, therapies) and outcomes of interest (eg, loss of visual acuity, development of glaucoma, corneal graft failure, complications of cataract surgery). In a case-control study, the researchers select a group of participants with the disease of interest *(cases)* and a group of comparable individuals who are free of disease *(controls)*. The past exposures and characteristics of the 2 groups are compared to determine whether differences exist between the groups (Fig 2-2). If so, the study will conclude that the exposures or characteristics that differ are associated with the disease. However, exposure data may be less accurate in case-control studies than in cohort studies, and case-control studies may be subject to selection bias if they do not have an appropriate control group. Further information on this and other types of bias can be found in general epidemiology textbooks.

Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. *Modern Epidemiology.* 4th ed. Lippincott Williams & Wilkins; 2021.

Cross-Sectional Studies

Cross-sectional studies correlate exposures and risk factors with the presence of disease without the benefit of knowing the timing or sequence of exposure and disease development. An example of a cross-sectional study is one in which a researcher collects a blood sample from patients and records their lens status (phakic, pseudophakic, or aphakic) at the same time. With this study design, it is also important to consider whether a confounding factor could be affecting the association. In the example above, age could be a confounding factor because cholesterol levels increase with age, as does the likelihood of cataract surgery.

Cohort Studies

Researchers may use *cohort studies* (also called *follow-up studies*) to investigate the association between exposures or potential risk factors and patient outcomes. These studies identify participants who, at baseline, are free of the disease of interest and classify them by the presence or absence of potential risk factors; participants are then followed for subsequent development of the disease (see Fig 2-2). The Los Angeles Latino Eye Study is an example of prospectively assessing the risk factors (blood pressure and age) for an outcome of interest (incidence of AMD).

The primary weakness of this study design is that participants with the risk factor of interest may differ in many ways from those without the risk factor, and those other characteristics can also affect the incidence of the disease. Statistical analysis techniques such

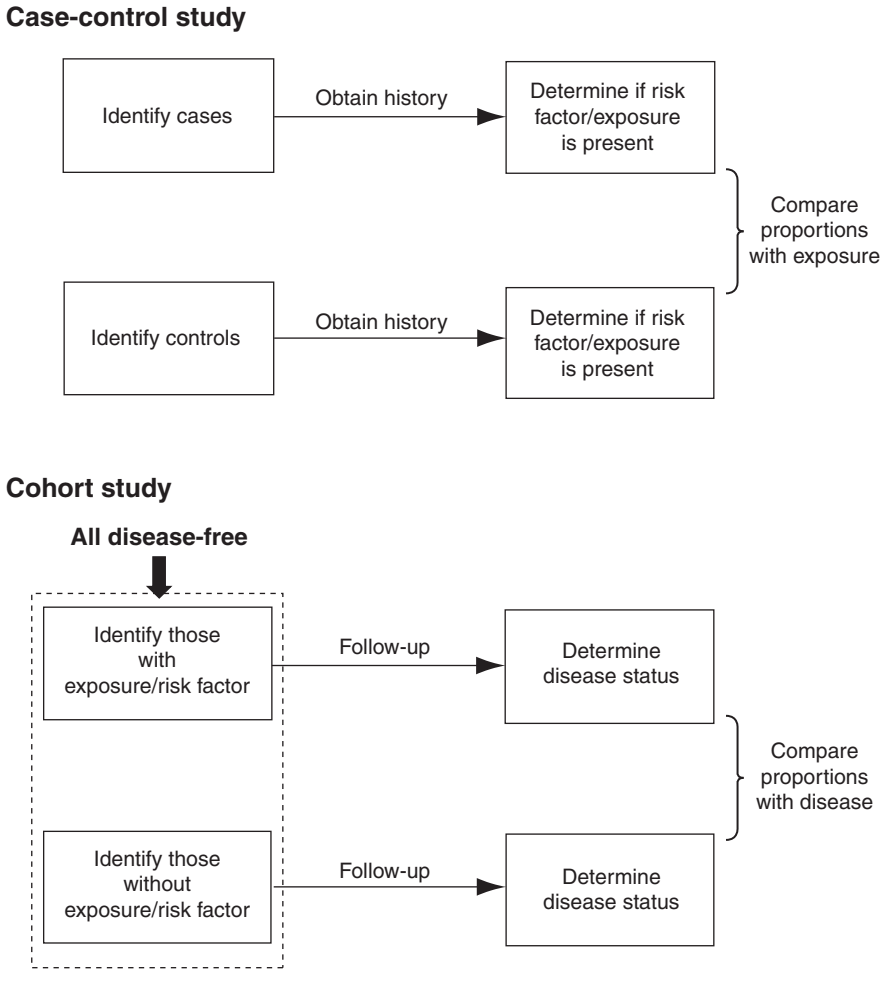

Figure 2-2 Simplified schematics of 2 observational study designs.

as stratified analysis and regression analysis can adjust for the effect of known confounding factors. However, in many cases, investigators do not understand all the factors that affect the incidence of a disease. Thus, although cohort studies can identify associations and disease incidence, these associations are not considered causal.

The international collaborative STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) initiative aims to improve the design and reporting of cohort, case-control, and cross-sectional studies. Checklists to ensure proper reporting of results, as well as other resources and guidance on observational studies, are available at the STROBE website (https://www.strobe-statement.org/).

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.

Clinical Trials

Unlike the preceding types of studies, *randomized clinical trials (RCTs)* assign participants by chance to different treatment groups (exposure groups). Random assignment yields treatment groups with similar characteristics with regard to variables that could alter outcomes or the risk of complications from the treatment. This control of confounding factors is a major advantage of RCTs over other study designs.

Apart from randomization, RCTs should also include all the features of high-quality observational studies, such as the following:

- a well-defined research question and objectives
- explicit inclusion and exclusion criteria
- a diverse study population
- an adequate sample size
- standardized procedures
- predefined, objective primary and secondary outcomes
- masking of participants, treating clinicians, and evaluators to the assigned treatment
- complete follow-up of all participants

The CONSORT (Consolidated Standards of Reporting Trials) Statement, an evidence-based set of recommendations, includes a checklist of features that should be included in the design and reporting of clinical trials (http://www.consort-statement.org/).

When evaluating a clinical trial, the clinician should consider 2 issues in addition to the other features of high-quality studies. The first is whether the study excluded participants from data analysis because they did not meet all of the eligibility criteria, experienced adverse effects and stopped treatment, or did not adhere to the treatment regimen. Exclusion of data from such participants is a source of bias because their results could differ from those of the participants included in the analysis. For this reason, clinical trials should include an intention-to-treat analysis, which includes the data from all enrolled participants, as well as separate analyses of those who completed the trial and those who did not.

Results from subgroups of patients (eg, young vs old, hypertensive vs nonhypertensive) should be regarded with suspicion. By statistical chance alone, a study might identify a subgroup of patients for whom the benefit of treatment is statistically significant. However, a subgroup evaluation may be considered valid if the subgroup had been prespecified in the study design, treatment results varied similarly across subgroups (eg, success steadily decreasing in each age stratum), and a biologically plausible explanation could be made for the finding.

Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.

Real-World Studies

While RCTs are used to evaluate treatment outcomes, *real-world data (RWD)* are an important complementary source of information. These data, collected outside the controlled environment of conventional RCTs, contribute to our understanding of treatment

effectiveness and safety, disease and treatment patterns, and patient behaviors in everyday clinical practice. RWD form the basis for *real-world evidence (RWE)* and can be extracted from a broad range of sources such as patient registries (eg, the IRIS [Intelligent Research in Sight] Registry), health care databases, claims databases, patient networks, social media, and patient-generated data from mobile or wearable devices. Patients who receive a treatment in the real world can differ in important ways from participants enrolled in the clinical trials for the same treatment. RWD must be interpreted thoughtfully, keeping in mind the various ways in which the data were collected and analyzed. Used together, real-world studies and RCTs contribute to a broader understanding of a treatment or disease.

Fang Y, He W, Wang H, Wu M. Key considerations in the design of real-world studies. *Contemp Clin Trials.* 2020;96:106091.

US Food and Drug Administration. Real-world evidence. Updated May 20, 2022. Accessed May 30, 2022. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Systematic Reviews and Meta-analyses of Clinical Trials

By combining evidence from 2 or more clinical trials, systematic reviews and meta-analyses provide the strongest evidence for assessing interventions for a particular condition. A *systematic review* attempts to gather all available empirical research by using clearly defined, systematic methods to obtain answers to a specific question, while a *meta-analysis* is the statistical process of analyzing and combining results from several similar studies. These 2 approaches may be combined as, for example, in a study by Bowen and colleagues comparing the safety and efficacy of intracameral cefuroxime, moxifloxacin, and vancomycin at the end of cataract surgery. The authors reviewed the results of 17 studies that included more than 900,000 eyes and found an 80% decrease ($P < .001$) in the risk of endophthalmitis with the use of intracameral antibiotics.

Ahn E, Kang H. Introduction to systematic review and meta-analysis. *Korean J Anesthesiol.* 2018;71(2):103–112.

Bowen RC, Zhou AX, Bondalapati S, et al. Comparative analysis of the safety and efficacy of intracameral cefuroxime, moxifloxacin and vancomycin at the end of cataract surgery: a meta-analysis. *Br J Ophthalmol.* 2018;102(9):1268–1276.

Interpreting Diagnostic and Screening Tests

The goal of this section is to help the reader interpret diagnostic and screening tests. The first example presents a relatively straightforward case: it involves a screening test with a binary (yes/no) outcome, a disease that the patient either has or does not have, and a patient about whom nothing is known at the time of screening. The subsequent discussions examine complicating features that often occur in ophthalmic practice and in research. The reader should consider these complicating features when evaluating results of diagnostic and screening tests. A list of formulas for widely used diagnostic statistics is displayed in Table 2-3.

Table 2-3 Diagnostic Statistical Formulas

Screening Test Result	Disease Present	Disease Absent
Positive	(a) True positive	(b) False positive
Negative	(c) False negative	(d) True negative

Diagnostic Statistic	Formula
Sensitivity	a/(a + c), where the denominator (a + c) represents all of the test subjects who have the disease
Specificity	d/(b + d), where the denominator (b + d) represents all of the test subjects who do not have the disease
Positive predictive value (PPV)	a/(a + b), where the denominator (a + b) represents all of the test subjects with positive test results
Negative predictive value (NPV)	d/(d + c), where the denominator (d + c) represents all the test subjects with negative test results
Accuracy	(a + d)/(a + b + c + d)
Prevalence	(a + c)/(a + b + c + d)
Likelihood ratio positive (LR+)	Sensitivity/(1 − specificity)
Likelihood ratio negative (LR–)	(1 − sensitivity)/specificity
Relative risk (RR)	[a/(a + b)]/[c/(c + d)]
Risk difference	[a/(a + b)] + [c/(c + d)]
Relative risk reduction (RRR)	1 − RR
Absolute risk reduction (ARR)	c/(c + d) − a/(a + b)
Number needed to treat (NNT)	1/ARR
Odds ratio (OR)	(a × d)/(c × b)

The Straightforward Case

A fictitious study evaluates the use of a simple, quick strabismus screening test in 100 children in a clinic, comparing it to a longer, more expensive, full examination with a pediatric ophthalmologist as the *gold standard.* The study finds that 30 children have strabismus and 70 do not. However, after undergoing the quick screening test, 60 children have abnormal results, and 40 children have normal results. Table 2-4 shows the screening test result data. The screening test performance is described as follows:

- *Sensitivity.* The test correctly identifies 20 of every 30 children who have strabismus (67%).
- *Specificity.* The test correctly identifies 30 of every 70 children who do not have strabismus (43%).
- *Positive predictive value (PPV).* If a child's test results are abnormal, there is only a 1 in 3 chance (20/60) that the child actually has strabismus (33%).
- *Negative predictive value (NPV).* If a child's test results are normal, there is a 3 in 4 chance (30/40) that the child is actually disease-free (75%).
- *Accuracy.* The screening test is correct in 50 of 100 cases (50%).

Table 2-4 Results of Strabismus Screening Test in Clinic

Screening Test Result	Strabismus	No Strabismus	Totals
Abnormal	Truly abnormal (20)	Falsely abnormal (40)	60
Normal	Falsely normal (10)	Truly normal (30)	40
Totals	30	70	100

Sensitivity is 20/30 (67%); specificity is 30/70 (43%); positive predictive value is 20/60 (33%); negative predictive value is 30/40 (75%); accuracy is 50%.

Table 2-5 Results for Strabismus Screening Test in Shopping Center

Screening Test Result	Strabismus	No Strabismus	Totals
Abnormal	Truly abnormal (2)	Falsely abnormal (58)	60
Normal	Falsely normal (1)	Truly normal (39)	40
Totals	3	97	100

Sensitivity is 2/3 (67%); specificity is 39/97 (40%); positive predictive value is 2/60 (3%); negative predictive value is 39/40 (98%).

Sensitivity is the percentage of test subjects who both have the disease of interest and have abnormal test results, and *specificity* is the percentage of disease-free people who have normal results. However, it is also important to remember that neither sensitivity nor specificity takes into account the prevalence of disease in the study population.

Table 2-5 illustrates the performance of the hypothetical strabismus test if it yields the same results (60 children with abnormal test results and 40 children with normal test results) when performed in a shopping center, where the prevalence of strabismus is only 3% (much lower than in the clinic situation previously discussed). The sensitivity is still 67%, and the specificity is about the same, at 40%. However, because of the high number of falsely abnormal results, 58 children without disease and only 2 children who truly have strabismus would be referred for complete examinations. In this example, the PPV is only 3% (2/60). The NPV is 98% (39/40). Because of the low prevalence of strabismus in this setting, most children whose test results were abnormal would actually be disease-free. This increases the costs of unnecessary follow-up testing and increases anxiety for the parents. Clearly, the prevalence of disease in the population of interest and the screening test's PPV and NPV should be considered before the test is used for screening a population.

Choosing a gold standard is a key aspect of conducting a diagnostic testing study. The reader of such a study should ascertain whether the pediatric ophthalmologist who carried out the gold standard examination was masked to the results of the strabismus screening test; if not, this might have created confirmation bias, with the potential to erroneously impute higher diagnostic precision to the test than is warranted. The gold standard should also have been previously published and accepted by contemporaneous experts. Finally, the gold standard should be repeatable under the same conditions; for example, would the pediatric ophthalmologist come to the same diagnosis (strabismus vs no strabismus) if he or she examined the child a second time? In conclusion, the gold standard should be scrutinized for its applicability to the clinical situation.

Complicating Features

Using ROC curves to compare different screening thresholds with a continuous predictive variable

When the screening test measures a continuous value, such as IOP, it becomes more complicated to evaluate the test. Figure 2-3 uses data from the Baltimore Eye Survey to graphically display sensitivity and specificity for each value of IOP. The usual cutoff for normal IOP, 21 mm Hg, has a sensitivity of 49% and a specificity of 90%. The intersection of sensitivity and specificity is the optimal threshold for maximum sensitivity and specificity in a screening test. This intersection occurs at 18 mm Hg, where the sensitivity is 65% and the specificity is 66%. With continuous variables, like IOP, there is a trade-off between sensitivity and specificity: a higher sensitivity results in a lower specificity, and vice versa.

Figure 2-4 presents another graphical representation of sensitivity and specificity, called a *receiver operating characteristic (ROC) curve*. By convention, an ROC curve plots sensitivity on the y-axis and (1 – specificity) on the x-axis. The larger the area under the curve, the more diagnostically precise is the screening test. The line with the diamond-shaped symbols represents a hypothetical screening test with optimal results; the line with the triangles represents a poor screening test with an ROC area of only 50%; and the line with the circles—the middle curve—represents the Baltimore Eye Survey data used in Figure 2-3. An ROC curve can inform selection of an optimal cutoff point for a screening test by identifying the sensitivity–specificity pair located closest to the upper left of the ROC plot.

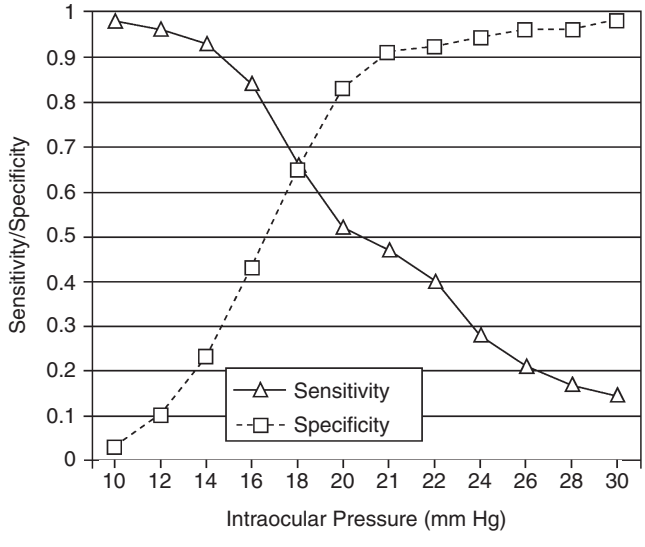

Figure 2-3 Sensitivity and specificity of an intraocular pressure (IOP) cutoff as a screening tool for glaucoma. For each IOP level (along the x-axis), the values for sensitivity and specificity are plotted. This demonstrates that with a higher level of IOP as a screening cutoff for glaucoma (for example, IOP >30 mm Hg), the sensitivity decreases and the specificity increases. *(Used with permission from Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey.* Am J Epidemiol. *1991;134(10):1102–1110.)*

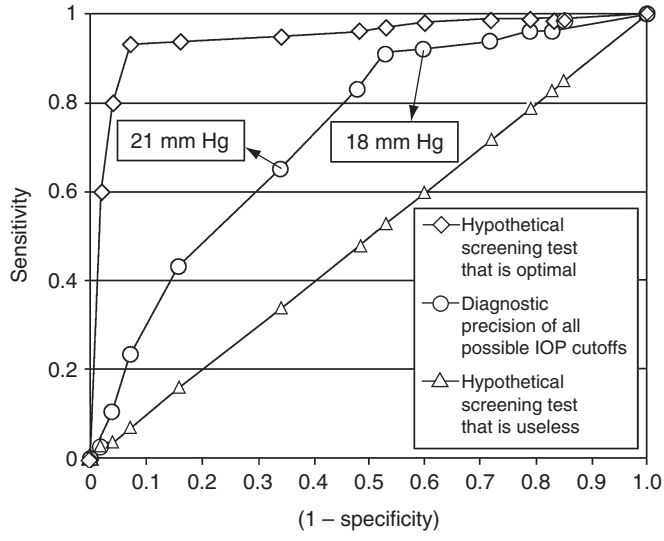

Figure 2-4 Receiver operating characteristic (ROC) curve of IOP as a screening tool for glaucoma with sensitivity on the y-axis and (1 – specificity) on the x-axis. The middle line replots the data from Figure 2-3, showing all combinations of IOP. Two boxes identify the diagnostic precision of IOP ≥18 mm Hg and IOP ≥21 mm Hg. The other lines represent an optimal *(upper line)* and a useless *(lower line)* screening test, respectively. *(Produced with data from Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey.* Am J Epidemiol. *1991;134(10):1102–1110.)*

Overall, these figures demonstrate that IOP measurement is not a very good screening tool for glaucoma because no cutoff reaches the ideal relationship of sensitivity and specificity (upper left of diamond line). Other significant factors in choosing a cutoff point for a screening test are the population to be screened and the relative importance of sensitivity and specificity. If the consequence of missing a diagnosis is very important, such as blindness, an investigator may choose a test with high sensitivity but poor specificity. For example, a low cutoff for erythrocyte sedimentation rate might be chosen for a person who has recent vision loss and who is suspected of having giant cell arteritis.

Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *Am J Epidemiol.* 1991;134(10):1102–1110.

Using ROC curves to compare different screening devices

ROC curves can be used to compare tests that employ different units or different scales; this can be useful in studies comparing new diagnostic methods or devices. Figure 2-5 shows 3 ROC curves illustrating the ability of 3 glaucoma imaging devices to discriminate between healthy eyes and eyes with glaucomatous visual field loss via imaging of the optic nerve head and nerve fiber layer. The area under each ROC curve represents a summary measure of the relative efficacy of the screening test. The figure suggests a higher diagnostic precision for scanning laser polarimetry and OCT than for confocal scanning laser ophthalmoscopy, although there was no statistically significant difference in the area under the ROC curves for these 3 parameters.

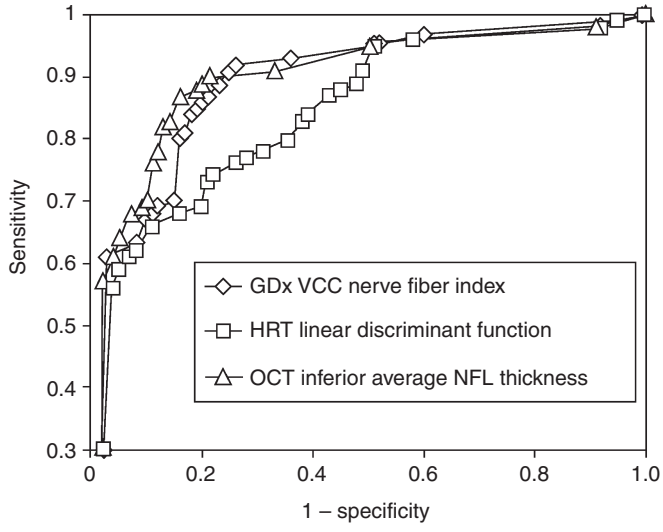

Figure 2-5 ROC curve of 3 glaucoma imaging devices. The single parameter chosen for display for each instrument was the one that performed the best in the authors' study. There was no statistically significant difference in the area under the ROC curves for these 3 parameters. GDx VCC = glaucoma diagnosis scanning laser polarimetry with variable corneal compensation (Zeiss); HRT = Heidelberg Retinal Tomograph (Heidelberg Engineering); OCT = optical coherence tomography. *(The HRT linear discriminant function is from a paper by Bathija et al, referenced by Medeiros et al; the GDx and OCT parameters are standard test outputs provided by the manufacturers. Graph drawn with data from Medeiros FA, Zangwill LM, Bowd C, Weinreb RN. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and Stratus OCT optical coherence tomograph for the detection of glaucoma.* Arch Ophthalmol. *2004;122(6):827–837.)*

Medeiros FA, Zangwill LM, Bowd C, Weinreb RN. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and Stratus OCT optical coherence tomograph for the detection of glaucoma. *Arch Ophthalmol.* 2004;122(6):827–837.

The effect of pretest probability of disease

Pretest probability of disease uses knowledge about a patient before any screening or diagnostic tests are performed. For example, the investigator may know that the patient has a first-degree relative with glaucoma as well as a thinner-than-average central corneal thickness, both of which are risk factors for glaucoma. This information suggests a pretest probability of glaucoma about 3 times higher than that of a person picked at random from the general population. How much would a diagnostic test improve the clinician's ability to diagnose glaucoma in this patient? How much higher is the relative risk of glaucoma if the test result is positive?

Bayes theorem allows the pretest probability of disease to be combined with the diagnostic precision of a screening test to produce a posttest probability of disease. To use this theorem, the *likelihood ratio* must be calculated. The formulas for positive likelihood ratio and negative likelihood ratio are outlined in Table 2-3. For the same sample test, the negative likelihood ratio is (1 − 0.8)/0.9, or 0.22. Positive likelihood ratios start at 1 and continue to infinity—the bigger, the better. Negative likelihood ratios range from 0 to 1—the smaller, the better. If the goal is to diagnose disease, the test with the larger positive

likelihood ratio is the better test; conversely, if the goal is to rule out disease, the test with the smaller negative likelihood ratio is better.

If the positive likelihood ratio is multiplied by the pretest probability of disease, the result is the *posttest probability of disease.* Thus, for the example patient with the positive family history, thin cornea, and pretest probability of 3, a positive test with a positive likelihood ratio of 8 will result in a posttest probability of glaucoma that is 24 times that of a person drawn at random from the population.

Table 2-6 demonstrates another important consideration regarding pretest probability of disease. Consider the case of a 65-year-old woman with no risk factors for glaucoma and a pretest probability of disease of 1.0%. A positive test result for glaucoma would raise her probability of disease to 7.5%. Most patients with a positive test result will not actually develop the disease. Similarly, an 85-year-old man with a strong positive family history, a thin central cornea, and an IOP of 30 mm Hg might have a pretest probability of disease of 50.0%. Even if his test result were negative, he would still have a posttest probability of disease of 18.2%, greater than that of the 65-year-old woman. This example illustrates the importance of considering the pretest probability of disease in deciding whether to employ a diagnostic test. In general, screening tests do not perform well when the prevalence of disease is low.

Intermediate diagnostic categories, such as "glaucoma suspect," are often encountered in clinical practice. Sensitivity–specificity and ROC curves cannot account for such categories because they require borderline subjects to be categorized as either having the disease (eg, glaucoma) or not having it (eg, no glaucoma). However, a likelihood ratio can be calculated for a borderline category, which reflects the risk of patients exhibiting that characteristic (eg, glaucoma suspect).

Clinical acceptance and ethics of testing

Clinicians should avoid tests that provide a small increment in the likelihood ratio of detecting disease or that are expensive or painful. Also, all tests carry some burden, including the potential for adverse effects (eg, corneal abrasion from gonioscopy), psychological fear of a disease (eg, related to a screening test for glaucoma), and additional testing and follow-up examinations for abnormal or unusual results. Further, clinicians should avoid a test if it will not change patient management. Similarly, screening for eye disease should include a process for follow-up of those who have abnormal results, regardless of their insurance status. Screening provides little value to participants who are told they might have a disease but have no way of obtaining a follow-up evaluation or treatment.

Table 2-6 Changes in PPV and NPV Depending on Pretest Probability in a Test With 80% Sensitivity, 90% Specificity

Pretest Probability of Disease, %	PPV, %	NPV, %
1	7.5	99.8
10	47.1	97.6
50	88.9	81.8
90	98.6	33.3

NPV = negative predictive value; PPV = positive predictive value.

Generalizability

Most studies investigate new screening or diagnostic tests in a clinical setting before evaluating them in a population-based sample, largely because of the high cost of performing population-based research. Clinicians should consider whether the data for a new test will apply to their screening population. Even a clinic-based study might not have patients like those in another practice. For example, a study may include only young glaucoma patients without other eye diseases such as macular degeneration. This leads to excellent sensitivity and specificity, but the results may differ in a sample of older patients who have borderline glaucoma.

Summary

Researchers use a variety of measures to evaluate the diagnostic precision of screening and diagnostic tests. Sensitivity and specificity are the simplest and easiest to understand, but they have the disadvantage of not accounting for the prevalence of disease in the target population. Positive predictive value and negative predictive value are more useful in that regard. ROC curves provide a comprehensive view of the relationship between the sensitivity and specificity of a continuous test result (eg, IOP) and can be used to compare diagnostic tests. Clinicians can use likelihood ratios and pretest probability of disease to critically evaluate screening and diagnostic tests in their clinical setting.

Riegelman RK, Nelson BA. *Studying a Study and Testing a Test: Reading Evidence-Based Health Research.* 7th ed. Lippincott Williams & Wilkins; 2020.

Discussing Benefits, Risks, Probabilities, and Expected Outcomes With Patients

Physicians and their clinical team members need to educate patients regarding their disease, including potential preventive measures, treatments, and outcomes.

Risk Differences and Probability

Clinical research defines *risk* as the conditional probability of an event, usually an adverse event. *Risk difference* is the absolute difference in the risk between 2 groups of individuals. *Relative risk* is the ratio of 2 risk measures. The risk difference depends on the unit of measure, whereas relative risk is dimensionless because it involves division of 2 risk measurements. The formulas for determining risk difference and relative risk are listed in Table 2-3. In the Ocular Hypertension Treatment Study (OHTS), the risk difference of glaucoma development among subjects who were not treated compared with those who were treated was 5 percentage points (9.5% vs 4.5%, respectively) across 5 years. The relative risk of not being treated compared with receiving treatment was 2.1 (9.5/4.5). Both measures are consistent with the data, but clinicians or patients may interpret them very differently. Numerically, a 5-percentage-point increased risk of glaucoma may seem small to a patient, while just over double the increased risk may seem large.

A key piece of information that can help in the interpretation of such results is the *baseline probability of the outcome.* For example, the baseline probability of developing glaucoma with

untreated ocular hypertension is 9.5%. In most cases, baseline probabilities or expected outcomes can help patients understand risk and make an informed decision about a procedure.

Number Needed to Treat

The *number needed to treat (NNT)* can also be helpful when describing how likely it is that a treatment or medication will improve an outcome for an individual patient. In the above example, the study shows a 5-percentage-point risk difference, or *absolute risk reduction (ARR),* in the proportion of patients without glaucoma if they use ocular hypotensive medications. If the ARR is 5 percentage points, the NTT is 20 (1/5%). In other words, a clinician could tell the patient that in order to prevent 1 patient from developing glaucoma over 5 years, 20 patients would need to be treated with ocular hypotensive medications. Armed with this information, the patient can decide whether to use an ocular hypotensive medication.

For those providers with capitated payments, it may be useful to consider the impact of the new procedure or treatment on societal cost. This can be determined by calculating the added cost using the NNT. For example, if the retail cost of a generic glaucoma medication for 1 patient is $70 per month, or $4200 over 5 years, the excess cost of using ocular hypotensive medications calculated with the NNT would be $84,000 ($4200 × 20) for 1 patient to see the benefits from using these ocular hypotensive medications.

The advantage of the NNT is that it is based only on ARR and is less likely to exaggerate the impact of a new procedure or medication. The NNT provides a straightforward attempt to describe the likelihood that a patient will be helped. However, it does not take other important factors into consideration, such as the negative effects on quality of life related to eyedrop use or other possible factors such as systemic adverse effects resulting from the use of ocular medications.

Odds Ratios

In observational studies, investigators may also present their results as *odds ratios.* In an odds ratio, the odds of a participant with the disease (case) having an exposure (eg, smoking) are compared with the odds of a participant without the disease (control) having the exposure. When the disease is rare, the odds ratio approximates the relative risk of the exposure because the denominators for both of the odds under comparison are close to 1. For example, in the meta-analyses on potential risk factors for late AMD, which occurs relatively infrequently, the odds ratio for smoking is 2.35, meaning that smokers have a 235% risk for development of late AMD compared with nonsmokers. As previously stated, the baseline risk is key; if it is low (ie, less than 1%), then an odds ratio of 2.0 still results in a low risk for an individual patient.

Exposure to specific factors may or may not be clinically significant, and it may not be *causal,* or one of the root causes of the disease. Because it is difficult to distinguish causal risk factors from noncausal risk factors in observational studies, researchers often use causal criteria to identify which risk factors are causal and which are not.

Risk Calculators

Medical providers use *risk calculators* in a number of ways, for example, to predict an individual patient's risk of cardiovascular disease, risk of having a child with Down syndrome,

likelihood of survival from an intensive care unit, and likelihood of experiencing other medical conditions. Ophthalmologists have used risk calculators to help simplify complex study results and apply these results to individual patients. For example, the OHTS regression equation used 5 variables (cup–disc ratio, central corneal thickness, untreated IOP, pattern standard deviation from the visual field, and age) to predict the risk that a patient will develop glaucoma as a result of ocular hypertension. The OHTS risk calculator is available for free online (https://ohts.wustl.edu/risk/). Other available risk calculators include those for macular degeneration, keratoconus, and glaucoma progression; and many of them can be downloaded to a mobile device.

Overall, the advantage of risk calculators is that they simplify complex results to provide an estimate of the mean baseline probability of disease development or surgery complications in individual patients. Risk calculators can also identify those patients at high risk of developing disease and select them for a lower NNT and lower societal costs.

De Moraes CG, Sehi M, Greenfield DS, Chung YS, Ritch R, Liebmann JM. A validated risk calculator to assess risk and rate of visual field progression in treated glaucoma patients. *Invest Ophthalmol Vis Sci.* 2012;53(6):2702–2707.

How to Measure and Improve Clinical Practice

Improving clinical performance is a compelling concern for individual ophthalmologists, practice groups, and larger organizations, as well as for the patients they serve. This necessitates determining the processes, procedures, and performance to be assessed; choosing the appropriate quality criteria and measures; and establishing monitoring systems for the factors of interest.

Using Big Data to Improve Clinical Practice

Large studies using claims data have demonstrated considerable regional differences in practice and in the quality of eye care in the United States and worldwide. For example, Stein and colleagues showed a large difference between ophthalmologists and optometrists in Oklahoma in the rate of additional laser trabeculoplasties after the initial procedure. Did the higher rates of re-treatment by optometrists reflect the standard of care, or did they represent overusage, particularly when compared to other treatments?

Big data can also be used to evaluate how individual ophthalmologists compare to their peers for an outcome of interest, such as the proportion of patients who need to return to the operating room after cataract surgery. If an ophthalmologist has a higher complication rate than that of his or her peers, this information may prompt that ophthalmologist to begin a quality improvement project to reduce complications via education and further training. Big data offer clinicians many opportunities to measure and improve eye care, particularly when accompanied by an organizing framework to understand the data and develop improvement activities. (See also BCSC Section 2, *Fundamentals and Principles of Ophthalmology*.)

Medicare Provider Utilization and Payment Data: Physician and Other Practitioners. Centers for Medicare & Medicaid Services. Accessed September 1, 2022.

https://data.cms.gov/provider-summary-by-type-of-service/medicare-physician-other-practitioners

Stein JD, Zhao PY, Andrews C, Skuta GL. Comparison of outcomes of laser trabeculoplasty performed by optometrists vs ophthalmologists in Oklahoma. *JAMA Ophthalmol.* 2016;134(10):1095–1101.

IRIS Registry

Clinical data registries can serve as a source of big data. In 2014, the American Academy of Ophthalmology (AAO) launched the IRIS (Intelligent Research in Sight) Registry, a centralized system for collecting electronic eye care data from ophthalmology practices. This registry automatically abstracts data from electronic health record systems. In contrast to large claims-based registries, which collect data about electronic billing, the IRIS Registry contains specific information related to eye disease and treatment (eg, visual acuity, IOP) and is agnostic to insurance status. This allows ophthalmologists to examine results of treatment of eye disease and develop improvement activities. The AAO's other goals for the registry include the development of benchmark reports for quality of care to help ophthalmologists identify opportunities for improvement.

Researchers can use the registry to create large data sets to examine the management and outcomes of many specific ocular diseases such as AMD, cataract, and glaucoma; and numerous published studies have been based on analyses of IRIS data. It is particularly useful in collecting data for research on rare diseases such as retinitis pigmentosa. The IRIS Registry can serve as an important tool in helping ophthalmologists to continually monitor and improve their performance quality.

Issues in Designing a Measurement System

A useful measurement system may include quality indicators. For example, a question that ophthalmologists commonly face is whether they have dilated a diabetic patient's eyes at least once every 2 years. How can the clinician validate that a dilated eye examination was performed? Validation methods include the following:

- video recording of the examination
- written documentation that dilating drops were placed in the eye
- notations in the medical record indicating that a peripheral dilated eye examination was performed, such as noting whether the results were normal or abnormal
- a diagram or drawing of the retinal periphery

Tests of reliability

Once a valid measure has been chosen, its *reliability* needs to be determined. First, the analysis should yield consistent results if performed by the same clinician at different time points. For example, are the same results obtained when a measure is made with the same instrument the second and third times? *Test–retest reliability* is typically used to measure biological variability, instrumentation error by the participant, and error by the rater. Test–retest reliability does not take account of the rater(s) but examines overall agreement/consistency between measurements made by the same set of raters. Measures that minimize errors when repeated have good test–retest reliability, or *reproducibility.* Second,

the analysis should yield the same results if performed on the same subject multiple times. To determine the consistency in ratings for each rater, the appropriate statistical measure would be *intrarater reliability.* If the person doing the measurement gets the same results on the same subject after multiple attempts, there is good intrarater reliability. Third, the analysis should yield the same results if performed by different clinicians. *Interrater reliability* is used to assess the degree to which different raters give consistent measurements for the same phenomenon of interest. Organizations should design measures (as well as a training system for the staff and a support system that will capture and analyze the data) that enable different examiners to use the same measure and obtain similar results. Measures that have this characteristic are said to have good interrater reliability.

In research, 2 statistical techniques are commonly used to determine the degree of agreement between 2 different tests that detect a particular disease in a group of patients. One method is to simply tally the number of times that the results of the 2 tests agree (ie, both tests indicate disease present or both tests indicate no disease) and then divide that number by the total number of items being assessed, thereby yielding the *percent agreement.* Another method, the κ (kappa) statistic, measures the agreement between 2 or more individuals or entities while taking into account the potential for agreement by chance alone. Kappas greater than 0.75 represent excellent agreement; those from 0.40 to 0.75, fair to good agreement; and those below 0.40, poor agreement. However, not all experts agree on these kappa cutoff points, and other cutoffs for agreement may be recommended.

Once a valid and reliable measure has been established, the organization should first consider the population of interest and the inclusion and exclusion criteria. For example, a study of the quality of cataract surgery might exclude retina specialists (exclusion criterion) and include only comprehensive ophthalmologists who spend at least 50% of their time seeing patients (inclusion criterion).

Frequency of event

Second, the organization needs to determine whether the studied event occurs at a frequency that will allow meaningful differences to be found. Are the events so rare *(floor effect)* or so common *(ceiling effect)* that little value is to be gained in using such a measurement system? Organizations should consider conducting a pilot study to investigate these issues before implementing a system.

Practical considerations

Third, whenever possible, organizations should use measures that are easily obtained yet are valid and reliable. Systems that do not require much additional work are more practical for the purpose of monitoring practices. For example, billing files may provide sufficient information to determine the completion of specific process quality steps, such as regular visual field testing in patients with glaucoma, and outcomes, such as incidence of suprachoroidal hemorrhage after intraocular surgery.

Implementation of a Monitoring System

Outcome quality and process quality

An ideal monitoring system would capture data on every patient of interest for a given practitioner. Doing so would collect the maximum number of cases for statistical analyses

and provide maximum statistical power for reliable estimates of uncommon or rare events. In addition, a 100% analysis would minimize bias due to missing patients. For example, electronic billing data could identify every patient who had intraocular surgery (identified by specific Current Procedural Terminology [CPT] codes) in a practice during a specified period and any subsequent operations (again, identified by CPT codes) within the next 30 or 90 days to determine a specific complication (identified by its International Classification of Diseases code), such as retinal detachment or endophthalmitis. This would reflect *outcome quality*.

In contrast, questions about *process quality*—such as whether a target pressure range was set for every patient with glaucoma—are not amenable to a 100% analysis because those data may not be entered in current administrative databases; instead, they may need to be extracted from medical records by a trained reviewer. Information obtained from billing databases may allow assessment of other process quality measures, such as gonioscopy.

Record reviews

An organization's next step is to review its records. What standards should be used for such a review? What criteria should be used? *Explicit* criteria, which have a yes/no outcome or limited categories (eg, optic nerve documentation that includes a statement regarding the nerve's condition, the vertical cup–disc ratio, or a drawing or photograph), have higher reliability than *implicit* criteria (the reviewer's judgment that overall quality was good or not good), particularly for interrater reliability. The AAO provides Preferred Practice Pattern guidelines and a summary benchmarks series, both of which can be used to obtain explicit criteria (www.aao.org/ppp). Similarly, the American Board of Ophthalmology includes explicit criteria in its Improvement in Medical Practice for maintenance of board certification (https://abop.org/maintain-certification/improvement-in-medical-practice/).

Record reviews may reveal that some medical records are unavailable or are missing data or information on visits. Every effort should be made to obtain unavailable records. If these records remain unavailable, the number of unavailable records should be recorded and replacement records from the randomization reviewed. A high proportion of missing medical records may suggest bias. For records with missing visits, it may be possible to capture important data from other available visits. If the review criteria require that every visit is checked, the options are to (1) exclude that patient, (2) exclude that patient only for analyses needing that missing-visit data, (3) impute the missing values through statistical modeling of available data, or (4) treat the missing visit as either meeting or not meeting the criteria (generally the latter). The key steps are to decide what to do, apply that decision consistently over time, and report the decision along with the data and results.

Power calculations

An important element of establishing a system for monitoring quality of care is performing power calculations to determine sample sizes. These calculations provide confidence that a nonsignificant difference is truly nonsignificant, rather than being the result of an insufficient sample size. See the section "Was the sample large enough to detect a difference?" earlier in this chapter.

Validity of measures

One final consideration is the external validity of the method used to determine whether a quality measure was met. Using chart review, McGlynn and colleagues determined that the rate of annual dilated eye examination among patients with diabetes mellitus was only 19%. But when they used billing codes, they found that the rate was 50%. Was the discrepancy due to poor documentation of the procedure or to inaccurate billing practices? The data might have been recorded incorrectly, by either the observer or the person abstracting the data from the data source. Other errors could be related to coding issues, data entry problems, and incorrect diagnoses. In summary, each discrepancy needs to be examined further, and the whole monitoring system may need to be redesigned. Conducting a pilot study with a handful of participants can aid in study design, increase validity, and save time when developing a monitoring system.

McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med.* 2003;348(26):2635–2645.

Analysis of the Results

Once the results have been compiled, organizations must interpret the data correctly. For projects designed to detect substantive deviations from expected performance, it is important to use tests that determine statistical significance. For many measures, comparisons of mean performance are satisfactory, for example, the percentage of AAO benchmark process indicators for cataract that providers have attained. However, for others, the best way to compare performance may be to analyze the number of patients whose care meets a given threshold. For example, investigators may want to know the percentage of patients whose care has achieved at least a 90% quality score. Once that measure is obtained, researchers can make comparisons among providers.

In addition, when evaluating quality results, investigators should consider clinical significance and difference as well as factors beyond the provider's control. Quality of care for chronic diseases like glaucoma may be affected by patients' ability to return regularly for care and adhere to their recommended treatments, as well as their socioeconomic status. Thus, measuring whether the provider performs specific examination steps, such as examining the optic nerve *(process)* is appropriate, whereas looking at rates of blindness over 20 years *(outcomes)* may not be appropriate.

Organizations can use statistical analyses to evaluate potential differences in quality between providers. They can control for patients' socioeconomic status and demographic characteristics, as well as for other factors that may be related to the outcome of interest. These analyses may show that a factor that cannot be "treated" by the provider (eg, socioeconomic status) is the issue and is outside the provider's control. Even with these caveats, quality improvement is critical to medicine. The purpose is not to be punitive but to encourage improvement for the individual provider—and for all providers—from year to year.

Methods of Presenting Data to Facilitate Continuous Improvement

Use of graphical displays

After the results have been analyzed, the next step is to graphically display and disseminate them. There are many ways to present data. First, the data can be displayed using a frequency

distribution such as a histogram (Fig 2-6) or presented in a scatter diagram (Fig 2-7). Are the data normally distributed (ie, distributed in a bell-shaped curve), or are they skewed? The answer to this question affects the selection of statistical tools and analyses, and it can provide important insights into potential underlying factors. Alternatively, 2 distinct subgroups may be found in the data and should be defined. For example, care in solo practices may differ from care in large single-specialty groups for a particular disease area.

Second, a Pareto chart (Fig 2-8) can provide insights into the cumulative distribution of key factors of interest. The chart combines a histogram with a cumulative frequency line, making it possible to assess performance across the range of values for the variable of interest.

Third, run charts or control charts (Fig 2-9) can help organizations understand changes that have occurred over time. Rates of events, especially uncommon ones, can fluctuate. Are the fluctuations significant, both statistically and clinically, compared with those during prior periods or from other institutions or practices? In run charts and control charts, event rates are plotted over time with both upper and lower control limits and averages. This presentation enables reviewers to determine (1) whether an aberrant data point is really a meaningful finding or is due to random error and (2) how the organization is performing compared with peer organizations, if data from peers are available.

Identification of variations

The purpose of these data analyses is to identify variation in the factor of interest. Factors that are due to the way the system is established and that are inherent in its current state of operations are called *common cause factors.* To improve performance in this area, the organization must redesign and reengineer the system. For example, there may be a known rate of

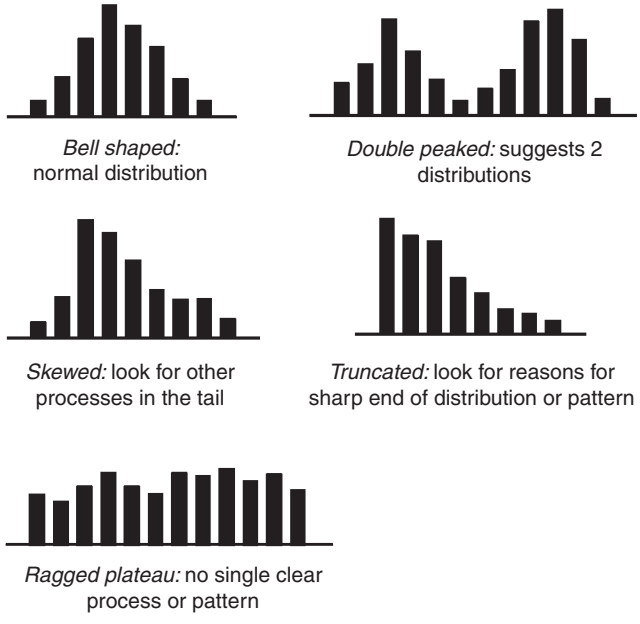

Figure 2-6 Types of histograms with different data distributions. *(Reproduced from the Quality Assurance Project.)*

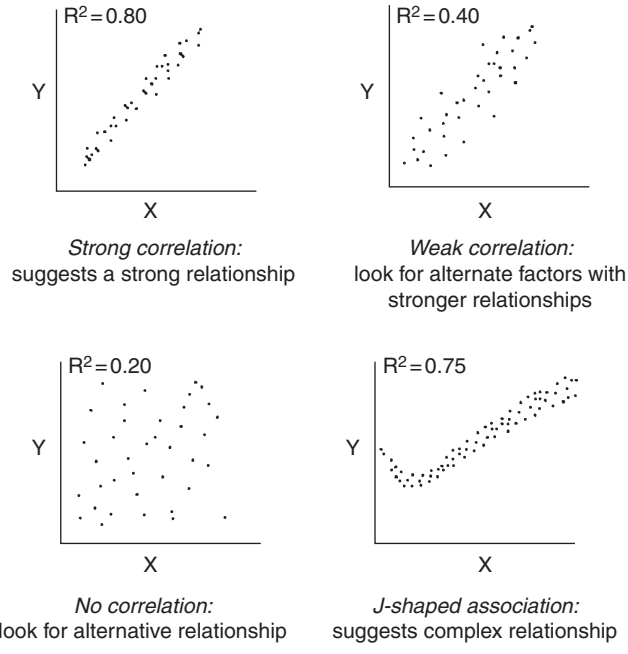

Figure 2-7 Scatter diagram interpretation. R^2 represents the coefficient of determination, which is a measure that indicates how much variation of a dependent variable is explained by the independent variable. An R^2 value of 0.80 means that 80% of the variation can be explained by the relationship between x and y. An R^2 of more than 0.50 is respectable, and results close to 0 mean that the variables are unrelated. *(Modified from the Quality Assurance Project.)*

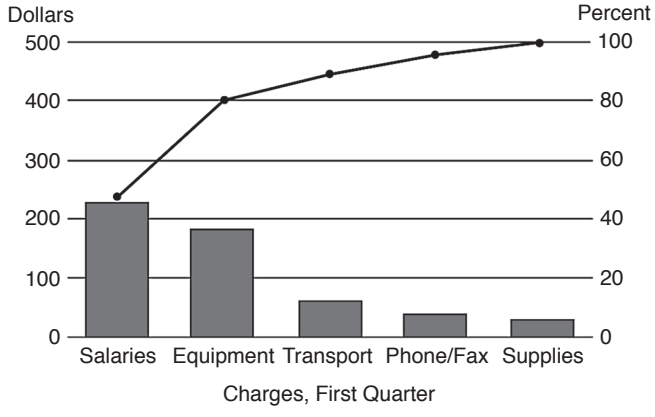

Figure 2-8 Pareto chart. This type of graphical representation combines a histogram and a frequency line. *(Modified from the Quality Assurance Project.)*

"unreliable" visual fields in glaucoma, despite the best training of technicians and screening of patients. In contrast, there are *special causes* of variation that are caused by a specific, identifiable factor, often a specific provider or person. Rapid identification of special cause variance allows for quick correction of variation that exceeds normal rates. However, improving the performance of the overall system and reducing the common cause variation will have a

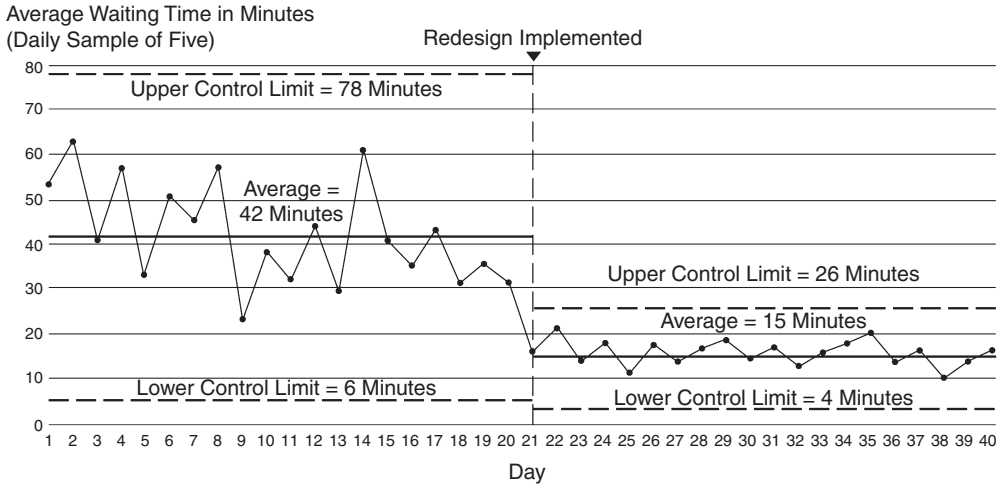

Figure 2-9 Control chart of average wait time before and after a redesign. *(Reproduced from the Quality Assurance Project.)*

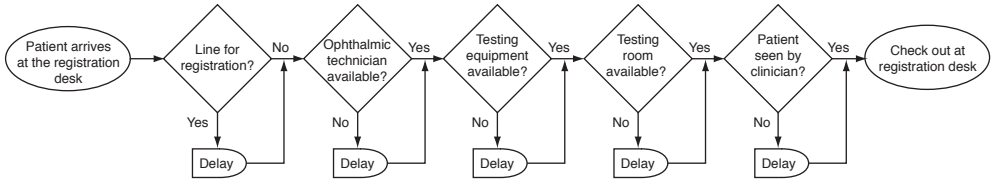

Figure 2-10 Flowchart of the patient registration process. *(Modified from the Quality Assurance Project.)*

greater effect than just identifying the outlier providers and assisting in their rehabilitation. By "shifting the curve," the organization can improve care for every patient.

Other Features of Continuous Quality Improvement

Studies suggest that, in itself, the act of measuring and reporting results improves performance indicators by up to 6%. However, organizations that continuously incorporate quality improvement activities demonstrate significantly greater performance gains than those that do not.

Use of continuous quality improvement tools requires concerted thought about how to improve care structures and processes. An essential step, before or after initial analysis, is developing a checklist of the steps and parties involved and then creating a flowchart (Fig 2-10) of the care system. By examining the overall process for a specific outcome (eg, making sure a patient with diabetes gets an annual eye examination), the organization can identify opportunities for improving the process.

Evidence-Based Medicine

Evidence-based medicine (EBM) is the conscientious, explicit, judicious, and reasonable use of contemporary best evidence in making decisions about the care of individual patients.

EBM integrates clinical experience and patient values with the best available research information. Application of EBM requires the physician to have—or to acquire—the ability to search medical literature and basic skills in the interpretation of epidemiologic and statistical results.

Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. *BMJ.* 1996;312(7023):71–72.

Summary

Efforts to improve the quality of care—and to ensure that fair and meaningful quality measures are part of this endeavor—bring key statistical concepts to the forefront. Because of the Medicare Access and CHIP Reauthorization Act (MACRA), reimbursements to ophthalmologists are increasingly linked with quality and improvement (eg, Merit-based Incentive Payment System [MIPS]) and eligible alternative payment models (APMs). Indeed, insurance companies are already selecting providers who have documented higher quality and lower cost for participation in insurance company provider panels. Thus, clinical research and statistics are useful not only for understanding the scientific literature and improving patient care but also for influencing the practices and livelihoods of providers, including ophthalmologists.

CHAPTER 3

Endocrine Disorders

Highlights

- Teprotumumab, approved by the US Food and Drug Administration in 2020, has been shown to slow the progression of ophthalmopathy in patients with moderate to severe thyroid eye disease.
- Diabetes mellitus is a group of metabolic diseases that increase the risk of microvascular and macrovascular complications.
- Metabolic syndrome is a serious health condition that affects approximately 34.7% of adults in the United States, putting them at higher risk of cardiovascular disease, diabetes, stroke, and diseases related to buildup of fatty plaque in artery walls.
- The classification system for multiple endocrine neoplasia syndromes has been updated.

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In 2018, 34.2 million Americans (10.5% of the population) were estimated to have DM; 26.8% of Americans older than 65 years have this diagnosis. Although nearly 1.5 million Americans are diagnosed with diabetes every year, a substantial percentage of affected individuals remain undiagnosed. Type 2 DM represents approximately 90% of all cases of DM, with type 1 DM and other causes representing the remaining 10%.

Persons with DM are at risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, and are at increased risk for macrovascular disease. Among adult patients, type 2 DM is often accompanied by hypertension (in approximately 75%) and hyperlipidemia (in more than 50%). It is considered a cardiac risk equivalent because of the high excess risk it poses for macrovascular disease, cardiovascular disease events, and mortality.

Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020.* Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020. Accessed June 1, 2022. www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Classification of Diabetes

Diabetes is classified into 4 clinical types.

Type 1 DM (<10% of all cases) results from a cell-mediated autoimmune destruction of β cells in the pancreas. It can present at any age; and because of its variable clinical phenotypes, the diagnosis can be challenging in adults. The rate of destruction of β cells is rapid in infants and children and slower in adults. Therefore, ketoacidosis as an initial presentation is more common in young patients than in older patients.

Latent autoimmune diabetes in adults (LADA), a subtype of type 1 DM, is characterized by mild to moderate hyperglycemia and, initially, often does not require insulin therapy. Adults with LADA have 1 or more β-cell–specific autoantibodies and tend to require insulin therapy sooner than patients with classic type 2 DM. Type 1 DM should be suspected when there is a positive family history, thyroid disease, or other autoimmune disease.

Type 2 DM (approximately 90% of cases) is characterized by insulin resistance followed by defective insulin secretion and loss of β-cell mass. The reason for this β-cell loss is unknown, but programmed cell death in response to genetic and environmental factors has been demonstrated in animal models. Type 2 disease is usually diagnosed in adults, with both incidence and prevalence increasing with age. However, it is becoming more common in children; up to one-third of new cases of DM are diagnosed in patients between the ages of 5 and 15 years.

This type of DM is associated with obesity, a positive family history, history of gestational diabetes or prediabetes, physical inactivity, and race and ethnicity. African American, Hispanic, and American Indian individuals have a greater risk of developing type 2 DM than White individuals. Type 2 DM may be asymptomatic and remain undiagnosed for months to years.

Gestational DM is glucose intolerance that has its onset or diagnosis during pregnancy (occurs in 5%–20% of pregnancies).

Other types of DM include those caused by genetic defects in insulin secretion or action, pancreatic surgery, disease of the exocrine pancreas (eg, cystic fibrosis), endocrinopathies (eg, Cushing syndrome), or drugs (eg, glucocorticoids, thiazide-type diuretics, and atypical antipsychotic medications).

Diagnosis of Diabetes

Diabetes is diagnosed by means of tests that evaluate glucose tolerance.

Prediabetes is diagnosed in a patient with

- hemoglobin A_{1c} (HbA_{1c}) of 5.7%–6.4% (39–47 mmol/mol)
- fasting plasma glucose (FPG) of 100–125 mg/dL (5.6–6.9 mmol/L)
- 2-hour plasma glucose following glucose tolerance testing of 140–199 mg/dL (7.8–11.0 mmol/L)

Persons with prediabetes have an increased risk of developing DM. Progression from impaired fasting glucose or impaired glucose tolerance to type 2 DM occurs at a rate of approximately 12% per year.

A definitive diagnosis of DM is made when 1 or more of the following criteria is present and confirmed with a second test:

- $HbA_{1c} \geq 6.5\%$ (48 mmol/mol)
- FPG ≥126 mg/dL (7.0 mmol/L)

- 2-hour plasma glucose after glucose tolerance testing ≥200 mg/dL (11.1 mmol/L)
- random plasma glucose ≥200 mg/dL (11.1 mmol/L)

Metabolic syndrome

Metabolic syndrome is a serious health condition that affects approximately 34.7% of adults in the United States, putting them at higher risk of cardiovascular disease, DM, stroke, and diseases related to the buildup of fatty plaques in artery walls. The underlying causes of metabolic syndrome include overweight and obesity, physical inactivity, genetic factors, and aging.

Metabolic syndrome is characterized by the presence of 3 or more of the following:

- FPG ≥100 mg/dL
- abdominal obesity (waist circumference >102 cm in men and >89 cm in women)
- triglyceride level ≥150 mg/dL
- HDL cholesterol <40 mg/dL in men or <50 mg/dL in women
- systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg

Individuals can decrease their risk of metabolic syndrome significantly by reducing their weight; increasing physical activity; eating a heart-healthy diet that is rich in whole grains, fruits, vegetables, and fish; and working with a health care provider or dietitian to monitor and manage blood glucose, blood cholesterol, and blood pressure.

Reduction of Risk for Diabetes

Several clinical trials have recently shown that the risk of progression from impaired glucose tolerance to type 2 DM can be markedly reduced (by approximately 50% over several years) through lifestyle modifications such as a combination of diet and exercise therapy. The amount of weight loss and exercise required to achieve this result is surprisingly modest. For instance, in the Diabetes Prevention Program, patients who were asked to perform 150 minutes of brisk walking per week (a little over 20 minutes per day) lost only about 12 pounds of weight on average but reduced their risk of DM development by 50% over 6 months. Other studies have suggested that early pharmacologic intervention with oral hypoglycemic agents also decreases the risk of progression to DM. There are, as yet, no known ways to prevent type 1 DM, but trials of interventions to regulate immune response are under way.

The importance of glycemic control

For patients with either type 1 or type 2 DM, glycemic control is of the utmost importance. The Diabetes Control and Complications Trial showed that intensive therapy aimed at maintaining near-normal glucose levels had a large and beneficial effect on delaying the development and progression of long-term complications for patients with type 1 DM. For example, intensive therapy decreased the risk of the development and progression of retinopathy, nephropathy, and neuropathy by 40%–76%. The beneficial effects increased over time, but they were accompanied by a threefold increased risk of hypoglycemia. Thus, intensive therapy is recommended for most patients with type 1 DM, but these patients should be instructed to self-monitor their blood glucose levels carefully to prevent hypoglycemic episodes. See also BCSC Section 12, *Retina and Vitreous*.

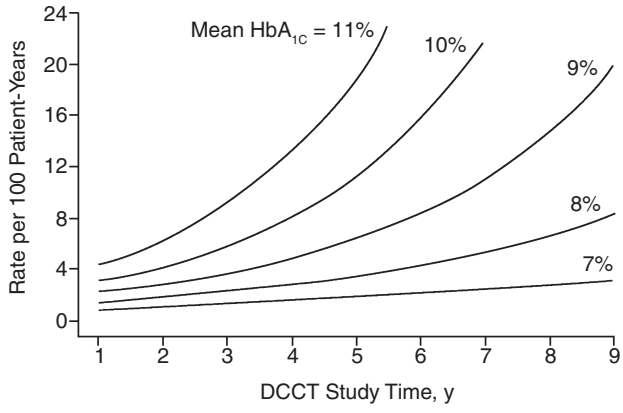

Figure 3-1 Rate of retinopathy progression relative to mean hemoglobin A_{1c} (HbA_{1c}). DCCT = Diabetes Control and Complications Trial. *(Redrawn from the DCCT Research Group. The relationship of glycemic exposure [HbA_{1c}] to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial.* Diabetes. *1995;44(8):968–983.)*

Tight glycemic control has a profound effect on the development of complications. The risk of retinopathy progression rises almost exponentially as the HbA_{1c} level increases (Fig 3-1). However, patients who decrease their HbA_{1c} by 1 percentage point (eg, from 8.0% to 7.0%) reduce their risk of retinopathy by approximately 30%, and this benefit also holds for other complications of DM, such as nephropathy and neuropathy. When working with patients with DM, health care providers should emphasize the importance of tight control and encourage patients to achieve it.

For patients with type 1 DM, intensive therapy also provides protection against macrovascular complications such as cardiovascular disease. For patients with type 2 DM, however, the role of glycemic control in reducing cardiovascular risk has not been established. In this group, macrovascular disease may be affected more by other risk factors, such as smoking, obesity, and lipid abnormalities.

Treatment

The goals of therapy are to alleviate symptoms; to achieve glycemic, blood pressure, and lipid targets; and to prevent acute and chronic complications of DM. The recommended targets for control of type 1 and type 2 DM are similar:

- fasting and preprandial capillary blood glucose 80–130 mg/dL
- postprandial capillary blood glucose <180 mg/dL
- HbA_{1c} <6.5%

This degree of glycemic control has been associated with the lowest risk of microvascular complications in both type 1 and type 2 DM.

Type 1 diabetes

Treatment of type 1 DM requires lifelong insulin replacement and careful coordination of insulin doses with food intake and activity. Insulin can be administered by subcutaneous

injection, continuous subcutaneous infusion, or inhalation. A regimen of multiple daily insulin injections that includes basal, premeal, and correction doses is preferred to obtain optimal control in patients. Capillary glucose monitoring 4 times daily, 10–30 minutes before meals and at bedtime, is required for such a regimen.

Continuous subcutaneous insulin infusion by means of an insulin pump is widely used in patients with type 1 and, increasingly, with type 2 DM. However, it does not automatically improve glycemic control without patient self-management. A typical regimen provides 50% of total daily insulin as basal insulin and the remainder as multiple preprandial boluses of insulin using a programmable insulin pump. Patients must check their blood glucose regularly because diabetic ketoacidosis can occur rapidly if the insulin infusion is disrupted.

Pancreas transplantation For patients with type 1 DM, pancreas transplantation can be performed alone or in conjunction with kidney transplantation. With modern techniques and immunosuppression, the transplant survival rate is high, and most patients become euglycemic without the need for insulin. Although quality of life is usually improved, the patient faces risks both from the surgery and from long-term immunosuppression. Thus, pancreas transplantation alone is limited to specific situations, such as in patients with frequent metabolic complications or in whom standard insulin therapy consistently fails to control disease. However, when pancreas transplantation and kidney transplantation are combined in patients with end-stage renal disease, the benefits far outweigh the risks.

Type 2 diabetes

The achievement of glycemic control requires individualized therapy in a comprehensive approach that incorporates lifestyle and pharmacologic interventions (Table 3-1). Following are considerations for noninsulin therapy in patients with type 2 DM:

- Noninsulin therapy should be considered early in the course of the disease, in conjunction with diet and exercise. Metformin is the recommended first-line therapy if tolerated.
- When used as monotherapy at the maximum dose, insulin secretagogues, metformin, and thiazolidinediones (TZDs) have comparable glucose-lowering effects. The glucose-lowering effects of these medications and analogues are observed within days to weeks, except for the maximum effect of TZDs, which may not be apparent for several weeks to months.
- Combination therapy with 2 or more oral or injectable agents may be needed to achieve targets for HbA_{1c} and blood glucose in patients presenting with significant hyperglycemia and will likely become necessary as β-cell function deteriorates over time. Dual therapy may be considered when the initial HbA_{1c} is ≥7.5%, and triple therapy or insulin when the initial HbA_{1c} is >9.0%.
- Because all noninsulin therapies require some pancreatic β-cell function to achieve glucose-lowering effects, many patients will eventually need insulin replacement therapy.

American Diabetes Association. *Standards of Medical Care in Diabetes—2022. Diabetes Care.* 2022;45(suppl 1). Accessed June 2, 2022. https://diabetesjournals.org/care/issue/45/Supplement_1

Table 3-1 Pharmacologic Approaches to Glycemic Treatment

Class	Compound	Additional Considerations
Biguanides	Metformin	First-line therapy Gastrointestinal adverse effects common Potential B_{12} deficiency
Sulfonylureas	Glimepiride Glipizide Glyburide	Black box warning: increased risk of cardiovascular mortality, based on older sulfonylurea (tolbutamide)
Thiazolidinediones	Pioglitazone Rosiglitazone	Black box warning: congestive heart failure Fluid retention
Alpha-glucosidase inhibitors	Acarbose Miglitol	
Meglitinides	Nateglinide Repaglinide	
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Pancreatitis reported in clinical trial Joint pain
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Cardiovascular risk reduction Should be discontinued prior to scheduled surgery to avoid potential diabetic ketoacidosis
GLP-1 RAs	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Cardiovascular risk reduction Black box warning: risk of thyroid C-cell tumors in rodents; human relevance unknown GI side effects common
Bile acid sequestrant	Colesevelam	
Dopamine-2 agonist	Bromocriptine	
Amylin mimetic	Pramlintide	

DPP-4 = dipeptidyl peptidase 4; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter 2.

Information adapted from American Diabetes Association. *Standards of Medical Care in Diabetes—2022. Diabetes Care.* 2022;45(suppl 1). Accessed June 2, 2022. https://diabetesjournals.org/care/issue/45/Supplement_1

Complications of Diabetes

Acute complications

The acute complications of DM are *nonketotic hyperglycemic hyperosmolar coma* and *diabetic ketoacidosis.* Either of these, if not recognized promptly and treated aggressively, can lead to death. These complications should be considered as part of a continuum of hyperglycemia rather than as separate entities; the main difference between the 2 is whether ketoacids accumulate. Both are often precipitated by some type of stress, such as an infection, that leads to increased production of glucagon, catecholamines, and cortisol, which in turn promotes gluconeogenesis. If not treated with adequate amounts of insulin or oral hypoglycemic

agents, the elevated glucose level will lead to osmotic diuresis and volume depletion. When insulin levels are extremely low or absent (eg, in a patient with type 1 DM), catabolic processes (eg, conversion of lipids to ketones) prevail and ketoacids are produced, superimposing severe metabolic acidosis on the hyperosmotic volume-depleted state.

Long-term complications

The long-term complications of DM are usually secondary to vascular disease. Nephropathy, neuropathy, peripheral artery disease, coronary atherosclerosis, secondary cerebral thrombosis, cardiac infarction, and retinopathy are all important causes of morbidity and/or mortality. The precise mechanism for the development of diabetic complications is elusive, but hyperglycemia plays a central role by triggering a number of processes that ultimately cause vascular damage. (Diabetic retinopathy is discussed in detail in BCSC Section 12, *Retina and Vitreous.*)

The blood glucose level is not the only risk factor that can be modified to reduce the complications of DM. In particular, hypertension and lipid abnormalities seem to be inextricably intertwined with glycemic control. Thus, any attempt to minimize complications must include aggressive control of these other factors.

Nephropathy Chronic kidney disease (CKD) occurs in 20%–40% of patient with DM. It typically develops after diabetes duration of 10 years in type 1 DM or may be present at diagnosis of type 2 DM. CKD is diagnosed by the persistent elevation of urinary albumin excretion, low estimated glomerular filtration rate, or other manifestations of kidney damage. CKD can progress to end-stage renal disease (ESRD), which requires dialysis or kidney transplant. Diabetic nephropathy is the leading cause of ESRD in the United States, and the 5-year survival rate of patients with DM on maintenance dialysis is 25%. Almost invariably, nephropathy and retinopathy develop within a short time of each other.

The progression of diabetic nephropathy occurs in the following sequence: microalbuminuria (urine albumin levels of 30–300 mg/24 hours), macroalbuminuria (urine albumin levels >300 mg/24 hours), nephrotic syndrome, and finally ESRD. Tight control of blood glucose can delay and perhaps prevent the development of microalbuminuria. In addition, controlling hypertension (particularly with angiotensin-converting enzyme inhibitors) and adhering to low-protein diets may help slow the decline in glomerular filtration rate. More recently, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-1 inhibitors have been shown to offer intrinsic renal protection.

Neuropathy Diabetic neuropathy is a common problem. After 30 years of DM, approximately 50% of patients have signs of neuropathy, and 15%–20% have symptoms of distal symmetric polyneuropathy. Changes in nerve metabolism and function are thought to be mediated in part through increased aldose reductase activity; Schwann cell synthesis of myelin is impaired, and axonal degeneration ensues. In addition, microangiopathy of the endoneural capillaries leads to vascular abnormalities and microinfarcts of the nerves, with multifocal fiber loss.

Symptoms in the feet and lower legs are the most common manifestations. Foot pain, paresthesias, and loss of sensation occur frequently and probably result from both ischemic and metabolic nerve abnormalities. Weakness may be present as part of mononeuritis or

a mononeuritis multiplex and is usually associated with pain. Cranial neuropathies may also occur (see BCSC Section 5, *Neuro-Ophthalmology*). Additional types of morbidity, stemming from autonomic dysfunction, include male and female sexual dysfunction, impaired urination, delayed gastric emptying, orthostatic hypotension, and tachycardia due to loss of vagal tone.

Other than improved glycemic control, there is no specific treatment for diabetic neuropathy. However, pharmacologic (pregabalin, duloxetine, or gabapentin) and nonpharmacologic treatments (lifestyle modifications) can provide some relief for painful diabetic peripheral neuropathy and autonomic neuropathy and improve the quality of life for patients with DM.

Large-vessel disease The risk of coronary heart disease is 2–10 times higher in patients with DM than in the general population, and the mortality rate of patients with DM who have anterior myocardial infarctions is twice that of patients who do not have DM. Because myocardial infarction may present without the classic symptom of chest pain in patients with DM, an increased index of suspicion is required to make the diagnosis. Hypertension further increases the risk of cardiovascular disease for persons with DM. Cerebral thrombosis is approximately twice as prevalent in the diabetic population as in the nondiabetic population, and peripheral artery disease is 40 times as prevalent. Recent studies have shown that combination therapy with a sodium-glucose cotransporter-2 inhibitor and a glucagon-like peptide-1 receptor agonist medication provides improved cardiovascular and kidney outcomes.

American Diabetes Association. *Standards of Medical Care in Diabetes—2022.* Abridged for Primary Care Providers. Updated May 31, 2022. Accessed June 8, 2022. https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022

Centers for Disease Control and Prevention. National Diabetes Prevention Program. Accessed June 8, 2022. https://www.cdc.gov/diabetes/prevention/about.htm

Ophthalmic considerations Management of patients with DM can be challenging. The ophthalmologist may be the first to identify a complication related to a patient's diabetes, whether diabetic retinopathy or a transient refractive change due to glucose level elevation. Moreover, an ophthalmologist may be a patient's only regular health care provider. Thus, it is important that both the patient and the ophthalmologist are aware of the patient's HbA_{1c} level, a specific and objective measure of glycemic control.

Patients may need to be educated about frequent blood glucose testing, the paramount importance of maintaining good glycemic control, and the possible consequences of poor control. In addition, patients should be reminded that other modifiable risk factors for retinopathy progression, including hypertension, lipid abnormalities, early renal failure, and anemia, are also important.

It is also important for the ophthalmologist to be aware of the patient's glycemic control status because it can affect the rate of retinopathy progression

and, in turn, influence decisions on treatment and follow-up frequency. For example, studies have shown that rapid improvement in glycemic control can hasten progression of retinopathy. This finding is independent of cataract surgery, and the mechanism of action is not fully understood. Therefore, attempting to rapidly improve glycemic control in a patient prior to cataract surgery may not be beneficial, as it may speed the progression of retinopathy and affect visual outcomes.

The importance of all of the risk factors for retinopathy progression should be communicated to the patient's primary care physician so that these factors can be controlled as well as possible. The ophthalmologist should strive to keep informed on the status of these issues because a patient with significant problems in any of these areas is likely to have less-than-optimal results with any ophthalmic surgical intervention. Educating patients who have poorly controlled DM about their prognosis before surgery may facilitate more realistic expectations. (Perioperative management in ocular surgery is reviewed in Chapter 16.)

Jingi AM, Tankeu AT, Ateba NA, Noubiap JJ. Mechanism of worsening diabetic retinopathy with rapid lowering of blood glucose: the synergistic hypothesis. *BMC Endocr Disord*. 2017;17(1):63.

Kelkar A, Kelkar J, Mehta H, Amoaku W. Cataract surgery in diabetes mellitus: a systematic review. *Indian J Ophthalmol*. 2018;66(10):1401–1410.

Thyroid Disease

Physiology

Functionally, the thyroid gland can be thought of as having 2 parts. The *parafollicular* (or C) cells secrete calcitonin and play a role in calcium homeostasis; they do not affect thyroid physiology. Thyroid *follicles* are made up of a single layer of epithelial cells surrounding colloid, which consists mostly of thyroglobulin, the storage form of thyroid hormones T_4 and T_3.

T_4 (thyroxine), the main secretory product of the thyroid gland, contains 4 iodine atoms. Deiodination of T_4, which occurs mainly in the liver and kidneys, gives rise to T_3 (triiodothyronine), the metabolically active form of thyroid hormone. Eighty percent of serum T_3 is derived through deiodination; the remainder is secreted by the thyroid. Only a small fraction of these hormones circulates freely in the plasma (0.02% of total T_4 and 0.30% of total T_3); the remainder is bound to the proteins thyroxine-binding globulin (TBG), transthyretin, and albumin.

Thyroid function is regulated by the interrelationship of hypothalamic, pituitary, and thyroid activity. Thyrotropin-releasing hormone (TRH), which is secreted by the hypothalamus, causes the synthesis of thyrotropin, or thyroid-stimulating hormone (TSH), and its release from the anterior pituitary. TSH, in turn, stimulates the thyroid, leading to the release of T_4 and T_3. In this negative-feedback loop, increased levels of T_4 and T_3 inhibit the release of TSH and the TSH response to TRH at the level of the pituitary.

The main role of the thyroid hormones is regulation of tissue metabolism through their effects on protein synthesis. Normal development of the central nervous system requires adequate amounts of thyroid hormone during the first 2 years of life. Congenital hypothyroidism results in irreversible cognitive disability (cretinism). Normal growth and bone maturation also depend on sufficient hormone levels.

Tests of Thyroid Function

Detection of thyroid disease and evaluation of the efficacy of therapy require the use of various combinations of laboratory tests. The American Thyroid Association recommends initial screening with tests of TSH and free T_4.

Measurement of serum TSH

Secretion of TSH by the pituitary is tightly controlled by negative-feedback mechanisms regulated by serum T_4 and T_3 levels. TSH levels begin to rise early in the course of hypothyroidism and fall in hyperthyroidism, even before free T_4 levels are outside the reference range. Therefore, the serum TSH level is a sensitive indicator of thyroid dysfunction.

Some extremely sensitive assays of TSH can detect levels down to 0.005 mIU/L, making it possible to differentiate low normal values from abnormally low values. The TSH test is useful for (1) screening for thyroid disease, (2) monitoring replacement therapy in hypothyroid patients (TSH levels respond 6–8 weeks after changes in hormone replacement dosage), and (3) monitoring suppressive therapy for thyroid nodules or cancer. In screening for thyroid disease, the combination of free T_4 and sensitive TSH assays has a sensitivity of 99.5% and a specificity of 98.0%. As a result, both of these tests are used together for screening in most situations. There is presently some controversy about the upper limit of normal for TSH, so endocrinologic consultation is indicated in borderline cases.

Measurement of serum T_4

Total serum T_4 comprises 2 parts: the protein-bound fraction and the free hormone. Total T_4 levels can be affected by changes in serum TBG levels, while euthyroidism is maintained and free T_4 levels remain normal. Levels of TBG and total T_4 are elevated during pregnancy and with use of oral contraceptives, while free T_4 levels remain normal. Low TBG and total T_4 levels are associated with chronic illness, protein malnutrition, hepatic failure, and use of glucocorticoids.

Measurement of serum T_3

Serum T_3 levels may not accurately reflect thyroid gland function for 2 reasons. First, T_3 is not the major secretory product of the thyroid. Second, many factors influence T_3 levels, including nutrition, medications, and mechanisms regulating the enzymes that convert T_4 to T_3. Determination of T_3 levels is indicated in individuals who may have *T_3 thyrotoxicosis,* an uncommon condition in which patients with clinical hyperthyroidism have normal T_4 and free T_4 but elevated T_3 levels.

Thyroid hormone–binding protein tests

Radioactive iodine uptake testing can be used to distinguish Graves disease from other causes of hyperthyroidism in the absence of other clinical features of Graves disease. However, it is not routinely performed.

Thyroid antibody tests

Several antibodies against thyroid antigens can be detected in the blood. The most common is thyroid peroxidase antibody, which has 99% sensitivity and specificity for Graves disease. Antibodies to thyroglobulin are also found in various thyroid diseases, including Hashimoto thyroiditis, Graves disease, and thyroid carcinoma. Patients with Graves disease usually have antibodies called *thyroid-stimulating immunoglobulins (TSIs),* which are directed at TSH receptors. These antibodies generally stimulate the release of thyroid hormone, but in rare cases, patients have antibodies that block thyroid hormone release. High serum levels of TSI and the absence of thyroperoxidase antibody are both risk factors for ophthalmopathy in patients with Graves disease.

Thyroid scanning

Thyroid scanning is useful in distinguishing functioning from nonfunctioning thyroid nodules and in evaluating chest and neck masses for metastatic thyroid cancer.

Thyroid ultrasonography

Ultrasonography, which can detect nodules as small as 1 mm, is used to identify the presence of cystic or solid thyroid nodules.

Biopsy

Biopsy to obtain tissue samples for evaluating thyroid nodules may be performed with fine-needle aspiration, core, or excisional techniques. Fine-needle aspiration specimens require interpretation by an experienced cytologist.

Hyperthyroidism

Hypermetabolism caused by excessive quantities of circulating thyroid hormones leads to the clinical syndrome of *hyperthyroidism (thyrotoxicosis).* Approximately 1.2% of the US population has hyperthyroidism. Clinical findings include exophthalmos, chest palpitations, excessive sweating, diarrhea, weight loss, and sensitivity to heat. Graves disease accounts for approximately 85% of cases of thyrotoxicosis. Toxic nodular goiter and thyroiditis account for most of the remaining cases.

Thyroid storm is a rare, acute, hypermetabolic state that is fatal if untreated. It is often precipitated by surgery, infection, or trauma in a patient with otherwise mild hyperthyroidism. Patients typically present with fever, tachycardia, nausea, vomiting, agitation, and psychosis; and they may become comatose secondary to hypotension. Modern treatments aimed at controlling the process have dramatically reduced mortality.

Graves disease

Thyroid eye disease (TED) is discussed in BCSC Section 5, *Neuro-Ophthalmology,* and Section 7, *Oculofacial Plastic and Orbital Surgery.* This section focuses on the thyroid disease.

Graves disease (also known as *diffuse toxic goiter*) is the most common form of hyperthyroidism, and patients exhibit various combinations of hypermetabolism, diffuse enlargement of the thyroid gland, TED, and infiltrative dermopathy. Graves disease is an autoimmune disorder. Up to 90% of patients have circulating TSH receptor antibodies; furthermore, the level of TSI has been shown to correlate with the severity of clinical disease.

Graves disease is common, with a lifetime risk of 3.0% for women and 0.5% for men. The incidence peaks in the third to fifth decades of life, and there is a strong familial component. Risk factors including stress and smoking are associated with increased incidence of TED.

Common clinical symptoms include fatigue, tremor, weight loss, palpitations, and heat intolerance. Manifestations can vary by age of patient at the onset of hyperthyroidism. For instance, atrial fibrillation is rare in patients younger than 60 years but occurs in >10% of patients 60 years or older. A palpable goiter develops in most patients younger than 60 years compared with <50% of patients older than 60 years. Approximately one-third of patients with Graves disease have clinically obvious TED at the time of diagnosis of the hyperthyroidism.

Management Treatment of Graves disease is aimed at returning thyroid function to normal. A significant proportion of patients (30%–50%) experience remission in association with drug treatment directed at the thyroid. Later in the course of the disease, patients may experience relapse, hypothyroidism, or both.

Thyroid secretion is suppressed with the use of one of the thiourea derivatives, propylthiouracil or methimazole. The drugs inhibit the use of iodine by the gland. Treatment is continued until clinical and laboratory indexes show improvement. Adverse effects include rash (common), liver damage (rare), vasculitis (rare), and agranulocytosis (occurs in 0.02%–0.05% of patients).

There are several options for long-term management of Graves disease: the aforementioned antithyroid drugs can be continued for 12–24 months in hopes of remission; part of the gland can be surgically removed, although approximately half of these patients eventually become hypothyroid; or radioactive iodine can be used. Iodine 131 (^{131}I) is highly effective, resulting in hypothyroidism in 80% of patients within 6–12 months; some require a second treatment. Although adverse effects of ^{131}I are minimal, its use is associated with worsening of TED.

Ophthalmic considerations A new drug, teprotumumab, received US FDA approval in January 2020. It has been shown to slow progression of ophthalmopathy in patients with moderate to severe TED. Teprotumumab, which inhibits insulin-like growth factor I receptor, represents a new therapeutic strategy for treating the underlying autoimmune pathogenesis of TED.

Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341–352.

Toxic nodular goiter

In toxic nodular goiter, thyroid hormone–producing adenomas (either single or multiple) make enough hormone to cause hyperthyroidism. These so-called *hot nodules* are almost never carcinomatous. Toxic nodules may be treated with radioactive iodine or surgery.

Hypothyroidism

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormone. *Myxedema* is the nonpitting edema caused by subcutaneous accumulation of mucopolysaccha-

rides in severe cases of hypothyroidism; the term is sometimes used to describe the entire syndrome of severe hypothyroidism.

Primary hypothyroidism accounts for >95% of cases and may be congenital or acquired. Most primary cases are due to Hashimoto thyroiditis (discussed in the following section), "idiopathic" myxedema (thought by many to be end-stage Hashimoto thyroiditis), and iatrogenic causes (^{131}I or surgical treatment of hyperthyroidism). *Secondary hypothyroidism,* caused by hypothalamic or pituitary dysfunction (usually after pituitary surgery), is much less common. As in Graves disease, the female preponderance among adults is significant. *Subclinical hypothyroidism* is defined as a normal T_4 concentration and a slightly elevated TSH level. These patients may or may not have symptoms suggestive of hypothyroidism. Most individuals with subclinical hypothyroidism can be observed without treatment, but the rationale for treatment is based on the potential decreased risk of adverse cardiovascular events and possible prevention of progression to overt hypothyroidism.

Clinically, a patient with hypothyroidism presents with signs and symptoms of hypometabolism and accumulation of mucopolysaccharides in the tissues of the body. Many of the symptoms are nonspecific—they include weakness, fatigue, memory loss, dry skin, hair loss, deepening of the voice, weight gain (despite loss of appetite), cold intolerance, arthralgias, constipation, and muscle cramps—and their relationship to thyroid dysfunction may not be recognized for some time. Clinical signs include bradycardia, reduced pulse pressure, myxedema, weight gain, loss of body and scalp hair, and menstrual disorders. In severe cases, personality changes ("myxedema psychosis") and death (following "myxedema coma") may occur.

Treatment of hypothyroidism is straightforward, consisting of oral thyroid replacement medication to normalize circulating hormone levels. Levothyroxine is the most commonly used preparation. Serum T_4 and TSH levels are monitored at regular intervals to ensure that euthyroidism is maintained.

Thyroiditis

Thyroiditis may be classified as acute, subacute, or chronic. *Acute thyroiditis,* caused by bacterial infection, is extremely rare. *Subacute thyroiditis* occurs in 2 forms: granulomatous and lymphocytic. Hashimoto thyroiditis is the most common type of *chronic thyroiditis.*

Patients with *subacute granulomatous thyroiditis* present with a painful, enlarged gland associated with fever, chills, and malaise. Thyroid function tests may be helpful because they may reveal the unusual combination of an elevated T_4 level and a low radioactive iodine uptake. Patients may be hyperthyroid because of the release of hormone from areas of thyroid destruction; pathologic examination reveals granulomatous inflammation. The disease is self-limited, and treatment is symptomatic, with use of either analgesics or, in severe cases, oral corticosteroids. After resolution, transient hypothyroidism (which becomes permanent in 5%–10% of patients) may occur.

S*ubacute lymphocytic thyroiditis* ("painless" thyroiditis) commonly occurs 2–4 months after a mother gives birth, but it can also occur in isolation. Patients present with symptoms of hyperthyroidism and a normal or slightly enlarged but nontender thyroid gland. Pathologic investigation shows lymphocytic infiltration resembling that in Hashimoto thyroiditis,

suggesting an autoimmune cause. This disease is self-limited, generally lasting <3 months, and treatment is symptomatic. Hypothyroidism may ensue.

Hashimoto thyroiditis is an autoimmune disease that causes goitrous hypothyroidism. Patients have antibodies to thyroid antigens and an increased incidence of other autoimmune diseases. Patients with Hashimoto thyroiditis may present with hypothyroidism, an enlarged thyroid, or both. Pathologic examination reveals lymphocytic infiltration. Treatment is aimed at normalizing hormone levels with thyroid replacement therapy. Patients with enlarged glands and airway obstruction who do not respond to TSH suppression may require surgery. The risk of primary thyroid lymphoma and papillary thyroid cancer is slightly increased in patients with Hashimoto thyroiditis.

Postpartum thyroiditis occurs in approximately 5% of women after delivery (often in subsequent pregnancies) and can cause hyperthyroidism or hypothyroidism (or first one problem and then the other). Postpartum thyroiditis is usually painless and self-limited and is often associated with thyroid peroxidase antibodies.

Thyroid Tumors

Virtually all tumors of the thyroid gland arise from glandular cells and are, therefore, adenomas or carcinomas. Functioning adenomas were discussed previously (see the section "Toxic nodular goiter").

On thyroid scan, 90%–95% of thyroid adenomas are *cold nodules* (ie, nonfunctioning) and come to attention only if they are large enough to be physically apparent. Diagnostic testing involves a combination of approaches, including ultrasonography (lesions that are identified as cysts are benign and can simply be aspirated), fine-needle aspiration, and surgery, depending on the clinical situation. Treatment options for benign cold nodules are suppressive therapy, in which thyroid hormone replacement is used to suppress TSH secretion and its stimulatory effect on functioning nodules, and surgery.

There are 4 types of carcinomas of the thyroid: papillary, follicular, medullary, and anaplastic (undifferentiated). *Papillary carcinoma* is the most common form of thyroid tumor. Tumors removed before extension outside the capsule of the gland appear to have no adverse effect on survival. *Follicular carcinoma* may also be associated with a normal life span if it is identified before it becomes invasive, but late metastases can occur. *Medullary carcinoma* arises from the C cells and produces calcitonin. The lesion can occur as a solitary malignant tumor or as part of multiple endocrine neoplasia type 2 (see the section Multiple Endocrine Neoplasia Syndromes). *Anaplastic carcinoma,* though rare, is the most malignant tumor of the thyroid gland and is found mainly in patients older than 60 years. For the giant cell form, the survival time is <6 months from time of diagnosis; for the small cell form, the 5-year survival rate is 20%–25%.

Disorders of the Hypothalamic-Pituitary Axis

The *hypothalamus* is the coordinating center of the endocrine system. It consolidates signals from higher cortical centers, the autonomic nervous system, the environment, and systemic endocrine feedback. The hypothalamus then delivers precise instructions to the pituitary gland, which releases hormones that influence most endocrine systems in

the body. The hypothalamic-pituitary axis directly affects the thyroid gland, the adrenal gland, and the gonads; and it influences growth, milk production, and water balance.

Table 3-2 outlines the major hypothalamic hormones and their actions on the anterior pituitary hormones. The hypothalamic hormones are released directly into a primary capillary plexus that empties into the hypophyseal portal venous circulation; they then travel down the pituitary stalk and bathe the anterior pituitary gland in a secondary capillary plexus. The hormones released by the hypothalamic neurons, therefore, reach their target cells rapidly and in high concentrations. This proximity allows a rapid, pulsatile response to signals between the hypothalamus and the anterior pituitary. The posterior pituitary is controlled by direct neuronal innervation from the hypothalamus rather than by blood-borne hormones. The main products of the posterior pituitary are vasopressin and oxytocin. *Vasopressin* (antidiuretic hormone) is primarily involved in controlling water excretion by the kidneys. *Oxytocin* stimulates uterine contractions during labor and delivery and milk ejection in lactation.

Pituitary Adenomas

Pituitary tumors account for 10%–15% of intracranial tumors. They are classified as *microadenomas* (<10 mm in the greatest diameter) or *macroadenomas* (≥10 mm in the greatest diameter). Typically benign, these tumors arise from hormone-producing cells and may be functionally active (ie, secrete large amounts of hormones) or inactive. The clinical presentation depends on what type of cell the tumor derives from and whether the tumor produces hormones. Any type of tumor can be clinically inactive and will become apparent only when it has enlarged enough to cause symptoms. Patients may present with headaches, visual symptoms such as visual field loss due to chiasmal compression, cranial neuropathies, and/or hypopituitarism from compression of normal pituitary tissue. (The ophthalmic effects of pituitary adenomas and other parasellar lesions are discussed in BCSC Section 5, *Neuro-Ophthalmology.*)

Accounting for approximately 15% of pituitary tumors, *somatotroph adenomas* produce growth hormone, which can cause gigantism in prepubertal patients and acromegaly in adults. Acromegaly often develops insidiously over several years, and patients may present with headaches and visual symptoms due to enlargement of the adenoma before the diagnosis is recognized. Characteristic findings include an enlarged jaw, coarse facial

Table 3-2 Hypothalamic Neurohormones and Neurotransmitters Involved in Anterior Pituitary Function

Thyrotropin-releasing hormone (TRH) → ↑TSH, PRL
Gonadotropin-releasing hormone (GnRH) → ↑FSH, LH
Growth hormone–releasing hormone (GHRH) → ↑GH
Corticotropin-releasing hormone (CRH) → ↑ACTH
Somatostatin → ↓GH, TSH
Dopamine → ↓PRL

ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; PRL = prolactin; TSH = thyroid-stimulating hormone; ↑ = stimulates release of; ↓ = inhibits release of.

features, and enlarged and swollen hands and feet. Patients may also have cardiac disease and diabetes in addition to the typical bone and soft-tissue changes.

Lactotroph adenomas (prolactinomas) account for approximately 25% of symptomatic pituitary tumors. Hyperprolactinemia produces amenorrhea and galactorrhea in women and decreased libido and impotence in men. The symptoms tend to develop gradually in men, and patients may present with compression symptoms caused by tumor enlargement before the hormonal effects are recognized.

Thyrotroph adenomas are rare, accounting for <1% of pituitary tumors. They may cause hyperthyroidism, hypothyroidism, or no change in thyroid function, depending on how the TSH subunits are processed in the tumor cells. These tumors tend to be large macroadenomas, and patients may present with compressive symptoms in addition to any thyroid changes.

Corticotroph adenomas account for approximately 15% of pituitary tumors. They are associated with *Cushing syndrome,* characterized by the classic features of centripetal obesity, hirsutism, and facial plethora. Fat deposits develop over the thoracocervical spine (buffalo hump) and temporal regions (moon facies). Psychiatric abnormalities occur in 50% of patients, and long-standing Cushing syndrome can cause osteoporosis. Patients bruise easily and have violet striae on the abdomen, upper thighs, and arms. Hypertension and glucose intolerance leading to diabetes can also occur. Cushing syndrome can also develop secondary to adrenal gland neoplasms and, most commonly, from iatrogenic administration of glucocorticoids.

Gonadotroph adenomas (about 10% of pituitary tumors) can produce serum follicle-stimulating hormone and, in rare cases, luteinizing hormone. Affected patients present with hypogonadism related to gonadal downregulation. Gonadotropin-producing pituitary tumors can also be clinically inactive, and patients may present with compression symptoms.

Accounting for approximately 15% of pituitary tumors, *plurihormonal adenomas,* as the name implies, produce more than 1 type of hormone. Common combinations include elevated growth hormone with prolactin and growth hormone with TSH.

Null-cell adenomas (about 20% of pituitary tumors) do not have any pathologic markers to suggest a certain cell type and do not produce excess hormone. Most tumors that present with signs of enlargement and compression are gonadotroph or null-cell adenomas.

Tumors of the pituitary gland are best diagnosed by means of contrast magnetic resonance imaging focused on the pituitary region. Endocrinologic testing is warranted when hypersecretion syndromes are suspected or when the patient has evidence of hypopituitarism. The treatment approach is complex and depends on a number of factors, including the size of the tumor and the nature of the hormonal activity. Treatment is discussed further in BCSC Section 5, *Neuro-Ophthalmology.*

Pituitary Apoplexy

Pituitary apoplexy results from hemorrhage or infarction in a pituitary adenoma; it can occur spontaneously or after head trauma. In its most dramatic presentation, apoplexy causes the sudden onset of excruciating headache, visual field loss, diplopia due to pressure on the oculomotor nerves, and hypopituitarism. Any type of pituitary hormone deficiency can occur, but cortisol deficiency is the most serious because it can cause life-threatening hypotension.

Imaging of the pituitary may show intra-adenomal hemorrhage and deviation of the pituitary stalk. Most patients recover but experience long-term pituitary insufficiency. Signs of reduced vision and altered mental status are indications for transsphenoidal surgical decompression. Ophthalmologists need to be aware of this entity because of the high incidence of visual symptoms on presentation.

Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia (MEN) syndromes are rare hereditary disorders of benign and malignant endocrine neoplasms. There are 4 syndromes: MEN1, MEN2 (formerly MEN2A), MEN3 (formerly MEN2B), and the recently identified MEN4 (Table 3-3). These syndromes are typically autosomal dominant, but sporadic cases exist.

The most common features of MEN1 are parathyroid, enteropancreatic, and pituitary tumors. Hyperparathyroidism is the most common endocrine abnormality. Enteropancreatic tumors include *gastrinomas,* which cause increased gastric acid output (Zollinger-Ellison syndrome), and *insulinomas,* which cause fasting hypoglycemia. Pituitary adenomas can also be present; they are usually prolactinomas, but other types can occur. Carcinoid and adrenal tumors can develop as well.

MEN2 and MEN3 are characterized by the presence of medullary thyroid cancer (MTC), which occurs in 90%–100% of patients and is the main cause of morbidity. The lifetime incidence of pheochromocytoma is approximately 50%. Hyperparathyroidism is seen in approximately 20%–30% of patients with MEN2 but is rarely seen in patients with MEN3.

MEN3 is characterized by ganglioneuromas, which occur in 95% of patients. They can be present on the lips, eyelids, and tongue, giving these patients a characteristic phenotype that may be apparent at birth. Patients with MEN3 may also have marfanoid features including pectus excavatum and scoliosis, but without lens subluxation and

Table 3-3 Multiple Endocrine Neoplasia (MEN) Syndromes: New Nomenclature

	Nomenclature	Features	Ophthalmic Manifestations
MEN1	No change in nomenclature	• Parathyroid, enteropancreatic, and pituitary tumors • Carcinoid and adrenal tumors	
MEN2	Formerly MEN2A	• Medullary thyroid cancer (MTC; main cause of morbidity) • Pheochromocytoma • Hyperparathyroidism	
MEN3	Formerly MEN2B	• MTC (main cause of morbidity) • Pheochromocytoma • Ganglioneuroma • Marfanoid features	• Ganglioneuromas on eyelids, subconjunctiva • Prominent corneal nerves (100% of cases) • Ophthalmic findings often seen before MTC
MEN4	Newly identified	• MEN1-associated tumors, including parathyroid and anterior pituitary tumors	

aortic disease. The eyelid margins may be nodular as a result of multiple small tumors (Fig 3-2); subconjunctival neuromas have also been reported. Perhaps the most striking ophthalmic finding is the presence of prominent corneal nerves in a clear stroma (Fig 3-3), a phenomenon reported in 100% of cases. Because MTC may not appear until the second or third decade of life, ophthalmic manifestations may be the initial sign of MEN3, making ophthalmologists potentially instrumental in the diagnosis of this disease.

MEN4 was first reported in 2006, and information on this entity is limited, given the small number of cases. Patients with MEN4 develop MEN1-associated tumors, including parathyroid tumors and anterior pituitary tumors, which tend to be smaller and less aggressive than those in MEN1.

The management of MEN depends on the nature of the tumors and usually involves medical treatment to control hormonal effects and/or surgical excision when possible. The genes that cause all types of MEN have been located, and genetic testing can identify patients at risk. Identification of affected family members is particularly important in MEN2 and MEN3 because prophylactic thyroidectomy can decrease the risk of death from MTC. Screening for pheochromocytoma is also warranted in order to identify problems that could lead to the development of complications such as hypertension.

McDonnell JE, Gild ML, Clifton-Bligh RJ, Robinson BG. Multiple endocrine neoplasia: an update. *Intern Med J*. 2019;49(8):954–961.

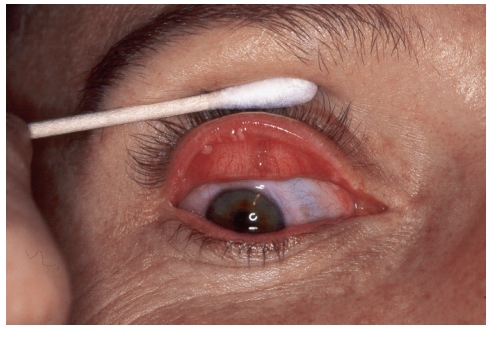

Figure 3-2 Eyelid nodules in multiple endocrine neoplasia (MEN) type 3 (formerly called *MEN2B*). *(Courtesy of Jason M. Jacobs, MD, and Michael J. Hawes, MD.)*

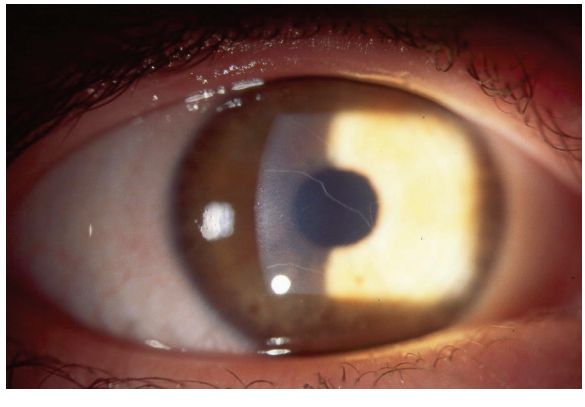

Figure 3-3 Enlarged corneal nerves in MEN3 (formerly called *MEN2B*). *(Courtesy of Jason M. Jacobs, MD, and Michael J. Hawes, MD.)*

CHAPTER 4

Hypertension

Highlights

- Recent US guidelines have lowered the threshold of "normal" blood pressure to 120/80 mm Hg. Blood pressure even 20/10 mm Hg above this threshold is the focus of more aggressive interventions.
- Cardiovascular complications in patients with diabetes, proteinuria, renal insufficiency, and congestive heart failure can be reduced by half through improved blood pressure control.
- Ambulatory blood-pressure monitoring or self-measured blood pressure can be helpful in identifying patients with masked hypertension.
- Depending on the history, comorbidities, and ethnicity of the patient with hypertension, treatment with a diuretic, renin-angiotensin-aldosterone system blockade, β-blocker, or calcium channel blocker may be initiated, with 2 or more medications indicated for some patients.
- Hypertension is increasingly common in children and adolescents as well as in women aged 45 years and older and has substantial long-term health implications.

Introduction

Hypertension affects approximately 1.4 billion individuals worldwide. In the United States, an estimated 116 million persons aged 20 years or older have hypertension, and in Europe, an estimated 94 million aged 15 years or older are affected. Interestingly, the incidence of hypertension across the European continent decreases from east to west. People with hypertension are at greater risk for stroke, myocardial infarction (MI), heart failure, peripheral vascular disease, kidney disease, and retinal vascular complications. The prevalence of hypertension increases with age; it is typically familial and is also related to lifestyle behaviors. Hypertension is more common in non-Hispanic Black persons than in Hispanic persons, and it is higher in both of those groups than in White persons. Blood pressure (BP) control rates are lowest in Mexican American and American Indian individuals. The severity of hypertension is also increased in Black persons.

The incidence of devastating complications is higher in lower socioeconomic groups because of greater prevalence, delayed detection, and poor control rates of multifactorial etiology. Antihypertensive therapy is effective in reducing cardiovascular morbidity and mortality, but only 59% of individuals with hypertension are treated, and only 69% of

those achieve a BP of 140/90 mm Hg or lower, according to National Health and Nutrition Examination Surveys (NHANES) in the United States and similar cohorts in Canada and Europe. Under the new US definition of hypertension (systolic pressure ≥130 mm Hg and/or a diastolic pressure ≥80 mm Hg), only 47% of individuals undergoing hypertensive therapy will achieve controlled BP. Unfortunately, for many patients in racial or ethnic minority groups, socioeconomic and lifestyle factors continue to be barriers to treatment.

Classification of Blood Pressure and Diagnosis of Hypertension

In recent years, the classification and diagnosis of BP have been updated. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines defined "normal" blood pressure as <120/80 mm Hg, while the 2018 European Society of Cardiology/European Society of Hypertension guidelines consider this level "optimal." While there are some key differences between the recommendations of the US and European groups, there is also much overlap, as shown in Table 4-1. These classifications are based on the average of 2 or more properly measured seated BP readings during each of 2 or more office visits or other outpatient assessments such as ambulatory BP monitoring or home BP monitoring with an approved device.

Clinical trial data have demonstrated additional benefits of aggressive lowering of BP to <130 mm Hg. Both US and European organizations recommend BP treatment targets of <130/80 mm Hg, particularly for hypertensive patients with coexisting coronary artery disease, chronic kidney disease, diabetes, and cerebrovascular disease.

In 10%–15% of patients, BP increases only when they are in a physician's office; these patients are said to have *white coat hypertension*. Home BP monitoring by self-measured BP (SMBP) or 24-hour ambulatory BP measurement (ABPM) is warranted in these individuals and in patients with labile hypertension, resistant hypertension, hypotensive episodes, or

Table 4-1 Comparison of ACC/AHA and ESC/ESH Blood Pressure Classifications

	ACC/AHA 2017 Guidelines	ESC/ESH 2018 Guidelines
Definition of hypertension (mm Hg)	≥130/80	≥140/90
Normal	Normal: <120/80	Optimal: <120/80
	Elevated: 120–129/<80	Normal: 120–129/80–84
		High normal: 130–139/85–89
Stages	Stage 1: 130–139/80–89	Grade 1: 140–159/90–99
	Stage 2: ≥140/90	Grade 2: 160–179/100–109
		Grade 3: ≥180/110
Age-specific blood pressure targets (mm Hg)	<65: <130/80 ≥65: <130/80	<65: <120–129/70–79 ≥65: <130–139/70–79

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; ESH = European Society of Hypertension.

postural hypotension, as well as in those with *masked hypertension* (normal BP in the office setting but abnormal readings at home). Other indications for obtaining out-of-office BP measurements include confirming a new diagnosis of hypertension, determining the effectiveness of therapy, and confirming elevated office BP in pregnant women when gestational hypertension or preeclampsia are suspected.

ABPM provides data on circadian variations of BP. ABPM readings are usually lower than measurements taken in a physician's office, and they correlate better with target-organ injury than do office measurements. BP in most individuals decreases by 10%–20% during sleep *(dipping pattern);* those without such a decrease *(nondipping pattern)* are at greater risk for cardiovascular and neurovascular events. Masked hypertension may occur in 10%–30% of patients and carries a worse prognosis than white coat hypertension with regard to the development of atherosclerosis. Thus, it is important to recognize that a normal office BP does not exclude hypertension, and home monitoring may identify patients with true hypertension.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13–e115.

Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021–3104.

Ophthalmic considerations There is a link between nocturnal blood pressure and glaucomatous optic neuropathy, and ABPM may be useful in determining the cause of glaucoma that progresses despite normal intraocular pressure. Some studies suggest that this may be caused by increased fluctuation and dipping of BP, leading to fluctuations in ocular perfusion and transient optic nerve head ischemia. In these patients, a shorter-acting BP medication at bedtime may be needed, especially in older adults, in whom dehydration is also a common cause of hypotension.

Melgarejo JD, Lee JH, Petitto M, et al. Glaucomatous optic neuropathy associated with nocturnal dip in blood pressure: findings from the Maracaibo Aging Study. *Ophthalmology*. 2018;125(6):807–814.

Etiology and Pathogenesis of Hypertension

Approximately 90% of cases of hypertension are *primary (essential),* in which the etiology is unknown, and 10% are secondary to identifiable causes. Primary hypertension most likely results from a dysregulation of various renal, hormonal, and cellular processes in conjunction with environmental factors such as diet and exercise. These processes include abnormal sodium transport, increased sympathetic nervous system activity, abnormal vasodilation, excess amounts of transforming growth factors β, and abnormalities in the renin-angiotensin-aldosterone system (Fig 4-1).

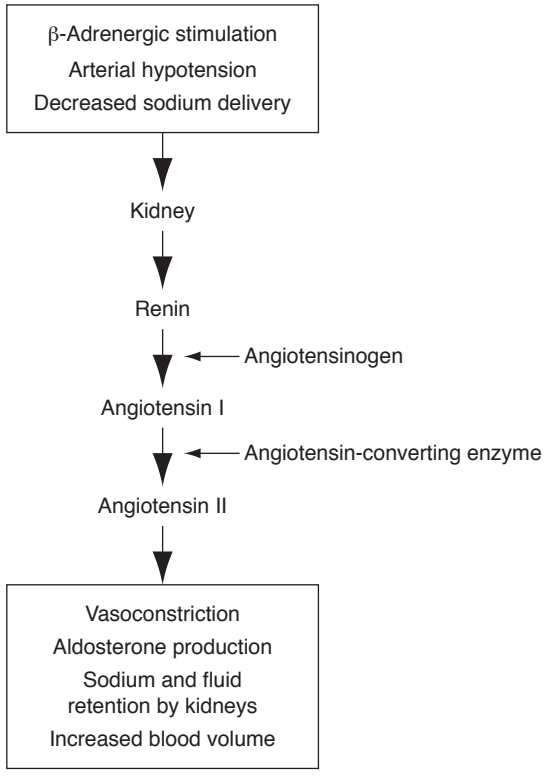

Figure 4-1 Renin-angiotensin-aldosterone system.

Causes of *secondary hypertension* vary. Following are some of these causes, along with signs associated with secondary hypertension:

- *polycystic kidney disease:* flank mass
- *renovascular disease:* unilateral abdominal bruit in a young patient with marked hypertension; new-onset hypertension with severe end-organ disease
- *pheochromocytoma:* markedly labile BP with tachycardia and headache
- *hyperaldosteronism:* persistent hypokalemia in the absence of diuretic therapy or marked drop with low-dose diuretics
- *coarctation of the aorta:* delayed or absent femoral pulses in a young patient
- *Cushing syndrome:* truncal obesity and abdominal striae

Other causes of secondary hypertension include certain genetic mutations, thyroid disease, obstructive uropathies, and alcohol use, as well as some medications and over-the-counter drugs. Secondary hypertension should be suspected in patients who have accelerating hypertension or hypertension unresponsive to medication or in those who have a sudden change in previously well-controlled BP. Patients with secondary hypertension are more likely to have *resistant hypertension,* which is defined as a failure to achieve goal BP even when the patient adheres to the optimal doses of 3 antihypertensive drugs, including a diuretic. The prevalence of resistant hypertension is currently not known, but indirect population study

evidence suggests it is more common than previously suspected. This prevalence may be secondary to an aging population, as well as the increased prevalence of obesity, diabetes, obstructive sleep apnea syndrome, and chronic kidney disease.

Most cases of diagnosed resistant hypertension are due to inadequate dosing of medication and patient nonadherence to treatment. The most common factors contributing to resistant hypertension are excess sodium intake, volume overload, and failure to treat the condition, whether with dietary modification or the proper diuretic and dosage.

Evaluation of Patients With Hypertension

The 2017 ACC/AHA guidelines expanded the recommended procedures for evaluation of patients with hypertension. The recommended evaluation includes an assessment of lifestyle and the identification of other cardiovascular risk factors, a search for causes of secondary hypertension, and determination of the presence or absence of target-organ damage and cardiovascular disease. Major cardiovascular risk factors include hypertension, cigarette smoking, obesity (body mass index [BMI] ≥30), physical inactivity, dyslipidemia, diabetes, microalbuminuria or glomerular filtration rate (GFR) <60 mL/min, and a family history of premature cardiovascular disease. Risk factors for organ damage include left ventricular hypertrophy, angina or prior MI, prior coronary revascularization, heart failure, stroke or transient cerebral ischemia (TCI), chronic kidney disease, peripheral arterial disease, and retinopathy. Current guidelines recommend the use of the Atherosclerotic Cardiovascular Disease Risk (ASCVD) calculator or the Systemic Coronary Risk Evaluation (SCORE), SCORE2, and SCORE2-OP (older persons) for determination of BP targets. For further discussion of risk assessment, see Chapter 5.

Physical examination of the patient should include the following:

- measurement of BP in both arms (from at least 2 readings taken on 2 or 3 different occasions)
- measurement of orthostatic BP
- ophthalmoscopic examination
- calculation of BMI
- measurement of waist circumference (considered the most important anthropometric factor associated with hypertensive risk)
- auscultation for carotid, abdominal, and femoral bruits
- examination of the thyroid gland
- examination of the heart and lungs
- examination of the abdomen for masses and aortic pulsation
- examination of the lower extremities for edema and pulses
- neurologic assessment

Tests to screen for secondary causes and exclude comorbidity (recommended before starting treatment) include an electrocardiogram, urinalysis, complete blood count, and serum chemistry studies, including uric acid tests and a fasting lipid profile. Patients with suspected cardiac morbidities should have a 2-dimensional echocardiogram. More extensive

testing for identifiable causes of hypertension is usually not indicated unless BP control is not achieved or if other clinical findings warrant further evaluation.

Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med.* 2010;363(23):2211–2219.

Christakoudi S, Tsilidis KK, Muller DC, et al. A Body Shape Index (ABSI) achieves better mortality risk stratification than alternative indices of abdominal obesity: results from a large European cohort. *Sci Rep*. 2020;10(1):14541.

Treatment of Hypertension

The primary objective of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Controlling systolic BP is the major concern, especially in patients older than 50 years, in whom systolic BP >140 mm Hg is a more important cardiovascular risk factor than diastolic BP. In addition, diastolic BP is usually controlled when the systolic goal is reached. Maintaining BP at <130/80 mm Hg decreases cardiovascular complications. In hypertensive patients with diabetes or renal disease, the BP goal is <120/80 mm Hg. These patients have a higher incidence of proteinuria, which is associated with hyperlipidemia, cardiovascular events, and overall higher morbidity. Although effective BP control can be achieved in most patients with hypertension, most of these patients require 2 or more medications to attain this state. It is important for patients to understand that lifelong treatment is usually necessary and that symptoms are not a reliable indicator of the severity of hypertension.

When selecting the appropriate therapy for a patient, the physician should consider multiple factors: stage of hypertension, target-organ disease, cardiovascular risk factors, cost, adherence, adverse effects, and comorbid conditions. In general, the higher the BP, the greater the damage to target organs; and the greater the risk factors for cardiovascular disease, the sooner treatment should be initiated. For example, patients with severe hypertension and encephalopathy require urgent treatment, whereas those with mild hypertension may wish to attempt lifestyle modifications before drug therapy is initiated.

Lifestyle Modifications

Obesity, smoking, sedentary lifestyle, excessive sodium intake, moderate daily alcohol consumption, and inadequate intake of vitamins and minerals, including potassium, calcium, magnesium, and folate, can contribute to the development of hypertension. Lifestyle modifications shown in Table 4-2 can decrease BP, enhance the effectiveness of antihypertensive drugs, and lower the risk of cardiovascular disease. The PREMIER trial demonstrated the benefit of adding behavioral modifications such as increased physical activity to the DASH (Dietary Approaches to Stop Hypertension) diet. Such healthful lifestyle habits are essential for the prevention and control of hypertension.

Pharmacologic Treatment

Several classes of drugs effectively lower BP and reduce the complications resulting from hypertension. The most commonly prescribed antihypertensive drugs include diuretics,

Table 4-2 2017 Recommended Nonpharmacologic Interventions for Prevention and Treatment of Hypertension[a]

			Approximate Impact on Systolic BP	
	Nonpharmacologic Intervention	**Dose**	**Hypertension**	**Normal Blood Pressure**
Weight/body fat	Weight loss	Expect a reduction of about 1 mm Hg for every 1-kg reduction in body weight in overweight patients.	–5 mm Hg	–2 to –3 mm Hg
Healthy diet	DASH eating plan	A diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	–11 mm Hg	–3 mm Hg
Dietary sodium	Reduced intake of dietary sodium	Optimal goal is <1500 mg/day, but aim for at least a 1000-mg reduction in most adults.	–5 to –6 mm Hg	–2 to –3 mm Hg
Dietary potassium	Enhanced intake of dietary potassium	Aim for 3500–5000 mg/day, preferably by consumption of a diet rich in potassium.	–4 to –5 mm Hg	–2 mm Hg
Increased physical activity	Aerobic	90–150 min/week; 65%–75% heart rate reserve	–5 to –8 mm Hg	–2 to –4 mm Hg
	Dynamic resistance	90–150 min/week; 50%–80%, 1 rep maximum	–4 mm Hg	–2 mm Hg
	Isometric resistance	3 sessions/week for 8–10 weeks	–5 mm Hg	–4 mm Hg
Alcohol consumption	Moderation in alcohol intake	In individuals who drink alcohol, reduce alcohol[b] to: Men: ≤2 drinks daily Women: ≤1 drink daily	–4 mm Hg	–3 mm Hg

BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.

[a] Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

[b] In the United States, 1 "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

Table 4-3 Oral Antihypertensive Drugs

Class	Drugs
Thiazide-type diuretics	Chlorthalidone, hydrochlorothiazide, indapamide, metolazone
Loop diuretics	Bumetanide, furosemide, torsemide
Potassium-sparing diuretics	Amiloride, triamterene
Mineralocorticoid receptor blockers	Eplerenone, spironolactone
β-Blockers	Atenolol, bisoprolol, metoprolol, metoprolol extended release, nadolol, nebivolol, propranolol, propranolol long-acting, timolol
β-Blockers with intrinsic sympathomimetic activity	Pindolol
ACE inhibitors	Captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin II antagonists	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Calcium channel blockers: nondihydropyridines	Diltiazem, verapamil
Calcium channel blockers: dihydropyridines	Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine
α_1-Blockers	Doxazosin, terazosin
Combined α- and β-blockers	Carvedilol, labetalol
Central α_2-agonists and other centrally acting drugs	Clonidine, clonidine patch, guanfacine, methyldopa, reserpine
Direct vasodilators	Hydralazine, minoxidil
Direct renin inhibitor	Aliskiren

ACE = angiotensin-converting enzyme.

Information from Chobanian AV, Bakris GL, Black HR, et al; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289(19):2565–2566.

β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). Table 4-3 lists these and other types of oral antihypertensive drugs. Figure 4-2 provides an algorithm for the treatment of hypertension.

The 2017 ACC/AHA guidelines focus on the pharmacologic treatment of hypertension. In these guidelines, thiazide-type diuretics are not necessarily the first-line therapy; CCBs, ACE inhibitors, ARBs, and β-blockers are alternatives. For patients who are not Black, the initial drug choice may be selected from 4 drug classes, on the basis of clinical setting and comorbidities: thiazide-type diuretics, CCBs, ACE inhibitors, and ARBs. For Black patients, the initial drug choice may be selected from 2 drug classes: thiazide-type diuretics and CCBs.

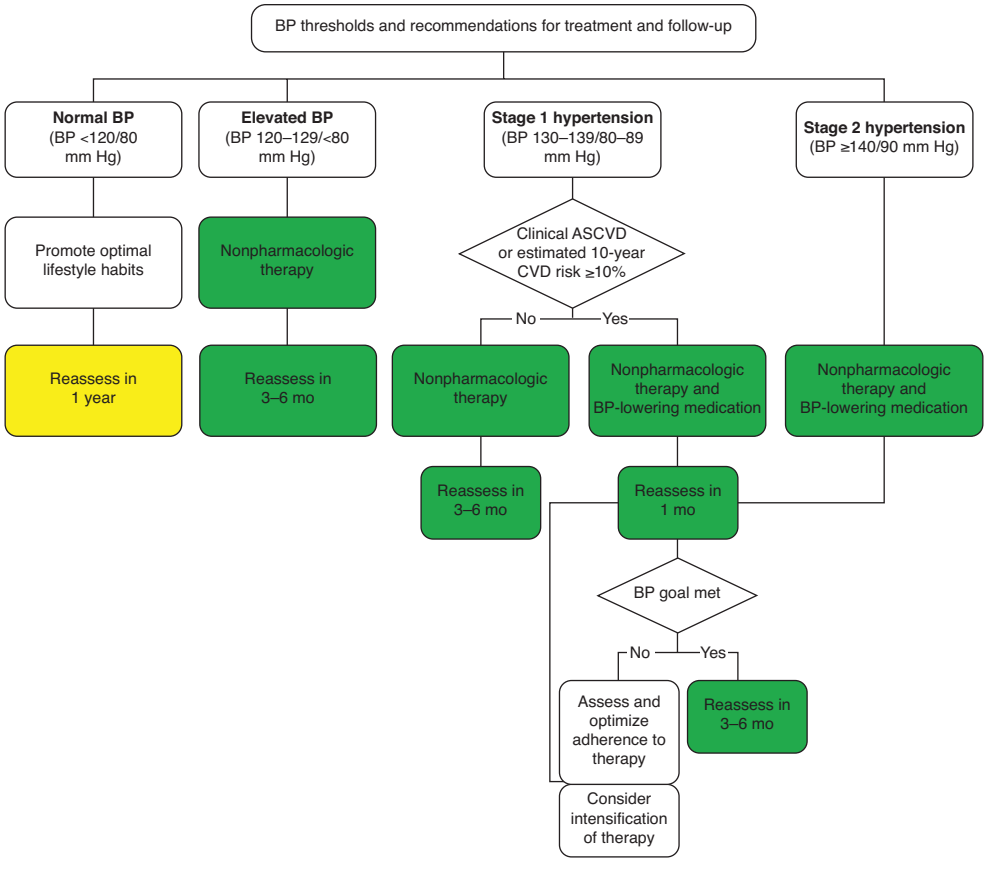

Figure 4-2 Blood pressure (BP) thresholds and recommendations for treatment and follow-up. ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease. *(Modified with permission. From Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Hypertension. *2018;71(6):e74. © 2017 American Heart Association, Inc.)*

Antihypertensive drugs

Diuretics Diuretics are categorized by their site of action in the kidney and are divided into thiazide, loop, and potassium-sparing types. Diuretics are particularly effective in individuals with salt-sensitive hypertension such as older persons and in Black persons.

Thiazide-type diuretics send more of a sodium load to the kidney's distal tubules, initially decreasing plasma volume and cardiac output through natriuresis. As the renin-angiotensin-aldosterone system compensates for the diminished plasma volume, cardiac output returns to normal and peripheral vascular resistance is lowered. Chlorthalidone can be used daily in patients with a GFR of <30 mL/min, and it has a strong safety and cardioprotective profile.

Loop diuretics act on the ascending loop of Henle and block sodium resorption, increasing free water loss and resulting in an initial decrease in plasma volume. As with thiazide-type diuretics, BP is eventually lowered because of decreased peripheral vascular resistance. Loop diuretics are used primarily in treating patients with moderate renal insufficiency.

Potassium-sparing diuretics may block the actions of aldosterone to prevent potassium loss from the distal tubule, or they may act directly on the distal tubule to inhibit aldosterone-induced sodium resorption in exchange for potassium. They are often used as adjuncts to the thiazide-type or loop diuretics to counteract potassium depletion, but they may be used alone in patients with suspected hyperaldosterone states.

Side effects of diuretics vary according to class. Thiazide-type diuretics can cause weakness, muscle cramps, impotence, hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia, hypomagnesemia, hyponatremia, azotemia, and pancreatitis. Thiazide-type diuretics may also unmask type 2 diabetes and aggravate lipid disorders. On a positive note, they may also slow the demineralization that occurs with osteoporosis. Loop diuretics can cause ototoxicity, as well as electrolyte abnormalities such as hypokalemia, hypocalcemia, and hypomagnesemia. Potassium-sparing diuretics can cause hyperkalemia, renal calculi, renal tubular damage, and gynecomastia.

Angiotensin-converting enzyme inhibitors ACE catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II, a potent vasoconstrictor, is the primary vasoactive hormone of the renin-angiotensin-aldosterone system, and it plays a major role in the pathophysiology of hypertension. ACE inhibitors block the conversion of angiotensin I to angiotensin II, resulting in vasodilation with decreased peripheral vascular resistance and natriuresis. They also decrease aldosterone production and increase levels of vasodilating bradykinins. Some ACE inhibitors stimulate production of vasodilatory prostaglandins. The efficacy of ACE inhibitors is enhanced when they are used in combination with diuretics, reducing hypokalemia, hypercholesterolemia, hyperglycemia, and hyperuricemia caused by diuretic therapy. ACE inhibitors are beneficial in patients with left ventricular dysfunction and with proteinuria, especially in patients with diabetes. ACE inhibitors may also help improve insulin sensitivity.

Adverse effects of ACE inhibitors include a dry cough (5%–20% of patients), angioneurotic edema, hypotension, hyperkalemia, abnormal taste, leukopenia, and proteinuria; in addition, 30% of patients may have a reduced GFR. Preexisting renal artery stenosis should be considered in this clinical situation. In patients with volume-reduced states, ACE inhibitors should be suspended and reassessed later. ACE inhibitors should be avoided in patients with a history of angioedema or known renal artery stenosis. They are contraindicated during pregnancy and in patients trying to become pregnant because of the adverse effects on fetal renal function and risk of fetal death.

Angiotensin II receptor blockers ARBs inhibit the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the angiotensin II receptors that are found in such tissues as vascular smooth muscle and the adrenal gland, resulting in decreased peripheral vascular resistance. ARBs are effective in managing hypertension in a variety of situations, including in patients with heart failure who are unable to tolerate ACE inhibitors. ARBs also have been associated with a reduced incidence of new-onset diabetes, and, like ACE inhibitors, they improve insulin sensitivity.

The adverse effects of ARBs are similar to those occurring with ACE inhibitors, although they occur less commonly with ARBs. The dry cough caused by ACE inhibitors generally does not occur with use of ARBs, and angioedema is rare. Like ACE inhibitors, ARBs

are contraindicated in pregnancy unless there is profound proteinuria; and in that situation, their use is very closely monitored. ACE inhibitors should not be combined with ARBs.

Calcium channel blockers CCBs block the entry of calcium into vascular smooth muscle cells, resulting in reduced myocardial contractility and decreased systemic vascular resistance. CCBs are divided into 2 types: dihydropyridine (DHP) and nondihydropyridine (non-DHP). DHP CCBs tend to be more potent vasodilators, whereas non-DPH CCBs have more marked negative inotropic effects.

Adverse effects of CCBs vary according to the agent but include constipation, headache, fatigue, dizziness, nausea, palpitations, flushing, edema, gingival hyperplasia, arrhythmias, and cardiac ischemia. Because of their negative inotropic effects, non-DHP CCBs should generally be avoided in patients with cardiac conduction abnormalities such as atrial fibrillation or heart failure associated with left ventricular dysfunction and in patients with acute MI. DHP CCBs may be helpful in patients with Raynaud syndrome and in some arrhythmias.

β-Blockers There are 2 types of β-adrenergic receptor sites: β_1 is present in vascular and cardiac tissue, and β_2 is found in the bronchial system. Circulating or locally released catecholamines stimulate β sites, resulting in vasoconstriction, bronchodilation, tachycardia, and increased myocardial contractility. β-Blockers inhibit these effects. They also decrease plasma renin, reset baroreceptors to facilitate lower BP, induce the release of vasodilatory prostaglandins, and decrease plasma volume; and they may have a central nervous system–mediated antihypertensive effect.

β-Blockers are divided into those that are nonselective (β_1 and β_2), those that are cardioselective (primarily β_1), and those that have intrinsic sympathomimetic activity (ISA). The cardioselective agents may be prescribed with caution in patients with pulmonary disease, diabetes, or peripheral arterial disease; but at higher doses they lose their β_1 selectivity and can cause adverse effects in these patients. Those agents with ISA minimize the bradycardia caused by other β-blockers. β-Blockers with α-blocking properties, such as carvedilol or labetalol, have additional vasodilatory effects caused by selective α_1-receptor blockade. In patients with heart failure due to systolic dysfunction, the use of certain β-blockers—particularly carvedilol, metoprolol succinate, and bisoprolol—reduces hospitalizations for heart failure and improves survival rates. Nebivolol has nitric oxide–potentiating vasodilatory effects. β-Blockers are beneficial in the treatment of atrial fibrillation and tachyarrhythmias, migraine, thyrotoxicosis, and essential tremor.

Adverse effects of β-blockers include bronchospasm, bradycardia, masking of insulin-induced hypoglycemia, insomnia, fatigue, depression, erectile dysfunction, impaired peripheral circulation, impaired exercise tolerance with blunted heart rate response (particularly in young patients), nasal congestion, and hypertriglyceridemia (except for β-blockers with ISA). Angina pectoris and increased BP can be precipitated by abrupt cessation of β-blocker therapy. β-Blockers should generally be avoided in patients with asthma, reactive airway disease, or second-degree or third-degree heart block.

Ophthalmic considerations Topical β-blockers are used in the treatment of glaucoma; they are effective in lowering intraocular pressure and have a long

duration of action. Systemic adverse effects may occur with the use of these topical agents, and such effects can be minimized by once-daily dosing and nasolacrimal occlusion for 3 minutes after drop instillation.

α_1-Blockers α_1-Adrenergic antagonists block postsynaptic α-receptors, resulting in arterial and venous vasodilation. Selective α_1-blockers have replaced older nonselective agents in the treatment of hypertension. Although these agents are not as effective as diuretics, CCBs, and ACE inhibitors, they may be prescribed as adjunct therapy in selected cases, not as a primary agent.

Adverse effects include the "first-dose effect," in which BP is decreased more with the initial dose than with subsequent doses, as well as orthostatic hypotension, headache, dizziness, and drowsiness.

Combined α-adrenergic and β-adrenergic antagonists Combined α-adrenergic and β-adrenergic antagonists block the action of catecholamines at both α-adrenergic and β-adrenergic receptor sites. Adverse effects are similar to those of other α-adrenergic and β-adrenergic antagonists.

Centrally acting adrenergic drugs Centrally acting adrenergic drugs are potent antihypertensive agents that stimulate presynaptic α_2-adrenergic receptors in the central nervous system, causing reductions in the tone and contractility of smooth muscle, cardiac output, and peripheral vascular resistance.

Adverse effects include fluid retention, dry mouth, drowsiness, dizziness, orthostatic hypotension, rash, impotence, and hepatitis; positive results on the direct antiglobulin (Coombs) test and the antinuclear antibody (ANA) test; and heart failure in patients with decreased left ventricular dysfunction. There may also be severe rebound hypertension if the drug is abruptly discontinued.

Methyldopa continues to be widely used in pregnancy because of its proven safety. Older centrally acting sympatholytic agents (eg, reserpine) have significant adverse effects and are seldom used.

Direct vasodilators Direct-acting vasodilators such as minoxidil and hydralazine decrease peripheral vascular resistance by direct arterial vasodilation. They are generally reserved for special situations, such as pregnancy or intractable hypertension. They should be avoided or used with caution in patients with ischemic heart disease.

Adverse effects include headache, tachycardia, edema, nausea, vomiting, a lupuslike syndrome, and hypertrichosis. Because of the sympathetic hyperactivity and the sodium and fluid retention caused by direct vasodilators, they are often used in conjunction with diuretics or β-blockers.

Direct renin inhibitors Direct renin inhibitors (DRIs) are more likely to be effective in younger White patients, who, in general, have a more active renin system, and in any patients receiving diuretics or CCBs, in whom the renin system has been activated. The main adverse effect of DRIs is possible diarrhea at higher doses. A DRI should not be combined with an ACE inhibitor or an ARB.

Combination therapy Combination therapy usually includes small doses of a diuretic, which potentiates the effects of other drugs such as ACE inhibitors, ARBs, and β-blockers. This

therapy may improve patient adherence and reduce BP to target levels more quickly than other classes of drugs. Another advantage of combination therapy is that low-dose therapy with 2 antihypertensive drugs is associated with fewer adverse effects than is higher-dose therapy with a single agent.

Unacceptable combinations include the dual inhibition of the renin-angiotensin-aldosterone system, which can increase the risk of syncope, hypotension, and renal dysfunction. The combination of a direct renin inhibitor with an ACE inhibitor or ARB can result in a nonfatal stroke, hyperkalemia, hypotension, and renal complications.

Parenteral antihypertensive drugs Parenteral antihypertensive therapy is indicated for immediate reduction of BP in hypertensive emergencies. Sodium nitroprusside, a direct arterial and venous vasodilator, is the drug of choice for most hypertensive emergencies. Nitroglycerin may be preferable in patients with severe coronary insufficiency or advanced kidney or liver disease. Labetalol is also effective and is the drug of choice in hypertensive emergencies that occur in pregnancy. Esmolol is a cardioselective β-adrenergic antagonist that can be used in hypertensive emergencies when β-blocker intolerance is a concern; it is also useful in treating aortic dissection. Phentolamine is effective in managing hypertension with acute drug intoxication or withdrawal. Nicardipine is a CCB that can be administered intravenously for postoperative hypertension. Intravenous enalapril is an ACE inhibitor that can be effective in the treatment of postoperative hypertension, although unpredictable results have been reported with its use. Hydralazine has a long-established safety profile, making it useful in pregnancy-related hypertensive emergencies.

Future Treatments and Targets for Hypertension

Data from the Conduit Artery Function Endpoint (CAFE) study showed that different classes of antihypertensive drugs have different effects on brachial versus central aortic systolic and pulse pressures and that central pressures may be a better predictor of cardiovascular outcomes in response to treatment. The Strong Heart Study also showed that central aortic pressures may be a better predictor of target end-organ damage and outcomes than are conventional brachial pressures. Soluble guanylate cyclase activators lower central aortic pressures by increasing cyclic guanosine monophosphate levels in target tissues, resulting in vasodilation and an antiproliferative effect. This drug may also lower BP, inhibit cardiac hypertrophy, and reduce large-artery stiffness.

Other investigational agents, known as *advanced glycation end-product cross-link breakers,* target vascular wall thickness and its effects on BP. The accumulation of advanced glycation end products in the vascular wall increases large artery stiffness, impairs endothelial function, and raises BP. Targeting these molecules to reduce their presence in vascular walls may decrease vessel stiffness and lower BP. Other potential future therapies include RNA interference to target angiotensin production in the liver, the development of a vaccine against hypertension, and the use of acupuncture.

With the increasing use of telehealth and personal electronic devices, a digital transformation may shift the delivery of some aspects of health care away from hospitals and clinics to settings such as the patient's home. Home BP management with automated devices that transmit BP data to providers and the electronic health record allows continuous

monitoring. APBM provides a more comprehensive assessment of BP over the course of the day and is a better predictor of health outcomes than BP measured in the clinic. Apps are also helping patients access their health information and encouraging behavioral change such as increasing physical activity or eating a healthier diet. Other apps provide noninvasive BP measurements that are based on pulse transit time. Big data, creation of precision real-time cohorts, and artificial intelligence using integrative apps have the potential to change the care of hypertensive patients through improved access, better monitoring, more accurate outcome prediction, improved clinical decision making, better adherence to guidelines, greater patient involvement, and a deeper understanding of disease pathogenesis.

Nonpharmacologic device-based therapies are being investigated to treat resistant hypertension. These approaches include renal denervation, baroreflex activation therapy, carotid body ablation, central iliac arteriovenous anastomosis, deep brain stimulation, median nerve stimulation, and vagal nerve stimulation.

Regenerative medicine using modalities such as stem cell therapy might reduce cardiac degeneration by regenerating cardiomyocytes or by inducing existing cardiomyocytes to enter the cell cycle and proliferate. Finally, changes in the gut microbiota composition associated with chronic multifactorial conditions such as obesity, hypertension, diabetes, and cardiovascular disease might be fruitful areas of future research.

Dzau VJ, Balatbat CA. Future of hypertension. *Hypertension.* 2019;74(3):450–457.

Ng FL, Saxena M, Mahfoud F, Pathak A, Lobo MD. Device-based therapy for hypertension. *Curr Hypertens Rep.* 2016;18(8):61.

Special Considerations

Ischemic Heart Disease

For patients with hypertension and stable angina pectoris, a β-blocker is generally the initial drug of choice; alternatively, CCBs can be used. ACE inhibitors and β-blockers are commonly used as first-line drugs in hypertensive patients with acute coronary syndromes (unstable angina or MI). In post-MI patients, β-blockers, ACE inhibitors, potassium-sparing diuretics, and mineralocorticoid receptor antagonists are beneficial.

Heart Failure

In asymptomatic patients with hypertension and ventricular dysfunction, ACE inhibitors and β-blockers are commonly used. In patients with symptomatic ventricular dysfunction or end-stage heart failure, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, loop diuretics, and β-blockers—especially carvedilol, bisoprolol, or nebivolol—are useful.

Diabetes and Hypertension

As mentioned earlier, hypertensive patients with diabetes usually require 2 or more antihypertensive drugs to achieve a BP goal of <130/80 mm Hg. ACE inhibitors or ARBs are preferred agents in the management of patients with hypertension and diabetic nephropathy. If the target BP is not achieved with an ACE inhibitor or ARB, the preferred second-line

therapy is the addition of a thiazide diuretic, followed by β-blockers and/or CCBs, which also reduce cardiovascular complications in these patients.

Chronic Renal Disease

Aggressive treatment, often with 3 or more drugs, may be necessary to achieve a BP goal of <130/80 mm Hg and to prevent deterioration of renal function and cardiovascular complications in hypertensive patients with chronic renal disease. ACE inhibitors and ARBs favorably alter the progression of diabetic and nondiabetic nephropathy. However, as the GFR nears 20 mL/min, less aggressive treatment may be appropriate, particularly in patients with renin-angiotensin-aldosterone system suppression.

Cerebrovascular Disease

The combination of an ACE inhibitor and the appropriate diuretic lowers the risk of recurrent stroke. The optimal BP level during an acute stroke remains undetermined, but consensus favors intermediate control in the range of 160/100 mm Hg until patient stabilization is achieved.

Obesity and Metabolic Syndrome

Obesity (BMI ≥30) is a risk factor for the development of hypertension and has become a major concern in the United States, where an estimated 160 million adults are overweight or obese. Closely related to obesity is *metabolic syndrome.* This syndrome is characterized by the presence of 3 or more of these conditions: central (abdominal) obesity, elevated triglyceride level, reduced high-density lipoprotein cholesterol level, hypertension, and elevated fasting blood glucose levels. Patients with these conditions should adopt healthful lifestyle habits and, if necessary, use pharmacologic therapy (except for thiazide-type diuretics, which may aggravate this syndrome). See Chapter 3 for additional discussion of metabolic syndrome.

Obstructive Sleep Apnea Syndrome

Hypertension and obstructive sleep apnea syndrome (OSAS) often coexist. OSAS is a sleep-related breathing disorder with cardinal signs including obstructive apneas, hypopneas, and sleep disturbances with snoring, restlessness, or resuscitative snorts. This disruption leads to reduced sleep, daytime fatigue, and poor concentration and has been associated with the development of heart disease and metabolic syndrome. There is an increased prevalence and incidence of hypertension in these patients as well as an observed dose-response effect between the severity of OSAS and the likelihood of hypertension. Treatment of OSAS can lower BP by clinically significant levels.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is a risk factor for cardiovascular disease, but regression of the hypertrophy is possible with treatment of hypertension. All antihypertensive drug classes, except the direct vasodilators, are effective in treating left ventricular hypertrophy.

Peripheral Arterial Disease

The risk factors for peripheral arterial disease parallel those for ischemic heart disease in patients with hypertension. All classes of antihypertensive agents are useful in treating hypertensive patients with peripheral arterial disease.

Ophthalmic considerations Most individuals experience a physiologic drop in systemic BP (dipping pattern) during sleep; BP normalizes when these individuals awaken. This decrease in BP may be exacerbated when antihypertensive medications are taken at night. Systemic nocturnal hypotension may be a risk factor for progressive glaucoma despite low intraocular pressure and for nonarteritic anterior ischemic optic neuropathy (NAION). OSAS may also increase the risk of NAION and normal-tension glaucoma by means of several potential mechanisms, including impaired autoregulation of optic nerve head blood flow, optic nerve vascular dysregulation, and direct optic nerve damage due to prolonged hypoxia. OSAS also plays a role in the development retinal microaneurysms, hypertensive retinopathy, and the intraocular production of postischemic molecules that are associated with neovascularization, apoptosis, and macular edema.

Orthostatic Hypotension

Orthostatic hypotension is defined as a postural drop in systolic BP of >10 mm Hg associated with dizziness or fainting. It occurs more frequently in older patients with systolic hypertension; in patients with diabetes; and in those taking diuretics, vasodilators, or certain psychotropic drugs. In these individuals, BP should be monitored while they are in the upright position, and hypovolemia should be avoided. Also, medication dosages should be carefully titrated, and various shorter-acting drugs considered for these patients.

Hypertension in Older Patients

Hypertension is present in most individuals older than 65 years. Treatment recommendations for patients in this age group are generally the same as for others with hypertension. In older patients with isolated systolic hypertension, the preferred treatment is a diuretic with or without a β-blocker, or a DHP CCB alone. Diastolic BP of <75 mm Hg increases these patients' risk of stroke and should be avoided.

Antihypertensive drug therapy in older patients can cause adverse effects that increase the risk of falls, such as dizziness and hypotension, because diastolic blood pressure typically decreases after the age of 60. Appropriate precautions should be taken to reduce this risk and enhance patient safety.

Dementia occurs more commonly in individuals with hypertension. In some patients, antihypertensive therapy may slow the progression of cognitive impairment.

Women and Pregnancy

Because the use of oral contraceptives increases the risk of hypertension, women taking oral contraceptives should have regular BP checks. Hypertension in women who are pregnant may be classified as follows:

- *preeclampsia:* hypertension, proteinuria, generalized edema, and possibly coagulation and liver function abnormalities after 20 weeks' gestation
- *eclampsia:* same abnormalities as for preeclampsia, plus generalized seizures
- *chronic hypertension:* BP >140/90 mm Hg before 20 weeks' gestation
- *chronic hypertension with superimposed preeclampsia or eclampsia*
- *transient hypertension:* hypertension without proteinuria or central nervous system manifestations during pregnancy, with the return of normal BP within 10 days of delivery

Hypertension during pregnancy can potentially increase maternal and fetal morbidity and mortality. However, if pharmacologic treatment for hypertension is planned, the possible adverse effects of antihypertensive drug therapy on fetal development must be considered. According to the AHA 2022 Scientific Statement, monotherapy with labetalol or methyldopa is widely established for initial treatment of hypertension in pregnancy. ACE inhibitors and ARBs are contraindicated in pregnancy because of teratogenic effects; they should also be avoided in women who are likely to become pregnant.

Garovic VD, Dechend R, Easterling T, et al. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. *Hypertension*. 2022;79(2):e21–e41.

Children and Adolescents

Considerable advances have been made in the detection, evaluation, and management of hypertension in children and adolescents. Current evidence indicates that primary hypertension in young individuals occurs more commonly than previously recognized and has substantial long-term health implications. There is little doubt that obesity in young people is a predictor for developing hypertension as well as associated metabolic risk factors. Hypertension in individuals aged 3–18 years is defined as average systolic BP and/or diastolic BP that is in the 95th percentile or higher for sex, age, and height, taken on 3 or more occasions. BP between the 90th and 95th percentiles in childhood is designated as *elevated* and is an indication for lifestyle modifications. The National High Blood Pressure Education Project recommends that children older than 3 years have their BP measured when they are examined in a medical setting.

Children and adolescents who are hypertensive are frequently overweight, and some may have sleep disorders. Secondary hypertension occurs more commonly in children than in adults.

Indications for initiating antihypertensive drug therapy in children include uncontrolled hypertension despite nonpharmacologic measures, symptomatic hypertension, secondary hypertension, hypertensive target-organ damage, and hypertension in patients

with diabetes. Acceptable drug choices for treating hypertension in children include diuretics, β-blockers, ACE inhibitors, ARBs, and CCBs.

Flynn JT, Kaelber DC, Baker-Smith CM, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3): e20171904.

Withdrawal Syndromes

Hypertension can be associated with withdrawal from alcohol or drugs such as cocaine, amphetamines, and opioid analgesics. Withdrawal syndromes can occur with acute drug intoxication or as the result of abrupt discontinuation of a drug after long-term use. Phentolamine, sodium nitroprusside, and nitroglycerin are all effective in the immediate management of hypertension in these situations. β-Blockers should not be used because unopposed α-adrenergic stimulation may exacerbate the hypertension.

Abrupt discontinuation of antihypertensive therapy can cause severe rebound hypertension. This occurs most commonly in patients taking centrally acting adrenergic agents (particularly clonidine) or β-blockers, but it can occur with other drug classes as well, including diuretics. When an acute withdrawal syndrome occurs and parenteral antihypertensive treatment is necessary, sodium nitroprusside is the drug of choice.

Monoamine Oxidase Inhibitor Drug and Food Interactions

Monoamine oxidase inhibitors taken with certain drugs or with tyramine-containing foods can increase catecholamine levels, thereby causing accelerated hypertension. Phentolamine, sodium nitroprusside, and labetalol are effective for treating this type of hypertension.

Hypertensive Crisis

Patients with severe BP elevation and acute target-organ damage (eg, encephalopathy, MI, unstable angina, pulmonary edema, stroke, head trauma, eclampsia, aortic dissection, optic disc edema) should be admitted to the hospital for emergency parenteral antihypertensive therapy. Patients with marked BP elevation but without target-organ damage may not require hospital admission, but they should be treated urgently with combination oral antihypertensive drugs. Identifiable causes of hypertension should be sought, and these patients should be carefully monitored for target-organ damage.

Ophthalmic considerations Retinal vascular complications (hypertensive retinopathy, retinal vein occlusions, retinal arterial occlusions), glaucoma, ischemic optic neuropathy, microvascular cranial nerve palsies, and stroke-related disorders of the afferent and efferent pathways of the visual system are commonly associated with hypertension. Moreover, patients with poorly controlled hypertension who undergo ophthalmic surgery may be more susceptible to intraoperative and postoperative complications.

Table 4-4 Classification of Hypertensive Retinopathy With Systemic Associations

Grade of Retinopathy	Retinal Signs	Systemic Associations
None	No detectable signs	None
Mild	Generalized and/or focal arteriolar narrowing, arteriovenous nicking, opacity ("copper wiring") due to thickening of arteriolar wall, or a combination of these signs	Modest association with risk of stroke, coronary artery disease, and death
Moderate	Hemorrhage (blot, dot, or flame-shaped), microaneurysm, cotton-wool spot, hard exudates, or a combination of these signs	Strong association with stroke, cognitive decline, and death from cardiovascular causes
Malignant	Signs of moderate retinopathy plus swelling of the optic nerve head	Strong association with death

Modified with permission from Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004; 351(22):2314. © 2004 Massachusetts Medical Society.

There is strong evidence that certain signs of hypertensive retinopathy, independent of other risk factors, are associated with increased cardiovascular risk. Based on these reported associations, a simplified classification of hypertensive retinopathy was proposed in 2004 (Table 4-4).

The renin-angiotensin system (RAS) exists in ocular tissues as well as in the kidneys and is overexpressed in the retina of individuals with diabetes. In the retina, angiotensin II activates receptors that stimulate pathways involved in diabetic retinopathy, such as inflammation, oxidative stress, cell proliferation, pericyte migration, remodeling of extracellular matrix, angiogenesis, and fibrosis. RAS blockade is thought to attenuate or inhibit these pathogenic effects.

The 2017 ACC/AHA guidelines emphasize the importance of patient assessment and education, increasing the motivation of patients to take their prescribed medications and to maintain healthful lifestyle habits. As members of the health care team, ophthalmologists have an important role in the identification, monitoring, and shared management of patients with hypertension.

CHAPTER 5

Hyperlipidemia and Cardiovascular Risk

Highlights

- Therapeutic lifestyle changes remain an essential modality in the management of hyperlipidemia.
- A number of tools (eg, HeartScore, the American Heart Association's pooled cohort equations, QRISK, MESA) are available to assess the cardiovascular risk for an individual patient.
- Numerous clinical trials have shown that effective reduction of low-density-lipoprotein cholesterol (LDL-C) levels substantially decreases the risk of coronary heart disease and stroke.
- Statin therapy is recommended for most dyslipoproteinemic adult patients with cardiometabolic risk.
- Patients at high risk of a cardiovascular event who do not attain their LDL reduction goals from statins alone should consider adding ezetimibe or a PCSK9 inhibitor.

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States and in most of the developed world, accounting for more deaths than all forms of cancer combined. Numerous major studies have confirmed that lowering elevated LDL-C levels reduces the risk of CHD. The National Cholesterol Education Program (NCEP) provided 3 sets of guidelines for treating elevated blood cholesterol levels in adults: Adult Treatment Panel (ATP) I, II, and III. The ATP III guidelines recommended total cholesterol levels of <200 mg/dL, LDL-C levels of <100 mg/dL, high-density-lipoprotein cholesterol (HDL-C) of ≥60 mg/dL (for HDL, more is better), and triglyceride levels of <150 mg/dL.

In 2013, a series of reports published in the United States questioned the value of having specific targets for LDL-C levels. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines prioritize the estimation of lifetime atherosclerotic cardiovascular disease (ASCVD) risk in children, adolescents, and young adults and promotion of lifestyle risk reduction across this age spectrum. These reports recommend the individual assessment of each patient's cardiovascular risk, followed by aggressive treatment

with statin drugs in those most likely to benefit. These recommendations are discussed later in this chapter.

Lipoproteins, Cholesterol, and Cardiovascular Disease

Cholesterol and triglycerides are transported in the body by *lipoproteins.* The various classes of lipoprotein differ in the relative concentrations of their components: cholesterol, triglycerides, phospholipids, and proteins *(apolipoproteins).* Chylomicrons carry triglycerides after dietary lipid absorption, whereas *very low-density lipoproteins (VLDLs),* which are produced by the liver, carry most circulating triglycerides. *Low-density lipoprotein,* or "bad cholesterol," is a product of the metabolism of VLDL and intermediate-density lipoprotein and is the primary carrier of cholesterol. *High-density lipoprotein,* or "good cholesterol," is the smallest and densest lipoprotein particle. The result of the inflammatory interaction among these lipoproteins, macrophages, and the cellular components of the arterial wall is called *atherosclerosis.* Although patients' cholesterol levels are what is typically measured, it is the lipoproteins that interact with the arterial wall, producing plaques. The narrowing of the arterial lumen that results from plaque growth or the rupture of a plaque with subsequent thrombosis leads to cardiovascular disease (CVD), which includes myocardial infarction (MI), stroke, aortic disease, and peripheral arterial disease.

Risk Assessment

Approximately half of the adults in the United States and Europe are estimated to have cholesterol levels that put them at significant risk. A *fasting lipoprotein profile* (measuring total cholesterol, LDL-C, HDL-C, and triglyceride levels) helps determine an individual's risk status. The US Centers for Disease Control and Prevention and the AHA recommend screening for lipid disorders every 4–6 years in adults older than 20 years at low risk for CVD, and more frequently in those with multiple cardiovascular risk factors. For adults older than 40 years, the frequency of testing is determined by an assessment of the 10-year risk of a cardiovascular event.

Experimental studies directly support the central role of LDL in atherogenesis, and lowering LDL-C levels is associated with a reduction in CVD risk. Therefore, the primary role of LDL-C measurement is to identify patients without known ASCVD who would benefit from treatment with statins and to assess therapeutic response. Conversely, HDL-C appears protective against atherosclerosis because of its anti-inflammatory properties and its ability to transport cholesterol from vessel walls to the liver for disposal. In general, current guidelines recommend a high HDL concentration and a low LDL concentration to decrease CVD risk.

Other CHD risk factors, such as hypertension, smoking, diabetes, short sleep duration, obesity, and limited physical activity should be assessed and managed appropriately in all adults (Table 5-1). The INTERHEART study (2004), which involved more than 15,000 patients with acute MI versus approximately 15,000 controls in 52 countries, found that current

Table 5-1 Risk Factor Modification Treatment Goals

Risk Factor	Goal	Intervention
Blood pressure	<130/80 mm Hg Lower goal if patient has chronic kidney disease or diabetes	Weight control, increased physical activity, alcohol moderation, sodium reduction, medications
Smoking	Smoking cessation; avoidance of environmental tobacco smoke	Smoking cessation programs, nicotine replacement, bupropion, varenicline
Lipid management	Decreased LDL-C with goal based on overall cardiovascular risk	Diet low in saturated fat, increased omega-3 fatty acids, weight control, increased physical activity, statins
Diabetes	HbA_{1c} <7% or tailored to individual patient	Diet, weight control, oral hypoglycemic agents, insulin
Physical activity	150 minutes/week moderate exercise or 75 minutes/week vigorous exercise	Walking, biking, swimming, gardening, household work, weight training
Weight management	BMI 18.5–24.9 kg/m^2 Waist circumference: ≤102 cm men ≤88 cm women	Physical activity, control of caloric intake, behavioral programs

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; LDL-C = low-density-lipoprotein cholesterol.

Information from Smith S, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Circulation.* 2006;113(19): 2363–2372.

smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, and an elevated apolipoprotein B/apolipoprotein A-I ratio increased the risk of acute MI, while moderate or strenuous exercise, daily consumption of fruits and vegetables, and daily consumption of small amounts of alcohol were protective.

A number of risk assessment tools are available to estimate the 10-year risk of a cardiovascular event, including the pooled cohort equations on the American Heart Association website (United States), QRISK (United Kingdom), HeartScore (Europe), and MESA (Multi-Ethnic Study of Atherosclerosis; United States). Physicians are encouraged to use the risk tool best suited to the individual patient because relative cardiac risk varies among national, ethnic, and racial groups. Use of these tools can help guide the clinician in identifying patients requiring aggressive treatment and those most likely to benefit from such treatment.

2018 Prevention Guidelines Tool CV Risk Calculator. Accessed June 29, 2022. https://static.heart.org/riskcalc/app/index.html#!/baseline-risk

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *J Am Coll Cardiol.* 2019;73(24):e285–e350.

HeartScore. European Association of Preventive Cardiology. Accessed June 29, 2022. www.heartscore.org

MESA 10-Year CHD Risk With Coronary Artery Calcification. Accessed June 29, 2022. https://mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx
QRISK3-2018 Risk Calculator. Accessed June 29, 2022. http://qrisk.org

Management

In simplest terms, the management of hyperlipidemia consists of matching the intensity of LDL-lowering therapy with the absolute risk: the higher the risk, the lower the target LDL level. This approach is based primarily on data from clinical trials and epidemiologic studies, which, as mentioned previously, have suggested that a direct relationship exists between the level of LDL-C and the risk of CHD. The ATP III guidelines suggested measuring fasting lipoprotein levels in patients with hyperlipidemia and/or hyperlipoproteinemia. The clinician should also assess the patient for the presence of other risk factors (see Table 5-1) and the presence of clinical atherosclerotic disease, including clinical CHD, cerebrovascular or peripheral arterial disease, or abdominal aortic aneurysm. A risk calculator can help the clinician determine a patient's 10-year risk for CHD based on these factors on a scale from lower risk to high risk. LDL treatment goals are determined based on the patient's risk level.

When treatment with a statin drug is indicated, the 2018 guidelines from the ACC (www.acc.org) and AHA (www.heart.org) recommend that patients be given the maximum tolerated intensity of the statin. Similarly, in 2016, the European Society of Cardiology (ESC; www.escardio.org) recommended that patients undergo a risk assessment (systematic coronary risk evaluation, or SCORE) and that high-risk patients lower their LDL-C levels to 100 mg/dL, and very high-risk patients to 70 mg/dL. These groups no longer advocate treatment to a preset generalized goal but instead recognize that any reduction in LDL-C is beneficial and that some patients should be treated more aggressively because of their higher cardiovascular risk.

Lifestyle Modification

Therapeutic lifestyle changes, including dietary modifications, weight management, and increased physical activity, should be initiated. A diet that is high in fruits, vegetables, fiber, and omega-3 fatty acids and low in both red meat and foods with a high glycemic index, along with substitution of monounsaturated and polyunsaturated fats for saturated and trans fats, has repeatedly been shown to lower cardiovascular risk and mortality. If LDL goals are not achieved by lifestyle changes alone, drug therapy should be introduced and, if necessary, advanced. Current US and European guidelines strongly support the use of statin drugs as the primary intervention.

Once the goal LDL levels have been achieved, other lipid and nonlipid risk factors can be modified. Elevated triglyceride levels may respond to increased physical activity or weight management, but if the triglyceride levels are ≥200 mg/dL after the LDL goal is reached, a secondary treatment goal would be a non–HDL-C (ie, total cholesterol minus HDL) level of 30 mg/dL higher than the LDL goal. Statin therapy could also be considered if the ASCVD 10-year risk is >7.5% and the triglyceride level is ≥175 mg/dL.

Clinicians should consider the impact of social determinants of health in the modification of ASCVD risk. Health literacy should be assessed every 4–6 years, and barriers to access to healthful food considered. Other psychosocial stressors may affect blood pressure control, weight reduction efforts, or attempts at glycemic control. See Chapter 1 for other impacts of social determinants of health.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary. *Circulation.* 2019;140(11): e563–e595.

Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37(39):2999–3058.

The Role of Statins

For virtually all patients whose LDL-C goals cannot be achieved by therapeutic lifestyle changes alone, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more popularly known as *statins,* are the first choice for medical therapy. Table 5-2 presents information about the dosage and lipid-lowering effects of statins. Multiple trials involving the use of statin drugs have reinforced the value of LDL-lowering therapy in reducing the risk of ASCVD. Moreover, the statins are the only class of oral drugs whose use has been shown to improve overall mortality in primary and secondary prevention. The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) study (2000), the Heart Protection Study (2002), and the PROVE IT study (2004), among others, each demonstrated a decreased risk of major cardiovascular events in patients whose LDL-C levels had been lowered with statins. Findings from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; 2010) suggest that statins—which are known to lower C-reactive protein levels in addition to having positive effects on hyperlipidemia—may decrease the risk of stroke, coronary artery disease, and death in apparently healthy persons without hyperlipidemia but with a C-reactive protein level >2.0 mg/L. The beneficial effects of statins arise from the reduction of LDL-C levels, stabilization of atherosclerotic plaques, and decreased atherogenic inflammation.

Table 5-2 Intensity of Statin Therapy With Daily Dosing

High-intensity statin therapy (reduces LDL-C by ≥50%)	
Atorvastatin 40–80 mg	Rosuvastatin 20–40 mg
Moderate-intensity statin therapy (reduces LDL-C by 30%–50%)	
Atorvastatin 10–20 mg	Pitavastatin 2–4 mg
Fluvastatin 40 mg twice daily	Pravastatin 40–80 mg
Fluvastatin XL 80 mg	Rosuvastatin 5–10 mg
Lovastatin 40–80 mg	Simvastatin 20–40 mg

Information from Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889–2934.

The 2013 ACC/AHA guidelines, updated in 2018, identified 4 patient groups likely to benefit from statin use:

- individuals with ASCVD
- individuals with LDL-C levels of ≥190 mg/dL
- individuals aged 40–75 years with diabetes (but without ASCVD) and LDL-C levels of 70–189 mg/dL
- individuals aged 40–75 years without diabetes or ASCVD with LDL-C levels of 70–189 mg/dL and an estimated 10-year ASCVD risk of >7.5%

In these patients, the ACC/AHA recommendation is moderate to maximal intensity statin therapy (see Table 5-2), while those intolerant of high-intensity therapy or those at lower estimated cardiovascular risk may be treated with moderate intensity therapy. Current ESC and other international guidelines are similar, and they also recommend assessment of the risk for each patient, with LDL-C goals tailored to the patient's level of cardiovascular risk. Large studies have not established exact LDL-C goals, but many study authors recommend an LDL-C level of <100 mg/dL for high-risk patients and <70 mg/dL for very high-risk individuals. When the clinician is undecided about initiating statin therapy for a patient, it is reasonable to consider obtaining a coronary artery calcium score to guide therapeutic decisions.

Although statin drugs are largely safe and effective, patients taking them must be monitored for serious adverse effects, especially in the first few months of treatment. Adverse effects of statin use are rare but can include elevated hepatic transaminases, diarrhea, liver failure, polyneuropathy, and myopathy. Statins can potentially cause drug–drug interactions, which predominantly increase their concentrations and thereby raise the risk of myopathy and rhabdomyolysis. Simvastatin should not be started at or increased to a dose of 80 mg per day because of the high risk of muscle injury. The risk of myopathy is also increased when simvastatin is used in conjunction with other medications, including amiodarone, some fibrates (gemfibrozil), and some calcium channel blockers. Cerivastatin was voluntarily withdrawn from the market after more than 52 reports of rhabdomyolysis and death related to its use. Pregnant women should not take statin drugs because of possible teratogenic effects.

Other LDL-Lowering Drugs

When maximal statin therapy fails to reduce LDL to the desired level in high-risk patients, other drugs such as a cholesterol absorption inhibitor (ezetimibe) or PCSK9 inhibitor (evolocumab, alirocumab) may be added. The PCSK9 inhibitors are injectable drugs consisting of monoclonal antibodies to proprotein convertase subtilisin kexin 9 (PCSK9), which lower LDL levels and reduce the risk of cardiovascular events even when added to maximal statin therapy. Although the PCSK9 antibody agents have been shown to reduce LDL-C levels by 60%–70%, their expense and delivery method (injection) have limited their outpatient use thus far. A novel nonstatin LDL-lowering agent, bempedoic acid targets the cholesterol synthesis pathway in the liver but not in muscles, making it a possible option for patients intolerant of statins. Although studies have demonstrated its LDL-lowering effects, further research is needed to assess the effect on ASCVD outcomes and mortality.

Other drugs used to lower LDL-C levels include nicotinic acid, bile acid sequestrants, fibric acids, and cholesterol absorption inhibitors. Although many of these drugs have

been shown to lower LDL-C levels, there is a general lack of large randomized controlled trials demonstrating their effects on ASCVD or mortality. Fibrates and niacin are not recommended as adjuncts to statin therapy to reduce LDL cholesterol levels. These drugs are often used worldwide; however, the most recent ACC/AHA and ESC guidelines do not support their use in place of statins when statin therapy is effective and well tolerated.

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. *J Am Coll Cardiol.* 2017;70(14):1785–1822.

Piepoli MF, Hoes AW, Agewall S, et al; Authors/Task Force Members. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol.* 2016;23(11):NP1–NP96.

Metabolic Syndrome

Metabolic syndrome, also referred to as *insulin resistance syndrome,* comprises a constellation of lipid and nonlipid risk factors of metabolic origin. In 2009, the International Diabetes Federation and other organizations developed a consensus definition for metabolic syndrome that includes central (abdominal) obesity (as measured by waist circumference), elevated triglyceride levels, high blood pressure, reduced HDL-C, and elevated fasting blood glucose.

Metabolic syndrome is closely linked to insulin resistance. Excess body fat (particularly abdominal fat) and physical inactivity promote impaired responses to insulin; such impaired responses may also result from genetic predisposition. The risk factors for metabolic syndrome are highly concordant; in aggregate, they increase the risk of CHD at any given LDL level. Insulin resistance and adipocyte cytokines associated with metabolic syndrome seem to play a crucial role in causing inflammatory changes that contribute to ASCVD. Management of metabolic syndrome includes those measures previously discussed for elevated LDL and triglyceride levels, as well as treatment of hypertension and the use of aspirin to reduce the prothrombotic state in CHD patients. See Chapter 3 for further discussion of metabolic syndrome.

Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120(16):1640–1645.

Ophthalmic considerations Hyperlipidemia is a significant risk factor for ischemic heart disease, cerebrovascular disease, and peripheral arterial disease. The ophthalmologist may be the first physician to detect or recognize manifestations of atherosclerosis, particularly transient monocular visual loss, retinal vascular emboli or occlusions, ischemic optic neuropathy, or cortical visual field deficits from a previous cerebral infarction. Detection of atherosclerosis may initiate a diagnostic evaluation that reveals significant carotid artery stenosis or coronary artery disease.

Corneal arcus, an irreversible lipid deposit at the corneal limbus, is associated with age and hyperlipidemia. In the Blue Mountains Eye Study, the presence of arcus in persons aged 49 years and older was associated with higher total cholesterol and triglyceride levels.

Xanthomas are lipid deposits in the connective tissue of the skin, tendons, or fascia. They are often associated with primary and secondary hyperlipidemias, and the different types of xanthomas correlate with the type of lipoprotein that is elevated. *Xanthelasma,* a type of xanthoma localized to the periorbital area and eyelid, can be associated with familial dyslipidemias in a younger person but can also occur in nonhyperlipidemic states in older adults.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to assess the effect of tight glycemic, dyslipidemic, and blood pressure control on cardiovascular events in patients with type 2 diabetes. A subset of these patients (ACCORD EYE) was examined to assess the effects of this control on the progression of diabetic retinopathy (DR). Previous studies had shown mixed results for the effect of tight glycemic control on DR. In the ACCORD EYE study, the tight control of glycemia resulted in a 33% reduction in the relative risk of progression of DR, although it did not decrease the risk of moderate vision loss. Treating patients with simvastatin plus fenofibrate for dyslipidemia control yielded a 40% reduction in the risk of DR progression. Tight blood pressure control did not appear to affect DR progression in ACCORD. Previous studies (eg, the Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] study) have also suggested a possible protective effect of the use of fenofibrate on DR.

Statin use may also be associated with a lower risk of glaucoma progression, although additional clinical research is needed. Patients being treated with topical timolol for elevated intraocular pressure or glaucoma have a small but statistically significant elevation of serum LDL and reduction in HDL, but they do not appear to have increased mortality.

The relationship of statin use to age-related macular degeneration (AMD) is unresolved. Several population-based studies (Atherosclerosis Risk in Communities [ARIC], the Melbourne Collaborative Cohort Study, Blue Mountains Eye Study) have suggested that the use of statins is associated with a decreased risk of advanced AMD, whereas other studies (Beaver Dam, Age-Related Eye Disease Study 2 [AREDS2]) suggested that there is no change in AMD risk with statin use. More data are required to assess the nature of this relationship.

The effect of statins on the development of cataracts is unclear. Although the Blue Mountains study suggested a protective effect, the AREDS2 study points to an increased risk of cataract development in patients taking a statin, particularly in women older than 75 years.

Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) follow-on study. *Diabetes Care.* 2016;39(7):1089–1100.

Al-Holou SN, Tucker WR, Agrón E, et al. The association of statin use with age-related macular degeneration progression: the Age-Related Eye Disease Study 2 Report Number 9. *Ophthalmology.* 2015;122(12):2490–2496.

Al-Holou SN, Tucker WR, Agrón E, et al; AREDS2 Research Group. The association of statin use with cataract progression and cataract surgery: the AREDS2 Report Number 8. *Ophthalmology*. 2016;123(4):916–917.

Ooi KG, Khoo P, Vaclavik V, Watson SL. Statins in ophthalmology. *Surv Ophthalmol.* 2019;64(3):401–432.

Talwar N, Musch DC, Stein JD. Association of daily dosage and type of statin agent with risk of open-angle glaucoma. *JAMA Ophthalmol.* 2017;135(3):263–267.

CHAPTER 6

Acquired Heart Disease

Highlights

- Atherosclerotic coronary heart disease (CHD) remains by far the leading cause of death in the United States and around the world.
- Primary prevention of CHD at a public health level requires lifestyle changes, including reduced intake of saturated fat and cholesterol, increased physical activity, and weight control.
- Smoking remains the number-one preventable risk factor worldwide for vascular disease, which includes CHD, cerebrovascular disease, and peripheral vascular disease.
- Primary percutaneous coronary intervention performed by experienced operators is superior to thrombolysis for the treatment of acute myocardial infarction (MI).
- Prophylactic implantable cardioverter-defibrillators (ICDs) are indicated for patients who have survived a cardiac arrest or an episode of hemodynamically unstable ventricular tachycardia. ICDs are also indicated for severe left ventricular dysfunction after MI.

Ischemic Heart Disease

Atherosclerotic *coronary heart disease (CHD)* is by far the number-one killer not only in the United States but also in the world. In the United States, it is estimated that 1 person dies of CHD every minute. The number of women who die of CHD is 10 times that of women who die of breast cancer.

Pathophysiology

Excessive cholesterol intake and metabolism leading to atherosclerosis are central factors in the development of *ischemic heart disease (IHD)*. The "fatty streak," an early sign of atherosclerosis, is an accumulation of lipids and lipid-laden macrophages, called *foam cells,* under the endothelium of the coronary arteries. These cells organize into a plaque, and as the plaque becomes calcified, the lumen of the vessel narrows. The plaque can also become unstable and rupture, leading to turbulence and activation of the coagulation cascade and, ultimately, to intravascular thrombosis. The result is partial or complete vessel occlusion, which causes the symptoms of unstable angina or myocardial infarction (MI).

Ischemia is defined as local oxygen deprivation that results in reduced tissue perfusion and inadequate removal of metabolites. IHD is typically caused by decreased perfusion of

the myocardium secondary to stenotic or obstructed coronary arteries. The balance between arterial supply of and myocardial demand for oxygen determines whether ischemia occurs. Significant coronary stenosis, thrombosis, occlusion, reduced arterial pressure, hypoxemia, or severe anemia can impede the supply of oxygen to the myocardium. On the demand side, an increase in heart rate, ventricular contractility, or wall tension (which is determined by systolic arterial pressure, ventricular volume, and ventricular wall thickness) may increase utilization of oxygen. When the demand for oxygen exceeds the supply, ischemia occurs. If the ischemia is prolonged, infarction and myocardial necrosis result. The necrotic process begins in the subendocardium, usually after approximately 20 minutes of coronary obstruction, and progresses to transmural and complete infarction in 4–6 hours.

Risk Factors for Coronary Heart Disease

Most patients with CHD have identifiable risk factors. Epidemiologic studies have implicated a positive family history, male sex, lipid abnormalities, diabetes, hypertension, physical inactivity, short sleep duration, obesity, and smoking as risk factors. Many of these factors are modifiable; see Chapter 5 for a more detailed discussion on risk reduction. Markers of inflammation, particularly high-sensitivity C-reactive protein (CRP), may also indicate the presence of strong risk factors for CHD.

CHD is the leading cause of death in women, accounting for one-third of all deaths, and kills more women than men each year. The average lifetime risk of CHD in women is very high, nearly 1 in 2. Compared with a man of the same age, a 50-year-old woman with a single additional risk factor has a substantially higher lifetime risk for CHD. Fortunately, most CHD risk in women is modifiable with the recommendations previously discussed; optimizing modifiable risk is of crucial importance in women.

In addition, up to 6% of postmenopausal women presenting with a possible MI are affected by a stress-induced cardiomyopathy called *takotsubo cardiomyopathy*. This disorder may mimic an acute MI, but testing reveals no occlusive vascular disease. The etiology is unclear.

Clinical Syndromes

Clinical presentations of CHD include angina pectoris (ie, stable angina and variant, or Prinzmetal, angina), the acute coronary syndrome (ie, unstable angina, acute MI), congestive heart failure (CHF), sudden cardiac death, and asymptomatic CHD.

Angina pectoris

The cardinal symptom in patients with CHD is *angina pectoris*. It is usually manifested as precordial chest pain or tightness that is often triggered by physical exertion, emotional distress, or eating. Angina pectoris is usually caused by atherosclerotic heart disease. Coronary vasospasm may occur at the site of a lesion or even in otherwise normal coronary arteries. Angina typically lasts 5–10 minutes and is usually relieved by rest, nitroglycerin, or both. Patients may present with pain radiating into other areas, including the jaw, arm, neck, shoulder, back, chest wall, or abdomen.

Often, angina is misinterpreted as indigestion or musculoskeletal pain. The level of physical activity that results in angina pectoris is clinically significant and is useful in

determining the severity of CHD, as well as its treatment and prognosis. Because myocardial ischemia may be painless in diabetic patients and in women, the diagnosis is often delayed in these patients until the disease is more advanced. The pain associated with MI is similar to that of angina but is usually more severe and more prolonged.

Stable angina pectoris Angina is considered stable if it responds to rest or nitroglycerin and if the patterns of frequency, ease of onset, duration, and response to medication have not changed substantially over 3 months.

Variant (Prinzmetal) angina Variant angina occurs at rest and is not related to physical exertion. The ST segment is elevated on electrocardiography during the anginal episodes, which are caused by coronary artery spasm. Underlying atherosclerosis is present in 60%–80% of cases, and thrombosis and occlusion may result during the episodes of coronary artery spasm.

Acute coronary syndrome

Acute coronary syndrome (ACS) comprises the spectrum of unstable cardiac ischemia, from unstable angina to acute MI. Plaque rupture is considered the common underlying event. Unstable angina and acute MI should be considered closely related events; if the patient has chest pain at rest, unstable angina is the diagnosis. If the ischemia is severe enough to cause myocardial necrosis, infarction results. Unstable angina and MI are clinically differentiated by the presence or absence of markers of myocardial injury.

Myocardial infarction Since 2007, task forces representing groups from the United States and Europe have established and updated a definition of MI; it includes the detection of cardiac biomarkers (eg, troponin), ischemia symptoms, electrocardiogram (ECG) changes indicating new ischemia, pathologic Q waves on ECG, and evidence of loss of viable myocardium or wall-motion abnormalities on imaging. The joint task force further refined the definition of MI based on presumed cause:

Type 1: MI caused by atherosclerotic plaque disruption
Type 2: MI caused by mismatched oxygen supply and demand
Type 3: Death from presumed MI, no biomarkers available
Type 4: MI associated with percutaneous coronary intervention (PCI)
Type 5: MI associated with coronary artery bypass graft (CABG)

If an occlusive coronary thrombus persists, MI can result. The location and extent of the infarction depend on the anatomical distribution of the occluded vessel, the presence of additional stenotic lesions, and the adequacy of collateral circulation. *Acute MI* is further differentiated into *non–ST-segment elevation MI (NSTEMI)* and *ST-segment elevation MI (STEMI).* Typical findings used to differentiate between these entities include the following:

- *Unstable angina (chest pain at rest).* The ECG shows ST-segment depression and/or T-wave inversion. No cardiac biomarkers are detected, indicating the absence of myocardial necrosis.
- *NSTEMI (subendocardial, nontransmural).* The ECG shows ST-segment depression and/or T-wave inversion. Cardiac biomarkers are present. The MI may be considered incomplete; thus, patients may be more susceptible to reinfarction or extension. Aggressive workup and treatment are required to prevent progression to STEMI.

- *STEMI.* The ECG shows early ST-segment elevation and later Q waves. (Figure 6-1 depicts a normal ECG; Figure 6-2 depicts the ECG pattern in STEMI.) This condition involves full-thickness or nearly full-thickness necrosis of the ventricular wall. If the necrosis has not yet involved the full thickness of the ventricular wall, early reperfusion therapy is required to avoid progression to full-thickness necrosis.

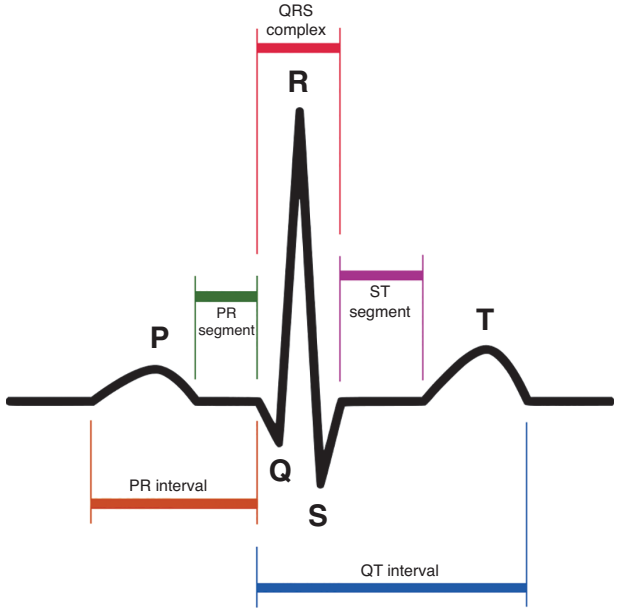

Figure 6-1 Nomenclature of the deflections, intervals, and segments of the normal electrocardiogram (ECG). *(Courtesy of Anthony Atkielsk Agateller.)*

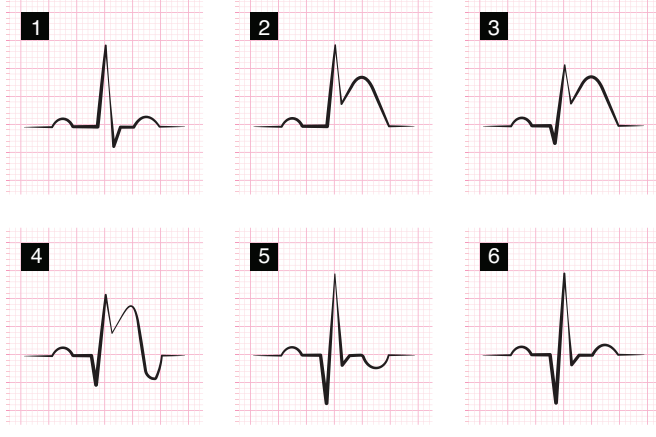

Figure 6-2 ECG changes in acute ST-segment elevation myocardial infarction (STEMI). (1) Normal ECG tracing; (2) ST-segment elevation; (3) pathologic Q wave appears; (4) T wave flips; (5) resolution of ST-segment elevation; Q-wave and T-wave inversion persist; (6) flipped T wave resolves; Q wave persists. *(Courtesy of Puwadol Jaturawutthichai/Shutterstock.com.)*

MI may occur suddenly, without warning, in a previously asymptomatic patient or in a patient with stable or variant angina; MI may also follow a period of unstable angina. Patients commonly experience chest pain, nausea, vomiting, diaphoresis, weakness, anxiety, dyspnea, lightheadedness, and palpitations. However, nearly 25% of myocardial infarcts are painless. Symptoms may begin during or after exertion or at rest.

The clinical findings in MI vary and depend on the location and severity of the ischemia or injury. Approximately half of all infarctions involve the inferior myocardial wall, and most of the remaining half involve the anterior regions. Examination may reveal pallor, coolness of the extremities, low-grade fever, signs of pulmonary congestion and increased central venous pressure (if left ventricular dysfunction is present), an S_3 or S_4 gallop, an apical systolic murmur (caused by papillary muscle dysfunction), hypertension, or hypotension. The ECG may demonstrate a variety of ST-segment and T-wave changes and arrhythmias.

Approximately 60% of patients who die of cardiac disease die suddenly, before reaching the hospital. However, the prognosis for patients hospitalized with MI has become remarkably good. Some studies in which fibrinolytic therapy or PCI was used reported a mortality rate in the range of 5%–8%. Mortality is affected by a wide variety of factors, such as the degree of heart failure, extent of myocardial damage, severity of the underlying atherosclerotic process, heart size, and previous ischemia.

Immediate coronary angiography and primary PCI (including stenting) of the infarct-involved artery have been shown to be superior to fibrinolysis when done promptly by experienced operators in high-volume centers. If the time from first medical contact to intervention ("door-to-balloon time") is less than 90 minutes, the outcome is better and is superior to that of fibrinolysis. This intervention, in conjunction with antiplatelet and anticoagulant therapy, is widely used in patients with acute MI.

The complications of MI depend on its severity and may include CHF (see the section Congestive Heart Failure), rupture of the ventricular wall, pericarditis, and arrhythmias. Regional and global ventricular contractile dysfunction may result in CHF or pulmonary edema. Mild to moderate heart failure occurs in nearly 50% of patients following MI. Some patients experience post-MI pericarditis, characterized by a pericardial friction rub 2–3 days after infarction. Injury along the conduction pathways of the atria or ventricles may lead to bradycardia, heart block, supraventricular tachycardias, or ventricular arrhythmias. Arrhythmias often exacerbate ischemic injury by reducing the perfusion pressure in the coronary arteries. Most acute deaths from MI are caused by arrhythmia.

Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* 2018;72(18):2231–2264.

Sudden cardiac death

Sudden cardiac death (SCD) is defined as unexpected, nontraumatic death that occurs within 1 hour after onset of symptoms in clinically stable individuals. A disproportionate number of SCDs take place in the early morning hours. SCD is usually caused by a severe arrhythmia, such as ventricular tachycardia, ventricular fibrillation, profound bradycardia, or asystole. SCD may result from MI, occur during an episode of angina, or strike without warning in a patient with frequent arrhythmias secondary to underlying IHD or ventricular dysfunction.

Other causes of SCD are Wolff-Parkinson-White syndrome, long QT syndrome, torsades de pointes, atrioventricular block, aortic stenosis, myocarditis, cardiomyopathy, ruptured or dissecting aortic aneurysm, and pulmonary embolism. An implantable cardioverter-defibrillator (ICD) is indicated for patients who have survived a cardiac arrest or an episode of hemodynamically unstable ventricular tachycardia and for patients with severe left ventricular dysfunction after MI.

Asymptomatic ischemic heart disease

Asymptomatic patients with CHD are at particular risk for unexpected MI, life-threatening arrhythmias, and SCD. Advanced CHD may develop in these patients, and they may experience multiple infarcts before the correct diagnosis is made and appropriate treatment is initiated. Older adults, women, and individuals with diabetes are more likely to have painless ischemia. Approximately 25% of MIs are asymptomatic, but they may be detected on a subsequent ECG. A patient who has unexplained dyspnea, weakness, arrhythmias, or poor exercise tolerance requires cardiac testing to evaluate for the presence of undiagnosed CHD.

Noninvasive Cardiac Diagnostic Procedures

Noninvasive diagnostic testing for patients with suspected CHD includes electrocardiography, serum biomarker measurements, echocardiography, various types of stress testing, and imaging studies. Assessment of cardiac risk using various measures (see Chapter 5) will identify those patients most likely to benefit from testing.

Electrocardiography

The ECG may appear normal (see Fig 6-1) between episodes of ischemia in patients with angina. During angina, the ST segments often become elevated or depressed by up to 5 mm. T waves may be inverted, they may become tall and peaked, or inverted T waves may normalize. These ECG findings, when associated with characteristic anginal pain, are virtually diagnostic of IHD. However, absence of ECG changes does not definitively exclude myocardial ischemia.

During MI, QT-interval prolongation and peaked T waves may appear. The ST segments may be depressed or elevated (see Fig 6-2). ST-segment elevation may persist for several days to weeks before returning to normal. T-wave inversion appears in the leads corresponding to the site of the infarct. Q waves or a reduction in the QRS amplitude appears with the onset of myocardial necrosis. Q waves are typically absent in a subendocardial (nontransmural) infarction. Tachycardia and ventricular arrhythmias are most common within the first few hours after the onset of infarction. Bradyarrhythmias, such as heart block, are more common with inferior infarction; ventricular tachycardia and fibrillation are more common with anteroseptal infarction.

Serum biomarker testing

Cardiac enzymes are released into the bloodstream when myocardial necrosis occurs and, therefore, are valuable in differentiating MI from unstable angina and noncardiac causes of chest pain. With the advent of assays for cardiac-specific troponins, serum biomarker testing has also proved useful in identifying patients with ACS who are at greatest risk for adverse outcomes.

Cardiac-specific troponins are accepted as the most sensitive and specific biochemical cardiac markers in ACS. Creatine kinase (CK-MB) and myoglobin are no longer recommended. Cardiac isoforms of troponins (troponins T and I) are important regulatory elements in myocardial cells and are not normally present in the serum of healthy individuals. Troponins T and I have been shown to be more cardiac specific and cardiac sensitive than CK-MB, allowing for more accurate diagnosis of cardiac injury. Troponin levels remain elevated from 3 hours to 14 days after MI. Mildly elevated troponin levels may be found in patients with NSTEMI who otherwise would be considered to have unstable angina. Troponin levels are elevated after MI, but they may also be elevated in patients with myocarditis, pulmonary embolism, stress cardiomyopathy, and chronic kidney disease.

In addition to being diagnostically valuable, troponin levels provide prognostic information. Patients with ACS who present with elevated troponin levels have an increased risk of CHF, cardiogenic shock, death, and recurrent nonfatal MI, as well as an increased need for revascularization with PCI or CABG (discussed later in this chapter). Finally, a quantitative relationship has been demonstrated between the peak amount of troponin measured and the risk of death in patients who present with ACS. Patients who are at greatest risk for adverse outcomes can be identified in the emergency department, allowing for more appropriate medical decisions and therapeutic triage.

Echocardiography

Echocardiography employs 2- and 3-dimensional ultrasound and color flow Doppler techniques to image the ventricles and atria, the heart valves, left ventricular contraction and wall-motion abnormalities, left ventricular ejection fraction, and the pericardium. Patients with IHD, particularly following infarction, commonly have regional wall-motion abnormalities that correspond to the areas of myocardial injury. Other, less frequent, complications of infarction, such as mitral regurgitation from papillary muscle injury, ventricular septal defect, ventricular aneurysm, ventricular thrombus, and pericardial effusion, can also be detected with echocardiography. Color flow Doppler imaging provides information on the flow of blood across abnormal valves, pressure differences within the chambers, intracardiac shunts, and cardiac output. However, cardiac biomarkers are far more sensitive and specific than echocardiography in detecting cardiac injury.

Stress echocardiography (exercise echocardiography) is useful for imaging cardiac-valve and wall-motion abnormalities and ventricular dysfunction induced by ischemia during exercise or after pharmacologic challenge with dobutamine or dipyridamole. Predischarge exercise stress echocardiography provides useful prognostic information following acute MI.

Exercise stress testing

Patients with angina may have normal findings on clinical examination, electrocardiography, and echocardiography between episodes of ischemia. Standardized exercise tests have been developed to induce myocardial ischemia under controlled conditions. The ECG, heart rate, blood pressure, and general physical status of the patient are monitored during the procedure. The endpoint in angina patients is a symptom or sign of cardiac ischemia, such as chest pain, dyspnea, ST-segment depression, arrhythmia, or hypotension. A modified exercise stress test can also be performed in patients with a recent MI to help determine functional status and

prognosis. Stress testing is useful both in establishing the diagnosis of ischemic heart disease and in assessing its severity.

Nuclear stress testing and other imaging

Radionuclide techniques can be used to increase the sensitivity of exercise testing. Left ventricular dysfunction can result from necrotic tissue, myocardial hibernation after injury, or myocardial stunning. Approximately 20%–40% of patients with left ventricular dysfunction on echocardiography or stress testing still have viable myocardial tissue, which may improve with reperfusion. Several agents are available for injection during testing; these include thallium-201, technetium-99m (Tc99m) sestamibi, and technetium-99m tetrofosmin.

Thallium accumulates in healthy myocardium and reveals a perfusion defect in areas of myocardial ischemia. Reversible thallium or Tc99m sestamibi defects are those that are present during exercise but resolve during rest. This correlates with myocardial ischemia. In contrast, a fixed (persistent) thallium or Tc99m defect is present during both exercise and rest and represents a region of prior infarction or nonviable tissue. For patients unable to exercise vigorously enough to reach the required heart rates during the exercise stress test, a thallium scan or ECG in conjunction with a pharmacologic stress test may provide information similar to that of an exercise examination. Tomographic imaging of myocardial perfusion is possible with thallium-201 or Tc99m by means of a technique called *single-photon emission computed tomography (SPECT),* which provides better imaging of infarcts, enhanced detection of multivessel disease, and fewer artifacts.

Other imaging technologies that may add clinically useful information include the following:

- *Positron emission tomography (PET),* which differentiates metabolically active myocardium from scar tissue.
- *Coronary CT angiography,* which is useful in evaluating occlusive vascular disease and ruling out atherosclerotic disease. This test compares well to invasive coronary angiography and may be preferred in stable patients with equivocal results on other noninvasive testing.
- *Coronary artery calcium scoring,* which utilizes multidetector CT scans to measure coronary artery calcification, is a metric that correlates with atherosclerosis and is highly sensitive but not specific. It may be an alternative to invasive angiography in some patients.
- *Cardiac magnetic resonance imaging (MRI),* which provides excellent imaging, and perfusion testing with gadolinium. MRI may be contraindicated in some patients with ICDs or pacemakers, but it can be safely used in the presence of coronary stents. Cardiac CT and MRI are also useful in assessing congenital or acquired coronary abnormalities.

Invasive Cardiac Diagnostic Procedures

As noninvasive imaging techniques have improved, the indications for invasive coronary angiography have decreased. Nevertheless, *coronary angiography* and *ventriculography* provide valuable information about the presence and severity of CHD and about

ventricular function. These techniques can indicate the specific areas of coronary artery stenosis or occlusion, the number of involved vessels, the ventricular systolic and diastolic volumes, the ejection fraction, and regional wall-motion abnormalities. *Radionuclide ventriculography* scans can also be performed for these purposes. This information helps the cardiologist and cardiac surgeon plan appropriate treatment for the patient. *Intravascular ultrasound imaging* at the time of cardiac catheterization is useful for studying the intraluminal coronary anatomy and the effects of stents or angioplasty.

Common indications for coronary arteriography are ACS, post-MI angina, stable angina unresponsive to medical therapy or revascularization, a markedly positive exercise stress test result, and evidence of extensive myocardium at risk from ischemia that might benefit from revascularization.

Ophthalmic considerations Many of the adult patients seen and treated by ophthalmologists are in the age group at risk for IHD and its many complications. They often undergo stressful eye surgery under local or general anesthesia, and ophthalmologists need to be cognizant of these patients' risks of myocardial ischemia, MI, CHF, and arrhythmias. In addition, ophthalmologists need to be aware that patients with nonproliferative or proliferative diabetic retinopathy have an increased risk of MI, stroke, and death from cardiovascular disease. This information should be shared with the primary care provider of patients with significant diabetic retinopathy but without a diagnosis of IHD so that appropriate screening tests for cardiovascular disease can be considered.

Targher G, Bertolini L, Zenari L, et al. Diabetic retinopathy is associated with an increased incidence of cardiovascular events in Type 2 diabetic patients. *Diabet Med.* 2008;25(1):45–50.

Management of Ischemic Heart Disease

The goals of disease management for the patient with CHD are to reduce the frequency of or eliminate angina, prevent myocardial damage, and prolong life. The first line of attack should include eliminating or reducing risk factors for atherosclerosis. Smoking cessation, dietary modification, weight loss, exercise, and improved control of diabetes and hypertension are critical steps. Regression of atherosclerotic lesions following intensive lipid-lowering therapy has been reported; and, unless contraindicated, statins are recommended by the American College of Cardiology (ACC) and American Heart Association (AHA) for all CHD patients. Antiplatelet therapy with low-dose daily aspirin has also been advocated for all patients with CHD because it significantly reduces the risk of MI.

Aspirin appears to offer equal benefit to women and men in reducing primary MI risk, and it is also useful in secondary prevention. Aspirin may also help protect against stroke; however, in low-risk patients, the risk of bleeding complications may outweigh the benefits. Aspirin use should be guided by an assessment of the patient's risk of stroke or MI versus their risk of bleeding complications. Hormone therapy, antioxidant vitamin supplementation, and folic acid therapy do not appear to provide any benefit in preventing cardiovascular disease.

Antithrombotic agents

Prevention of stroke, MI, and numerous other thromboembolic diseases requires selective inhibition of the hemostasis process. Numerous medications have been developed to inhibit platelet aggregation or block specific steps in the coagulation cascade (Fig 6-3), including several oral agents, which are frequently used in the outpatient setting (Table 6-1). The drugs that require intravenous or subcutaneous injection are predominantly used in an inpatient setting (Table 6-2).

Treatment of stable angina pectoris

Medical Medical management of angina pectoris is designed to deliver as much oxygen as possible to the potentially ischemic myocardium, to decrease the oxygen demand to a level at which symptoms are eliminated or reduced to a comfortable level, or both.

Therapeutic agents include the following:

- *β-Adrenergic blockers.* Also called *β-blockers,* these drugs represent the first line of treatment. They reduce heart rate and contractility (decreasing oxygen demand) and have been shown to prolong life in patients with CHD. They should be avoided in patients with Prinzmetal angina.
- *Slow calcium channel blockers*. These agents, including diltiazem, verapamil, and amlodipine, are useful for long-term treatment of angina. They should be used with caution in patients with left ventricular dysfunction.
- *Nitrates and nitroglycerin.* These agents increase oxygen delivery through coronary vasodilation. Systemic effects (eg, venous dilation, reduction in blood pressure) decrease oxygen demand. They should be used with caution in patients taking erectile dysfunction drugs.
- *Aspirin with or without clopidogrel, prasugrel, or ticagrelor.* These drugs can be used for anticoagulation. The regimen of aspirin plus 1 of these other drugs is called *dual antiplatelet therapy (DAPT).*
- *Statins.* Statins are recommended for use in virtually all ACS patients, regardless of serum lipid levels, if not contraindicated.

Improving the oxygen-carrying capacity of the blood by treating anemia or coexisting pulmonary disease provides some additional benefit. Patients in whom medical therapy is unsuccessful may be candidates for revascularization procedures.

Revascularization Procedures for revascularization include *percutaneous coronary intervention (PCI)* with or without stenting or *coronary artery bypass grafting (CABG)*. These approaches may improve coronary blood flow, control angina, and increase exercise tolerance. In high-risk patients, the risk of infarction is reduced, and long-term survival is enhanced. Revascularization is indicated in otherwise healthy patients with advanced left main coronary artery disease, left ventricular dysfunction with 3-vessel disease, or angina that is not adequately controlled with medical treatment. Either PCI or CABG is effective for relieving angina; however, CABG is superior to PCI in terms of survival for some patients who have significant areas of at-risk myocardium or substantial left ventricular dysfunction. Recently, some authors have questioned whether PCI is superior to maximal medical therapy in the treatment of stable angina.

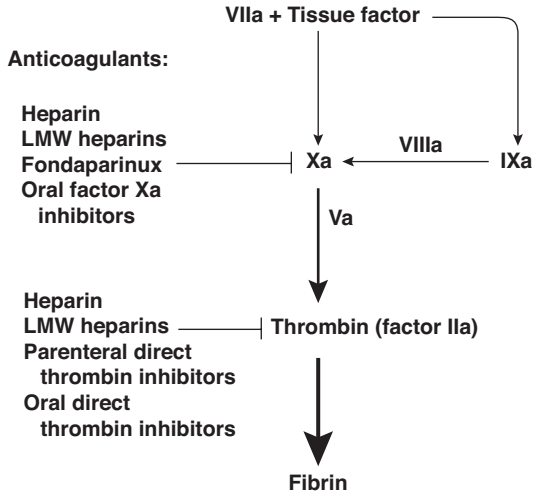

Figure 6-3 Coagulation cascade. The various anticoagulant drugs interrupt the cascade at different points in the process. LMW = low molecular weight. *(Adapted with permission from Leung LLK. Direct oral anticoagulants and parenteral direct thrombin inhibitors: dosing and adverse effects. In:* UpToDate. *Post TW, ed.* UpToDate, Inc. *Accessed October 10, 2022.)*

Table 6-1 Oral Antithrombotic Agents

Class	Drug (trade name)	Mechanism of Action
Antiplatelet agents	Aspirin	Blocks cyclooxygenase and inhibits platelet aggregation
Antiplatelet agents (P2Y12 receptor blockers)	Cangrelor (Kengreal) Clopidogrel (Plavix) Prasugrel (Effient) Ticagrelor (Brilinta) Ticlopidine (not available in the United States)	Prevents activation of glycoprotein IIb/IIIa and inhibits platelet aggregation
Vitamin K antagonists	Warfarin (Coumadin) Other coumarins (not available in the United States) including acenocoumarol, fluindione, phenprocoumon	Reduces the synthesis of numerous clotting factors that require vitamin K
Direct thrombin inhibitors	Dabigatran (Pradaxa)	Prevents thrombin from cleaving fibrinogen to fibrin; can be reversed with idarucizumab (Praxbind)
Factor Xa inhibitors (Note: all drugs in this class end in "-xaban")	Apixaban (Eliquis) Edoxaban (Lixiana, Savaysa) Rivaroxaban (Xarelto)	Prevents factor Xa from cleaving prothrombin to thrombin; rivaroxaban and apixaban can be reversed with andexanet alfa (Andexxa)

Table 6-2 Intravenous and Subcutaneous Antithrombotic Agents

Class	Drug (trade name)	Mechanism of Action
Heparin and low-molecular-weight heparins	Dalteparin (Fragmin) Enoxaparin (Lovenox) Fondaparinux (Arixtra) Heparin Nadroparin (Fraxiparine) Tinzaparin (Innohep)	Inactivates thrombin and factor Xa by enhancing activity of serum antithrombin (fondaparinux is a synthetic pentasaccharide with a similar mechanism of action)
Direct thrombin inhibitors	Argatroban (Acova) Bivalirudin (Angiomax) Desirudin (Iprivask; not available in the United States)	Prevents thrombin from cleaving fibrinogen to fibrin
Glycoprotein IIb/IIIa inhibitors	Abciximab (ReoPro) Eptifibatide (Integrilin) Tirofiban (Aggrastat)	Prevents platelet aggregation by blocking fibrinogen binding to platelets

PCI was developed as an alternative to surgical revascularization. One PCI technique, *angioplasty,* involves passing a balloon catheter into a stenosed vessel and inflating the balloon at the site of the narrowing to widen the lumen. Although 85%–90% of vessels can be opened with PCI, the rate of restenosis is approximately 25%–40% at 6 months. The insertion of a wire-mesh *stent* at the time of PCI improves patency and reduces the risk of restenosis by nearly 50%. Drug-eluting stents are superior to bare-metal stents in preventing restenosis but are also more likely to lead to late stent thrombosis.

Stent thrombosis can result in MI or death, so patients receiving stents should be given aggressive anticoagulation at the time of placement. European and US guidelines for anticoagulant use during stent placement are similar. DAPT (aspirin plus clopidogrel, prasugrel, or ticagrelor) should continue for at least 1 month after stenting for a bare-metal stent and 6–12 months for a drug-eluting stent. DAPT should not be stopped during this period, and elective surgery should be postponed unless the patient is able to continue with DAPT. Patients intolerant of aspirin may use clopidogrel alone.

When angioplasty is inappropriate or ineffective and medical therapy has failed to control symptoms in patients with severe multivessel disease, CABG may be considered. CABG may be indicated in patients with high-risk disease, including those with significant left main, proximal left anterior descending, or 3-vessel disease, especially if accompanied by left ventricular dysfunction. During CABG, a shunt is installed from the aorta to the diseased coronary artery to bypass the area of obstruction and increase blood flow. CABG has been shown to increase left ventricular function, improve quality of life, relieve angina, and, often, reduce the risk of infarction and cardiac death. Some patients now receive off-pump bypass surgery, in which the bypass grafts are sewn onto the beating heart. This technique decreases the risk of adverse effects of cardiopulmonary bypass, which include memory, cognitive, and other neurologic deficits; but it may result in worse graft patency and less complete vascularization than on-pump techniques.

PCI and CABG have similar mortality rates, but patients undergoing PCI are more likely to require a second procedure. Moreover, CABG has better long-term survival outcomes than PCI in most studies.

Although revascularization may produce good outcomes, the underlying disease process requires ongoing management. The Bypass Angioplasty Revascularization Investigation demonstrated that even after PCI or CABG, arterial disease will continue to progress unless cardiac risk factors are reduced. Optimal medical management is also required.

Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol.* 2014;64(18):1929–1949.

Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *J Thorac Cardiovasc Surg.* 2016;152(5):1243–1275.

Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med.* 2020;382(15):1395–1407.

Treatment of acute coronary syndrome

Patients with ACS are admitted to a hospital or a chest pain observation unit for monitoring and treatment. They are initially treated aggressively with anti-ischemic pharmacotherapy. Once these initial measures are instituted, further management and triage of patients with ACS are based on the presence or absence of ST-segment elevation. Patients with ST-segment elevation undergo reperfusion therapy with thrombolysis, CABG, or catheter-based interventions; patients with non–ST-segment elevation may be managed with medical treatment alone or a more aggressive interventional approach. The use of a risk calculator (eg, TIMI, GRACE, PURSUIT) helps to identify high-risk patients and determine subsequent management. The TIMI and GRACE risk calculators are available at www.timi.org/calculators and www.mdcalc.com/calc/1099/grace-acs-risk-mortality-calculator, respectively.

Management of non–ST-segment elevation ACS During the initial evaluation, before biomarker results are available, unstable angina and NSTEMI may be indistinguishable and, if so, are treated the same way. In general, myocardial oxygen demands are managed with medications and supplemental oxygen. β-Blocker therapy, which reduces myocardial oxygen demands and improves survival, should be considered for all patients with evolving MI in the absence of contraindications. Medical therapy for NSTEMI includes the following:

- β-blockers in nearly all patients (avoid in cases of cocaine-associated MI or if the patient is already hemodynamically compromised)
- nitrates or nitroglycerin or both
- DAPT
- anticoagulant therapy (heparins, factor Xa, and direct thrombin inhibitors)
- statins, regardless of serum lipid levels, if not contraindicated
- possible use of angiotensin-converting enzyme (ACE) inhibitors (eg, captopril, enalapril, lisinopril, ramipril)

CHF and pulmonary edema should be treated if present. If β-blockers cannot be used, the clinician may consider verapamil or diltiazem. ACE inhibitors decrease the risk of death if given within 24 hours of MI, but they should be avoided in patients with hypotension or renal insufficiency.

Anticoagulant therapy is beneficial in ACS. It involves a variety of agents, including unfractionated heparin, low-molecular-weight heparins, direct thrombin inhibitors, and factor Xa inhibitors (see Table 6-1). Choice of the optimal regimen depends on what other medications are being used and whether the treatment strategy is conservative or interventional. Glycoprotein IIb/IIIa inhibitors are of limited use in patients with NSTEMI, although they may be tried if other agents have failed to provide sufficient anticoagulation.

Once unstable angina and NSTEMI have been managed as described, patients may be treated with either a conservative noninvasive approach or an early invasive (angiographic) strategy, depending on their level of risk for adverse outcomes. Controlled trials have shown the superiority of an invasive approach in managing ACS patients, particularly those who have refractory angina, hemodynamic instability, or elevated risk as measured by bedside risk stratification tools (eg, TIMI, GRACE). The decision to proceed from diagnostic angiography to revascularization (PCI or CABG) is influenced not only by the coronary anatomy but also by several other factors, including anticipated life expectancy, ventricular function, comorbidity, functional capacity, severity of symptoms, and quantity of viable myocardium at risk. Fibrinolysis should *not* be performed on patients with unstable angina or NSTEMI.

Management of ST-segment elevation ACS Current therapy for evolving Q-wave MI involves rapid and effective reperfusion because necrosis is a time-dependent process. Optimal myocardial salvage requires nearly complete reperfusion as soon as possible: reperfusion within 1 hour of symptom onset yields maximal benefit. The benefit of reperfusion therapy 12 hours after symptom onset has not been established.

Methods of reperfusion include fibrinolysis and catheter-based PCIs (balloon angioplasty with or without stent placement). Numerous clinical trials have shown the superiority of early PCI over fibrinolysis, particularly if performed in the first 90 minutes following medical contact. Hospitals without PCI capability should transfer the patient to a facility that can perform PCI if the procedure can be done within 90 minutes after first medical contact. Otherwise, fibrinolytic therapy should be started within 30 minutes of first medical contact. PCI following full-dose fibrinolytics carries significant risks but may be done in high-risk patients or if fibrinolytic therapy has failed ("rescue PCI"). Totally occluded arteries generally do not benefit from PCI.

CABG may be considered if PCI or fibrinolysis fails, but the potential benefits must be weighed against an increased mortality risk in the first 3–7 days after STEMI.

Initial medical management before and after reperfusion therapy should include aspirin, clopidogrel, nitrates, statins, and β-blockers if there are no contraindications. ACE inhibitors are also initiated to prevent left ventricular remodeling. Morphine should be reserved for patients with severe pain, as it may interfere with antiplatelet drugs. Except for aspirin, nonsteroidal anti-inflammatory agents should not be used acutely or during hospitalization because they increase the risk of CHF and death. Other adjuncts to therapy may include low-molecular-weight heparins and glycoprotein IIb/IIIa inhibitors, particularly if PCI is anticipated.

Fibrinolysis Patients with a STEMI who are treated with thrombolytics in the first 3 hours show a 50% reduction in mortality; those treated at 12 hours show a 10% reduction. Thrombolytic agents lyse coronary thrombi and restore coronary blood flow in most patients. *Tissue plasminogen activators (tPAs)* are the most commonly used thrombolytics; they are more effective than streptokinase in opening arteries and reducing mortality. When any tPA is used, aspirin and intravenous unfractionated heparin should be administered concurrently.

Major bleeding complications occur in up to 5% of patients undergoing thrombolytic therapy. Contraindications to thrombolysis include known sites of potential bleeding, a history of a hemorrhagic cerebrovascular accident, recent surgery, and prolonged cardiopulmonary resuscitation efforts. Thrombolysis should *not* be used in the treatment of NSTEMI because of decreased benefits and, possibly, increased hemorrhagic risks.

Collett JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289–1367.

O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation.* 2013;127(4):e362–e425.

Ophthalmic considerations The use of some β-blockers can lead to a keratoconjunctivitis sicca–like syndrome, probably due to decreased lacrimation. They may also exacerbate migraine scotomas and may decrease intraocular pressure (IOP). Topical β-blockers, particularly timolol, may be less effective in lowering IOP in patients concurrently taking systemic β-blockers. Visual disturbances and vivid visual hallucinations may also be associated with the systemic use of β-blockers. ACE inhibitors may cause angioedema involving the eye and orbit. The presumed mechanism is the disruption of bradykinin metabolism.

Congestive Heart Failure

The epidemiologic magnitude of CHF is staggering. Approximately 6 million patients in the United States and 23 million worldwide have CHF. It is estimated that CHF will develop in 20% of the population older than 40 years. Many patients who consult an ophthalmologist belong to the older age group that is particularly liable to this condition. *Heart failure* occurs when the heart cannot meet the metabolic demands of the tissues. The cardiac pump itself may be failing, or it may be nearly normal but unable to keep up with demand. The direct result of heart failure is circulatory failure.

Classification

The ACC/AHA guideline classifies heart failure into 4 stages, including stages for patients at risk for heart failure and those without current signs or symptoms (Fig 6-4). Symptomatic heart failure due to left ventricular dysfunction is subdivided according to *ejection fraction (EF),* which is the calculated proportion of blood ejected by the ventricle during a single or

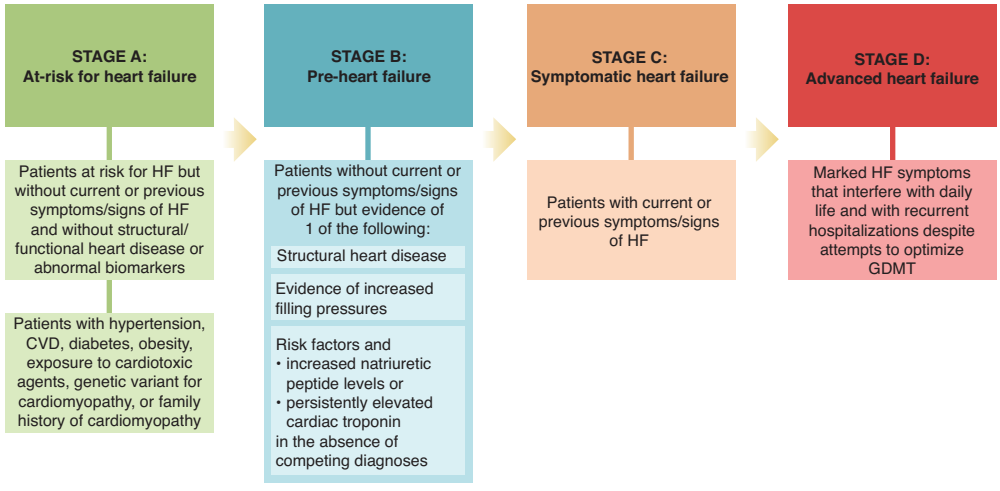

Figure 6-4 American College of Cardiology/American Heart Association classification of stages in the development of heart failure. CVD = cardiovascular disease; GDMT = guideline-directed medical therapy; HF = heart failure. *(Reproduced with permission from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation. *2022;145(18):e895–e1032.)*

average contraction. The EF is more than 50% in an average person without HF. A left ventricular EF ≤40% is classified as *heart failure with a reduced ejection fraction (HFrEF),* and a patient in heart failure with an EF >50% is classified as *heart failure with a preserved ejection fraction (HFpEF). Heart failure with a midrange ejection fraction (HFmrEF)* has an EF of 41%–49%. About two-thirds of all CHF is HFrEF, but HFpEF is more common in women.

Symptoms

Although heart failure may be asymptomatic in its earliest stages, a variety of symptoms may develop, depending on the severity of ventricular dysfunction. Symptoms may result from inadequate tissue perfusion caused by pump failure or from the failing heart's inability to empty adequately, leading to edema and fluid accumulation in the lungs, extremities, and other sites. The most frequent symptoms of left ventricular failure are dyspnea with exertion or at rest, orthopnea, paroxysmal nocturnal dyspnea, diaphoresis, generalized weakness, fatigue, anxiety, and lightheadedness. With more severe CHF, the patient may also experience a productive cough; copious pink, frothy sputum; and confusion. Angina may also occur if the CHF results from ischemia. *Right-sided heart failure* may occur separately from or secondary to chronic left-sided heart failure. Peripheral edema typically develops in patients with right-sided heart failure.

Clinical Signs

Examination findings in acute left ventricular failure can include respiratory distress, use of the respiratory accessory muscles, pinkish sputum or frank hemoptysis, coarse rales on

pulmonary auscultation, expiratory wheezes, a rapid heart rate, an S gallop, diaphoresis, and deterioration in mental status. Blood pressure is often markedly elevated but may be reduced during MI. Long-standing cases of CHF show signs of right ventricular failure, especially elevated central venous pressure, pedal edema, hepatomegaly, and cyanosis. In some patients, pleural effusion or ascites may be detected.

Diagnostic Evaluation

The history and clinical examination are the most important components in the diagnosis of CHF. Diagnostic studies that are helpful in evaluating CHF and its underlying causes include echocardiography, chest radiography, electrocardiography, blood gas analysis, complete blood counts, serum electrolyte tests, blood urea nitrogen and creatinine tests, liver function tests, and urinalysis.

Echocardiography is critically important in identifying the many cardiac causes and comorbidities of CHF (eg, IHD, valvular heart disease, cardiomyopathies, cardiac arrhythmias) and measuring the left ventricular EF. Although the EF can also be measured by radionuclide ventriculography or contrast ventriculography, echocardiography is the most useful and least invasive method for determining and sequentially following EF and the systolic state of the ventricles. Measuring the EF allows the clinician to differentiate between HFrEF and HFpEF, a distinction that is of paramount significance in managing a patient with CHF.

Measurement of serum *brain natriuretic peptide (BNP)* or its metabolite (NT-proBNP), a peptide associated with reduced left ventricular EF and increased left ventricular filling pressure, may be helpful in confirming the diagnosis of CHF, assessing its severity and prognosis, and guiding the treatment. BNP may also be useful as a screening tool to identify early CHF or to prevent its development.

If the primary mechanism of heart failure is unclear, additional tests may prove useful in selected patients. Such tests may include exercise stress testing, cardiac nuclear imaging studies, right-sided and/or left-sided heart catheterization, Holter monitoring, pulmonary function tests, HIV testing, and thyroid function tests. Coronary angiography can be helpful in identifying patients with ongoing cardiac ischemia and CHF, in whom revascularization may lead to symptomatic improvement.

The ECG may reveal acute ischemic changes, acute or previous ventricular hypertrophy, chamber enlargement, and atrial fibrillation or other arrhythmias. Typical chest radiographic findings are prominent pulmonary vessels, interstitial or alveolar pulmonary edema, cardiomegaly, and pleural effusions. Patients with severe pump failure may have abnormal serum electrolyte levels because of poor renal perfusion. Abnormalities in the blood or urine may help detect severe anemia or renal failure as precipitating factors in CHF. Abnormal liver enzyme levels are common if venous congestion is present as a result of right ventricular failure.

Etiology

As noted previously, IHD is the most common cause of CHF. Cumulative injury to the ventricular myocardium from ischemia and infarction can lead to impaired ventricular

systolic and diastolic function and, ultimately, pump failure. Additional causes of systolic dysfunction include

- valvular heart disease (aortic stenosis and aortic or mitral regurgitation)
- cardiomyopathies (idiopathic, metabolic, infectious, toxic, or connective tissue disease)
- myocarditis (secondary to viral or inflammatory diseases)
- infiltrative diseases (amyloidosis, sarcoidosis, and metastatic disease)
- left ventricular hypertrophy

Right- and left-sided heart failure often occur simultaneously in the common causes of CHF—namely, IHD, valvular disease, and the congestive cardiomyopathies. The causes of HFpEF include severe anemia, hyperthyroidism, arteriovenous fistulas, beriberi, and Paget disease.

In HFpEF, the demand for oxygen is so great that the heart eventually fails because it cannot maintain the excessive cardiac output indefinitely. In some patients, heart failure may be more complex; for example, CHF may develop in a patient with IHD who has become severely anemic. Pure right ventricular failure may result from chronic obstructive pulmonary disease, pulmonary hypertension, tricuspid or pulmonary valve disease, right ventricular infarction, or constrictive pericarditis.

Medical and Nonsurgical Management

In both HFrEF and HFpEF, treatment of underlying causes and exacerbating conditions (eg, cardiac ischemia, hypertension, diabetes, thyroid dysfunction, sleep apnea) is of critical importance in managing symptoms and preventing deterioration. Although patients with HFrEF will also benefit from treatment specifically for CHF, patients with HFpEF rely almost entirely on the treatment of their associated disease processes.

Management of HFpEF

Heart failure with preserved EF can be improved by reducing preload, which in turn lowers filling pressures in the ventricle. Preload can be reduced by decreasing circulating blood volume, by increasing the capacitance of the venous bed, and by improving systolic function to empty the ventricle more effectively. Therapy for patients with HFpEF should focus on managing the contributing disease processes. For example:

- Hypertension may be managed with diuretics and β-blockers.
- Atrial fibrillation is present in two-thirds of HFpEF patients. Treatment with β-blockers and calcium channel blockers may be considered to control rate and rhythm.
- Cardiac ischemia is present in two-thirds of these patients. The use of PCI or CABG may be considered if medical therapy (β-blockers, calcium channel blockers) fails.
- Hyperlipidemia may be treated with statins in patients with HFpEF (statins are not beneficial in HFrEF).
- Obesity may be managed with weight loss, exercise training, and cardiac rehabilitation.

Management of HFrEF

In most clinical situations, reducing afterload is the most effective way to manage heart failure with a reduced EF. Lowering vascular resistance and arterial blood pressure decreases

the burden on the left ventricle and enhances contraction and ejection. Regardless of the baseline values, reducing blood pressure (while maintaining adequate tissue perfusion) is the mainstay of treatment of HFrEF. Therapeutic options include the following:

- *Combination therapy.* Most patients with HFrEF will require a diuretic, a β-blocker, and a renin-angiotensin system inhibitor (ACE inhibitor, angiotensin II receptor blocker, or angiotensin receptor–neprilysin inhibitor). This combination of medications prolongs survival better than any single agent.
- *Other afterload-reducing agents.* These include hydralazine; nitrates; clonidine; and, for patients intolerant of ACE inhibitors due to renal disease, α-adrenergic blockers (eg, prazosin, doxazosin).
- *Treatment of anemia.* Intravenous iron replacement may be used to treat anemia, but erythropoietin should be avoided.
- *Lifestyle modification.* Helpful lifestyle changes include smoking cessation, salt restriction, weight loss, exercise, and cardiac rehabilitation.

For patients with HFrEF, the contractility of the left ventricle can be enhanced with inotropic agents. *Digoxin* is reserved mainly for patients who remain symptomatic despite the use of diuretics and ACE inhibitors and for patients with CHF and atrial fibrillation requiring rate control. The other oral inotropic agents have not proved safe or effective in patients with chronic CHF; however, intravenous inotropic agents play a key role in treating hospitalized patients with worsening heart failure. Digoxin should not be used in patients with HFpEF. Patients with heart failure with a midrange ejection fraction (HFmrEF) should have their associated conditions (ischemia, hypertension, atrial fibrillation) managed as in HFpEF, but they also respond well to the pharmacologic therapy used in HFrEF. Serial assessment of symptoms, clinical findings, and echocardiography of patients with heart failure is required.

Other approaches to CHF

Whenever possible, the underlying causes and contributing factors for CHF should be identified and addressed. Precipitating factors can include excessive salt or fluid intake, poor medication adherence, excessive activity, obesity, obstructive sleep apnea, pulmonary infection or embolism, MI, kidney disease, anemia, thyrotoxicosis, and arrhythmias.

Intermittent arrhythmias may seriously compromise ventricular function. Tachyarrhythmias may aggravate ischemia; bradyarrhythmias may further decrease cardiac output and blood pressure. β-Blockers should be considered for all patients with CHF for their effects on overall mortality, although they appear to be more effective in HFrEF than in HFpEF. Amiodarone was not found to be beneficial in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), and most other antiarrhythmic agents are contraindicated in CHF because they may decrease cardiac function and, paradoxically, be proarrhythmic. (See the following section, Invasive or Surgical Management, for discussion of ICDs in CHF.)

Patients with a dilated cardiomyopathy and atrial fibrillation should receive anticoagulation therapy unless there are contraindications. Many physicians also prescribe anticoagulation for patients with a dilated cardiomyopathy, low EF, and normal sinus rhythm, in the absence of contraindications. Options include warfarin; DAPT; and newer agents such as dabigatran, apixaban, and rivaroxaban. Risk factors, cost, tolerability, and potential drug interactions should all be considered during agent selection.

Other measures that can help in managing CHF are restricting dietary sodium, avoiding fluid overload by carefully monitoring oral and intravenous fluid intake, controlling pain and anxiety, treating concomitant metabolic and pulmonary diseases, and providing supplemental oxygen to hypoxemic patients. Finally, all patients with CHF should receive the pneumococcal vaccine and an annual influenza vaccination.

Invasive or Surgical Management

Implantable cardioverter-defibrillators (ICDs) can be useful adjuncts to medical therapy in patients with CHF, arrythmias, cardiomyopathy, and an EF of ≤35%; and they reduced mortality in both the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and SCD-HeFT studies. Biventricular pacing also reduces mortality rates and decreases rehospitalization rates in patients with CHF and a wide QRS complex by improving contraction efficiency. Patients with heart block or other severe bradyarrhythmias may also require cardiac pacing.

Patients with CHD, the leading cause of CHF, may benefit from coronary revascularization by either CABG or PCI. Depending on the underlying causes, other surgical procedures that may be helpful in CHF include percutaneous balloon valvuloplasty, mitral or aortic valve replacement, and pericardiectomy. Left ventricular reconstruction to reduce the volume of a dilated left ventricle has been performed but has not yielded favorable outcomes in the Surgical Treatment for Ischemic Heart Failure (STICH) and other trials. Cardiac transplantation can be an effective surgical treatment for patients with refractory or end-stage CHF, but the availability of organs and facilities is limited. Many transplant centers have achieved a 1-year survival rate that exceeds 85% for a first graft. Implantable ventricular assist devices may help to maintain patients awaiting cardiac transplantation.

Finally, because many patients with advanced CHF are older and have multiple comorbidities, palliative care directed only at symptomatic improvement may also be considered.

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022; 145(18):e895–e1032.

Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016;37(27):2129–2200.

Disorders of Cardiac Rhythm

Abnormalities of cardiac rhythm can vary widely, from asymptomatic premature atrial complexes and mild sinus bradycardia to life-threatening ventricular tachycardia and fibrillation. Disorders of cardiac rhythm can be categorized into several groups, including bradyarrhythmias and conduction disturbances, ectopic or premature contractions, and tachyarrhythmias.

Although many rhythm and conduction disturbances are caused by underlying IHD, they are also attributable to valvular heart disease, myocarditis, cardiomyopathy, congenital aberrant conduction pathways, pulmonary disease, toxic or metabolic disorders, neurogenic causes, and cardiac trauma.

The electrical impulse that initiates each heartbeat normally begins in the *sinoatrial (SA) node* and is conducted down through the atria and ventricles, resulting in a coordinated series of contractions of these chambers. The SA node is the primary pacemaker of the heart. It controls the heart rate and is influenced by neural, biochemical, and pharmacologic factors. If the SA node function is depressed or absent, secondary pacemakers in the *atrioventricular (AV) junction,* the *bundle of His,* or the *ventricular muscle* can generate stimuli and maintain the heartbeat. Normally, stimulus formation in these secondary pacemaker sites is slower than in the SA node. However, abnormal stimuli can also be generated at any of these sites at a rapid pace, resulting in tachycardia.

Bradyarrhythmias and Conduction Disturbances

A *bradyarrhythmia* is any rhythm resulting in a ventricular rate of <60 beats per minute (bpm). *Conduction block,* or *heart block,* is a condition in which electrical signals are slowed or interrupted between the atria and ventricles. Bradyarrhythmias and conduction blocks are generally asymptomatic, although they may cause lightheadedness or syncope in rare cases. If the condition is linked to medication use, simply discontinuing the inciting medication may lead to resolution of the bradycardia. Treatment is generally unnecessary except in patients with syncope or hemodynamic instability. In those cases, placement of a cardiac pacemaker is usually the definitive treatment.

Ophthalmic considerations The use of topical timolol for glaucoma may cause bradycardia, atrioventricular block, hypotension, and worsening of heart failure; and it may induce bronchospasm. Discontinuation of topical timolol will often lead to resolution.

Mäenpää J, Pelkonen O. Cardiac safety of ophthalmic timolol. *Expert Opin Drug Saf.* 2016;15(11):1549–1561.

Premature Contractions

The principal types of premature contractions are *premature atrial complexes (PACs), premature junctional complexes (PJCs),* and *premature ventricular complexes (PVCs).* These complexes result from ectopic premature depolarization arising from the atria (PACs), the AV node or proximal His-Purkinje system (PJCs), or the ventricles (PVCs). Often, patients have no symptoms, or they may have a sensation of "skipped beats." In many cases, no treatment is needed, but β-blockers or calcium channel blockers can be helpful in symptomatic patients. The correction of underlying abnormalities (eg, drug toxicity, electrolyte imbalance, hyperthyroidism) is often curative.

PVCs typically do not require therapy. However, frequent or complex PVCs in the presence of cardiac disease are markers of an increased risk of SCD. Symptomatic patients requiring treatment are best managed with β-blockers because sodium channel blockers and potassium channel blockers appear to worsen the arrhythmia in 5%–20% of patients.

Tachyarrhythmias

Tachyarrhythmia is defined as a heart rate in excess of 100 bpm in an individual at rest. Tachycardias are classified as *supraventricular* or *ventricular,* depending on the mechanism and site of origin. *Narrow complex tachycardias* are almost exclusively supraventricular in origin; *wide complex tachycardias* may be either supraventricular or ventricular in origin. Correct identification of the origin and mechanisms of the tachycardia is critical to selecting appropriate treatment. The exact site of the pacing focus may be difficult to determine when the heart rate is very rapid.

Supraventricular tachycardias

The category of supraventricular tachycardias includes *paroxysmal atrial tachycardia, AV junctional tachycardia, atrial flutter,* and *atrial fibrillation.* Supraventricular tachycardias may be paroxysmal or chronic, as with chronic atrial fibrillation. Causes include emotional stress; caffeine, alcohol, or drug use; thyrotoxicosis; lung disease; and heart disease. A patient with a supraventricular tachycardia often experiences palpitations and, in some cases, syncope. β-Blockers are often useful in the management of these disorders, and catheter-guided radiofrequency ablation may be curative in patients with refractory supraventricular tachycardia. The prognosis for supraventricular tachycardia is usually better than that associated with ventricular tachycardia.

Atrial fibrillation Atrial fibrillation is caused by multiple simultaneous wavelets occurring in both the right and the left atria, leading to a chaotic electrical rhythm with ineffective atrial contraction (Fig 6-5). Cardiac output may be markedly reduced when the ventricular rate is very rapid, possibly resulting in CHF. Atrial thrombi may accumulate from stagnation of blood in the atrial appendages. These thrombi may embolize to the lungs, brain, or other organs. Anticoagulation therapy is indicated for patients with chronic atrial fibrillation and chronic atrial flutter associated with valvular disease, cardiomyopathy, or cardiomegaly and before conversion to sinus rhythm is attempted. Several risk calculation tools (eg, CHA_2DS_2-VASc) have been devised to weigh the risk of embolism against the risk of bleeding in these patients. Newer classes of oral anticoagulants, including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), are superior to warfarin in prevention of stroke, with comparable bleeding risks.

Conversion of atrial fibrillation can be attempted with flecainide, procainamide, ibutilide, or direct-current (DC) cardioversion. In many patients with chronic atrial fibrillation, maintenance therapy is directed toward controlling the ventricular rate, which can usually be accomplished with verapamil, diltiazem, β-blockers, or amiodarone.

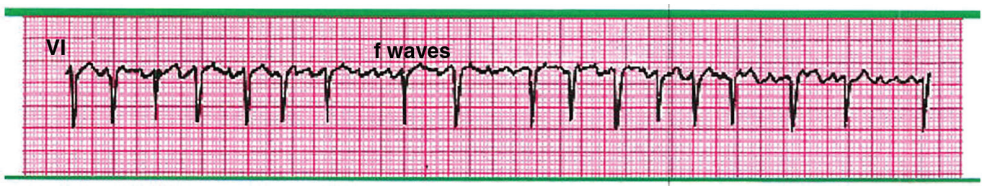

Figure 6-5 Single-lead ECG showing atrial fibrillation. Note the characteristic irregularly irregular rate and rhythm. *(Courtesy of Ary Louis Goldberger, MD.)*

Other curative approaches have been developed for both atrial fibrillation and atrial flutter. These treatments include radiofrequency catheter ablation and the surgical maze procedure. The *maze procedure* interrupts all possible reentry circuits to the atrium with multiple incisions. A single uninterrupted pathway is left intact to allow normal conduction from the SA node to the AV node. This and other ablative procedures can be performed at the time of CABG or valvular surgery to restore sinus rhythm.

Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2021;42(5):373–498.

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation.* 2019;140(6):e125–e151.

Ventricular tachyarrhythmias

Ventricular tachycardia The ventricular tachyarrhythmias include *ventricular tachycardia (VT), torsades de pointes* (a variant of VT), *ventricular flutter,* and *ventricular fibrillation.* These arrhythmias may present with palpitations, heart failure, or syncope or may progress rapidly to SCD. VT occurs infrequently in young patients with no organic heart disease. Brief episodes of VT cause palpitations; prolonged attacks in patients with organic cardiac disease can lead to heart failure or cardiac shock. If the rate is not very high, and there is no significant underlying heart disease, VT may be well tolerated. However, it may degenerate into ventricular fibrillation, resulting in hemodynamic collapse and death.

Treatment with immediate synchronized DC cardioversion is indicated for sustained VT associated with hemodynamic compromise, severe CHF, or ongoing ischemia or infarction. Pharmacologic cardioversion with lidocaine, procainamide, or amiodarone may be attempted in patients with clinically stable VT. Amiodarone is generally the agent of choice for recurrent VT if its adverse effects are tolerated.

Electrophysiologic testing is often performed in patients with suspected or documented ventricular arrhythmias. In this procedure, direct transcatheter electrical stimulation is applied to various sites in the ventricle to induce arrhythmias. Given their efficacy and the low risk associated with implantation, ICDs, in conjunction with antiarrhythmic drugs, have become the treatment of choice for patients with life-threatening ventricular arrhythmias. Radiofrequency catheter ablation can also be performed in patients resistant to medical therapy.

Ventricular fibrillation Ventricular fibrillation (VF) is the most ominous of all the cardiac arrhythmias because it is fatal when untreated or when refractory to treatment. It is a major cause of SCD outside the hospital. The ventricular contractions are rapid and uncoordinated, resulting in ineffective ventricular pumping that soon leads to syncope, convulsions, and death if the VF is not interrupted. The prognosis is generally poor because each episode can be fatal.

Cardiopulmonary resuscitation efforts must be initiated without delay. Immediate unsynchronized DC cardioversion is the primary therapy. After successful cardioversion, continuous intravenous infusion of effective antiarrhythmic therapy should be maintained until any reversible causes have been corrected. The choice of long-term antiarrhythmic therapy

depends on the conditions responsible for the initial VF episode. Primary VF occurring within the first few hours of an acute MI is not associated with an elevated risk of recurrence and does not require long-term antiarrhythmic therapy. However, VF without an identifiable and reversible cause requires implantation of an automatic defibrillator. If a patient refuses an ICD, prophylactic antiarrhythmic drug therapy (eg, amiodarone, sotalol) may be used, but multiple studies have demonstrated that an ICD is more effective in preventing SCD.

Implantable cardioverter-defibrillators

Implantable cardioverter-defibrillators monitor heart rhythm and, when a potentially lethal tachyarrhythmia is identified, deliver therapy. Their evolution has been impressive. Initially, a thoracotomy was necessary to implant an epicardial patch or patches. Most patients now receive a transvenous system, which significantly reduces the morbidity and mortality associated with the implantation of these devices. Current-generation ICDs are generally implanted in the prepectoral region (similar to pacemaker implantation). Although first-generation ICDs delivered only high-energy defibrillating shocks, current-generation devices provide tiered therapy, including pacing algorithms for tachycardia, low-energy cardioversion for stable VT, high-energy cardioversion for VT or VF, single-chamber or dual-chamber pacing support for bradycardia, and stored diagnostic information for rhythm discrimination.

ICDs treat arrhythmias when they occur but do not prevent them. Most patients require concomitant antiarrhythmic therapy (β-blockers, amiodarone) to reduce the frequency of device discharges or to facilitate antitachycardia pacing by slowing the ventricular rate. If the device fails to terminate an arrhythmia, cardiopulmonary resuscitation and external defibrillation should proceed normally. Three randomized prospective studies have demonstrated that automatic ICDs are the preferred first-line therapy for patients who have survived a cardiac arrest or an episode of hemodynamically unstable VT, with a 20%–30% relative reduction in the risk of death. The Multicenter Unsustained Tachycardia Trial (MUSTT) and MADIT studies have also proved the benefit of ICDs for primary prevention of sudden death in patients with CHD, reduced ejection fractions, nonsustained VT, or inducible ventricular arrhythmias during electrophysiologic testing. Following an MI, ICDs appear to be the best available therapy for preventing SCD. An ICD should be considered for patients receiving optimal medical therapy who have left ventricular dysfunction from an MI that occurred at least 40 days previously and an expected survival with good functional status of at least 1 year. Ongoing trials may expand the role of ICDs in the primary prevention of sudden death.

Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *J Am Coll Cardiol.* 2018;72(14):e91–e220.

Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. *Eur Heart J.* 2012;33(21):2719–2747.

Ophthalmic considerations Implantable cardioverter-defibrillators are increasingly used for the management of cardiac arrhythmias. Although no cases of discharge of an ICD during ocular surgery have been reported, the ophthalmologist should discuss the status and possible perioperative disabling

of the ICD with the cardiologist or anesthesiologist before ocular surgery to avoid surgical complications.

Ophthalmologists should be aware of the potential ocular adverse effects associated with medications commonly used in treating arrhythmias. Some of the medications of clinical relevance include the following:

- *Amiodarone.* Microdeposits that form a whorl-like pattern in the basal corneal epithelium *(corneal verticillata)* occur in nearly all patients who use amiodarone for an extended period (years). The deposition associated with amiodarone is indistinguishable from that caused by chloroquine. Visual changes are unusual; when symptoms are present, patients most often report hazy vision or colored halos around lights. Photosensitivity reactions from amiodarone may lead to discoloration (usually slate gray or blue) of periocular skin. A rare adverse effect is *amiodarone optic neuropathy,* which is characterized by an insidious onset, slow progression, bilateral vision loss, and protracted optic nerve head swelling that tends to stabilize within several months of discontinuing the medication.

  Patients on long-term amiodarone therapy should have a baseline ophthalmic examination, follow-up examinations every 6–12 months, and immediate evaluation of any new visual disturbances. Because of this drug's photosensitizing effects, UV-blocking spectacle lenses should be considered in selected cases of chronic eyelid disease or macular disease.
- *Digoxin.* Glare and disturbances of color vision are the most common and striking ocular adverse effects. They include decreased vision and problems with color vision, such as blue-yellow pattern defects; a yellow, green, blue, or red tinge to objects; and colored halos (mainly blue) around lights. Patients using digoxin may also describe yellow or green flickering vision, colored borders around objects, glare phenomena, light flashes, scintillating scotomas, a frosted appearance to objects, and formed visual hallucinations.

Cheng HC, Yeh HJ, Huang N, Chou YJ, Yen MY, Wang AG. Amiodarone-associated optic neuropathy: a nationwide study. *Ophthalmology.* 2015;122(12):2553–2559.

Stoller GL. Ophthalmic surgery and the implantable cardioverter defibrillator. *Arch Ophthalmol.* 2006;124(1):123–125.

CHAPTER 7

Cerebrovascular Disease

Highlights

- "Time is brain." The most important factor in successful thrombolytic treatment of patients with acute ischemic stroke is *early* treatment.
- Intravenous recombinant tissue plasminogen activator (rtPA) is the fibrinolytic agent of choice for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke.
- Patients with acute ischemic stroke who received rtPA should be given aspirin (160–325 mg/day) within 48 hours after symptom onset to prevent recurrent stroke, reduce stroke mortality, and decrease morbidity.
- In the United States, carotid endarterectomy (CEA) should be considered in patients with 70%–99% stenosis, but the benefit of CEA versus intensive medical management remains controversial.

Introduction

Stroke is a leading cause of death in developed countries, ranking behind heart disease and cancer. In the United States, it is the fifth leading cause of death and the leading cause of long-term disability. From 2000 to 2010, the relative rate of stroke death decreased by 35.8% in the United States, and the actual number of US stroke deaths declined by 22.8%; better control of hypertension, cholesterol levels, and diabetes, as well as smoking cessation, have contributed to this reduction in stroke mortality. Yet the number of strokes occurring annually in the United States remains approximately 795,000, of which 610,000 are first attacks. In Europe, there are 1.1 million cases annually. Worldwide, more than 13 million strokes and 5.5 million deaths from strokes occurred in 2016. The annual incidence of ischemic stroke has increased in Eastern Europe, China, and other nations where improved economic status has been accompanied by adoption of unhealthful lifestyles.

There are 2 main types of stroke: ischemic and hemorrhagic. Ischemic stroke accounts for approximately 87% of cerebrovascular accidents.

For more information on cerebrovascular disease, refer to BCSC Section 5, *Neuro-Ophthalmology*.

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Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of stroke in Europe: thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. *Stroke*. 2020;51(8):2418–2427.

Cerebral Ischemia

Transient Cerebral Ischemia

Cerebral ischemia results from interruption of blood circulation to the brain. Patients with suspected transient cerebral ischemia or a stroke, including those with a suspected acute thromboembolic event in the eye, should be referred immediately to a stroke center (note that not all hospitals in a given area have specialized stroke centers). The ischemic event can occur as a result of intrinsic vessel pathology that leads to thrombosis, of embolic phenomena, or of systemic hypoperfusion. Cerebral circulation is usually maintained by a very efficient collateral arterial system that includes the 2 carotid arteries and the 2 vertebral arteries, anastomoses in the circle of Willis, and collateral circulation in the cerebral hemispheres. However, atheromas and congenital arteriovenous malformations (AVMs) also can lead to a reduction in cerebral blood flow. Depending on the extent and duration of the cerebral ischemia, this reduction may be generalized or localized. Interruptions in cerebral blood flow can result in permanent neurologic deficits.

Transient cerebral ischemia (TCI) is now defined as a transient episode of neurologic dysfunction caused by focal ischemia *without* infarction. The previous, time-based definition of TCI (formerly referred to as a *transient ischemic attack,* or *TIA*), which described the episode as a sudden-onset focal loss of neurologic function persisting for <24 hours, is inadequate; infarction can occur after even a brief period of ischemia, even if the presenting focal neurologic symptoms resolve in <1 hour. The new term TCI, with its tissue-based definition, more accurately reflects the pathophysiology and encourages the use of diagnostic testing to identify evidence of permanent tissue injury. The occurrence of TCI is not only an important prognostic indicator of a future ischemic stroke but is also associated with increasing mortality over time. Most TCIs last only a few minutes, and the symptoms are primarily associated with insufficiency of the internal carotid, middle cerebral, or vertebrobasilar circulation.

Ischemic Stroke

Each year, approximately 129,000 people in the United States die as a result of *ischemic stroke.* Most ischemic strokes consist of small regions of complete ischemia in conjunction with a larger area of incomplete ischemia. The area that is ischemic but not infarcted is called the *penumbra,* which is dynamic; saving this tissue is a main goal of acute treatment. Clinical manifestations of cerebral ischemia reflect the functions associated with the area of ischemia and include paresis, paresthesia, vision loss, language disturbances, vertigo, diplopia, ataxia, dysarthria, headache, nausea, and vomiting. A *completed stroke* is an ischemic event that results in a stable, permanent neurologic disability.

Emboli or thrombi caused by atherosclerosis, hypertension, or diabetes and located in large, medium, and small arteries account for most strokes. Strokes caused by emboli of cardiac origin account for 20% of total ischemic stroke incidence. Atrial fibrillation is the most common cause of cardioembolic strokes, occurring in up to 20% of these patients. Mural thrombi forming on the endocardium in conjunction with myocardial infarction (MI) account for 8%–10% of total stroke incidence worldwide. Other cardiac conditions associated with intracranial embolism include mitral stenosis and atrial myxoma. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a rare genetic small-vessel vasculopathy, can mimic multiple sclerosis and can cause ischemic stroke.

Nonarteriosclerotic causes of thrombotic occlusion leading to TCI and stroke include internal carotid dissection (causing the classic triad of Horner sign, neck pain/headache, and neurologic signs and symptoms) and inflammatory arteritis (eg, collagen vascular disease, giant cell arteritis, meningovascular syphilis, acute and chronic meningitis, and moyamoya disease).

Cerebral ischemia can also be caused by increased blood viscosity during pregnancy and the postpartum period, use of oral contraceptives, postoperative and posttraumatic states, hyperviscosity syndromes, polycythemia, and sickle cell disease. Finally, stroke can occur as a result of hypoxemia caused by conditions such as carbon monoxide poisoning, chronic obstructive pulmonary disease, profound anemia, and pulmonary emboli.

Diagnosis and Assessment

The differential diagnosis of ischemic stroke and TCI includes diabetic and convulsive seizures, migraine, vertigo, and neoplasms. Although the presentation of stroke is usually straightforward, other conditions may mimic strokes, including multiple sclerosis, subdural hematoma, cranial nerve palsy, encephalitis, hypoglycemia, seizures, brain tumor, hypertensive encephalopathy, syncope, migraine, and conversion disorder.

A detailed patient history with time and duration of onset and risk factor assessment is critical for treating a patient with suspected stroke. Nonmodifiable risk factors include age >60 years, male sex, and family history or prior history of stroke or TCIs. Modifiable risk factors include diabetes, hypertension, hyperlipidemia, cardiac arrhythmias, smoking, alcohol use, illicit drug use, migraine, and hypercoagulable states.

Although it is not often employed in clinical studies, the US National Institutes of Health Stroke Scale can be used to assess the clinical severity of a stroke on a scale of 0–42, with *0* representing normal function and *42* the most severe functional impairment. The scale includes measures for level of consciousness, gaze, visual fields, facial strength, motor function of the arms and legs, ataxia, sensation, language, dysarthria, and inattention, with a specified number of points given for each impairment found.

Patients presenting with TCI within 72 hours of the event should be hospitalized if they have a known, treatable source of embolic phenomena such as cardiac valvular disease, evidence of acute infarction on initial imaging, or significant comorbidities. Individuals who are not hospitalized should be instructed to undergo diagnostic workup within 48 hours and advised to return to the emergency department if symptoms recur.

Acute versus subacute testing

For practical purposes, diagnostic studies may be separated into those done in an acute care setting, such as in the emergency department, and those done in a subacute setting, such as in a stable inpatient or outpatient clinic. Urgent testing assesses the patient's clinical stability and the possibility of conditions that mimic stroke or that could contribute to stroke; the tests should include blood glucose, complete blood count, blood chemistry, coagulation studies such as prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT), troponins, and electrocardiography. Ideally, all suspected cases of stroke and TCI should be evaluated with urgent *noncontrast computed tomography (CT)* of the brain because contrast and blood appear similar on CT, and this similarity can result in misinterpretation of the image. Noncontrast CT is very sensitive for the presence of intracranial hemorrhage and remains the imaging modality of choice for urgent initial evaluation of stroke. However, enhancement in CT imaging has also improved its diagnostic capability in the evaluation of early cerebral ischemia.

Investigation of the systemic arteries and the heart is essential in determining the cause of cerebral ischemia. Differences between upper limb pulse rates and blood pressure (BP) may indicate serious subclavian disease. Multiple bruits may suggest widespread arterial disease but can be present without significant occlusion. Evidence of a cardioembolic source should be pursued aggressively, especially in younger normotensive persons with cerebral ischemia and in older patients for whom atrial fibrillation is included in the differential diagnosis. Electrocardiography and telemetry or Holter monitoring should be considered to exclude cardiac dysrhythmia and occult MI. Echocardiography is often helpful in excluding intracardiac thrombi; transesophageal Doppler echocardiography is most sensitive in this regard. Only in rare instances is lumbar puncture required in the evaluation of stroke or TCI, for example, if meningovascular syphilis, meningitis, or subarachnoid hemorrhage is a serious consideration.

Imaging studies for evaluation of cerebral ischemia

Current imaging techniques provide the clinician with numerous options for assessing the presence or absence of tissue injury, tissue at risk, and the anatomy of the regional circulation.

Multimodal computed tomography In *multimodal CT,* 3 CT modes are combined: noncontrast CT, CT perfusion imaging, and CT angiography. This type of imaging can rule out hemorrhage; permit early detection of acute infarction; and allow assessment of the site of occlusion, infarct core, and salvageable brain tissue. In addition, the angiography mode can assess collateral circulation.

Magnetic resonance imaging and magnetic resonance angiography *Magnetic resonance imaging (MRI)* is more sensitive than noncontrast CT in detecting an evolving stroke within hours of its onset. *Diffusion-weighted MRI* (*DWI* or *DW-MRI*) with *apparent diffusion coefficient (ADC) mapping* is useful in the evaluation of early cerebral ischemia and regional blood flow to determine the presence or absence of acute infarction. MRI *perfusion-weighted imaging (PWI)* assesses transit time of the contrast agent. *Magnetic resonance angiography (MRA)* can be used to detect vascular stenosis and/or occlusion. *Multimodal MRI,* which combines DWI with PWI, is useful in predicting outcomes in patients with TCI. To date, DWI appears to be the imaging modality of choice in the evaluation of a TCI.

Helical CT angiography This type of angiography can rapidly and noninvasively image the large cerebral arteries with very high specificity and sensitivity.

Carotid duplex ultrasonography This imaging modality may be used to evaluate the patency of the extracranial carotid arteries (see the section Carotid Occlusive Disease for further detail).

Transcranial Doppler ultrasonography This type of ultrasonography is used for evaluation of the intracranial arteries (see the section Carotid Occlusive Disease for further detail).

Cerebral arteriography Although it is the gold standard for angiographic technique, *cerebral arteriography* has high morbidity and is usually required only if the cause of the TCI is unclear or if intra-arterial thrombolysis or surgical intervention is being strongly considered.

Management of Cerebral Ischemia

The goals for treating ischemic stroke are to restore blood flow to the brain and to salvage ischemic brain tissue that is not already infarcted. Achieving these goals involves ensuring the patient's medical stability and determining whether the patient is eligible for thrombolytic therapy. There is a narrow window in which to accomplish these objectives, ideally within 3 hours of symptom onset.

Intravenous thrombolysis

Thrombolytic and antithrombotic agents are the primary drugs used in the treatment of ischemic stroke, and *recombinant tissue plasminogen activator (rtPA)* is the fibrinolytic agent of choice. In the US National Institute of Neurological Diseases and Stroke rtPA Stroke Study, the administration of rtPA within 3 hours of acute ischemic stroke was associated with improved function at 3 months but not with earlier neurologic improvement or lower mortality. The European Cooperative Acute Stroke Study III (ECASS III) demonstrated the benefit of rtPA initiated up to 4.5 hours after the onset of stroke. However, the exclusion criteria for patients treated 3.0–4.5 hours from symptom onset (age >80 years, severe stroke, diabetes with a previous infarct, and any anticoagulant use) were more restrictive than for those treated at 3 hours or less. Most studies indicate that the sooner rtPA is initiated, the more likely it is to be beneficial. The most serious complication of administering rtPA is symptomatic intracranial hemorrhage, which occurs in 6.4% of treated patients and has a mortality rate of 50%.

Mechanical (endovascular) thrombectomy

Patients with a large cerebral artery occlusion and a large clot burden are less likely to benefit from rtPA and are at high risk of a neurologically disabling outcome. More proximal occlusions are also more resistant to thrombolysis, as are those occlusions resulting from fibrin-rich clots. Furthermore, because some patients fail to meet the eligibility criteria for intravenous rtPA, thrombectomy techniques were developed with clot-retrieving devices, also called "stent retrievers," to improve canalization of the artery and arrest the ischemic stroke. Therefore, as part of the initial imaging evaluation of acute ischemic stroke, a noninvasive vascular study, such as CT angiography, should be performed to assess the patient's candidacy for endovascular intervention.

Mechanical thrombectomy (MT) performed with first-generation stent retrievers failed to show an improvement in patient outcomes. However, second-generation stent retrievers achieved significantly higher recanalization rates with correspondingly improved outcomes. Five clinical trials with second-generation stent retrievers (ESCAPE, EXTEND-IA, MR CLEAN, REVASCAT, and SWIFT PRIME) showed the efficacy of MT when compared with standard medical care in patients with acute ischemic stroke caused by occlusion of the large arteries of the proximal anterior circulation. Anatomical success with recanalization, functional independence, and major neurologic recovery was significantly better in the patients who received MT. However, mortality at 90 days, risk of intracranial hemorrhage, and risk of parenchymal hematoma involving >30% of the infarct territory did not differ between the 2 study populations. These data have resulted in a shift in the early treatment of ischemic stroke; MT with second-generation stent retrievers is now recommended in eligible patients. This procedure should be performed at centers with physicians skilled in the use of stent retrievers and can be initiated within 24 hours of stroke onset (the DAWN trial).

Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11–21.

Investigational reperfusion techniques

Currently under investigation are the use of alternative fibrinolytic agents, combined intravenous and intra-arterial thrombolysis, stenting, and combined use of fibrinolytics and glycoprotein IIb/IIIa antagonists. However, none of these techniques have yet demonstrated improved outcomes.

Postacute Management

An essential principle of stroke management is to prevent future events, especially because most stroke patients do not receive the acute care treatment previously discussed for a myriad of reasons, including knowledge, as well as racial, socioeconomic, and geographic factors. In addition to thrombolytic drugs and MT, the management of stroke includes antithrombotic therapy with antiplatelet agents, initiation of statins, and control of BP after the acute phase is over.

de Havenon A, Sheth K, Johnston KC, et al. Acute ischemic stroke interventions in the United States and racial, socioeconomic, and geographic disparities. *Neurology.* 2021;97(23):e2292–e2303.

Antithrombotic therapy

Although aspirin, clopidogrel, and aspirin/extended-release dipyridamole combination are acceptable drug choices for secondary stroke prevention, aspirin is the only antiplatelet agent that is effective in the early treatment of ischemic stroke. Two large clinical trials showed a benefit of treatment with aspirin over placebo in short-term mortality and recurrent stroke risk when aspirin is initiated within 48 hours of ischemic stroke onset. Early use of combination antiplatelet agents such as aspirin with clopidogrel for acute ischemic stroke may be beneficial, but the available evidence is not consistent and is limited to the specific populations studied. Heparin and related agents are not effective in reduction of mortality or recurrent stroke in patients with cardioembolic or noncardioembolic stroke; in fact, they

are associated with higher mortality and a worse outcome. However, use of heparin may be considered in the acute care setting for stroke resulting from postoperative atrial fibrillation in patients with mechanical heart valves or in those with cervicocephalic arterial dissections.

Statins

Initiation or continuation of statins early after presentation is critically important. Studies have shown that long-term intensive use of statins after stroke reduces risk of recurrent ischemic stroke and other cardiovascular events. In addition, numerous reports support the beneficial effects of statin administration during the acute phase of ischemic stroke.

Blood pressure control

Hypertension is the most important risk factor for stroke. Treatment with antihypertensives in the prevention of recurrent ischemic stroke is supported by data from multiple randomized clinical trials and from 2 meta-analyses of a total of 24 clinical trials including >70,000 patients. The 2021 guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend continued treatment with antihypertensive drugs in patients who had hypertension before the stroke event and initiation of antihypertensive treatment for patients with newly diagnosed hypertension. Antihypertensive therapy is *not* recommended in patients with BP <120/70 mm Hg, as there may be risk of harm in individuals with systolic BP <120 mm Hg. Although reduction of BP is critical in preventing recurrent ischemic stroke and other ischemic cardiovascular events, care must be taken to maintain it at a level that will not compromise cerebral perfusion.

For further discussion of hypertension, see Chapter 4.

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Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387(10029):1723–1731.

Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke.* 2021;52(7):e364–e467.

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344–e418.

Carotid Occlusive Disease

Carotid atherosclerosis occurs most frequently in the proximal internal carotid artery (origin) and at the carotid bifurcation. The progression of luminal narrowing and ulceration leads to ischemic stroke or TCI from embolization, thrombosis, or hemodynamic compromise.

Diagnostic Imaging for Carotid Stenosis

The following subsections discuss the main diagnostic techniques currently used to identify the degree of carotid stenosis.

Carotid duplex ultrasonography

Carotid duplex ultrasonography is relatively inexpensive, quick, and noninvasive, with high sensitivity and high specificity for diagnosing high-grade carotid stenosis. However, ultrasonography may overestimate the degree of stenosis and is less accurate in individuals with <69% stenosis. In addition, the accuracy of the results is strongly operator dependent, resulting in high variability among different ultrasound laboratories. If the ultrasonography findings suggest the need for surgical intervention, it may be prudent to confirm with a second imaging modality.

Magnetic resonance angiography

Magnetic resonance angiography is more expensive than carotid ultrasonography and cannot be done in patients who are unable to assume a supine position or in those who have ferromagnetic implants or pacemakers. However, the 3-dimensional image of the carotid artery produced by MRA is useful in diagnosing high-grade carotid stenosis and provides an anatomical complement to carotid ultrasonography. Advanced MRI techniques are being studied to help physicians identify changes in plaque composition that may be useful in predicting risk of rupture and stroke.

Computed tomography angiography

Computed tomography angiography (CTA) is superior to carotid ultrasonography for differentiating high-grade carotid stenosis from total occlusion and effectively excludes carotid stenosis >70%; thus, it is useful as a screening test. If there is disagreement between MRA and carotid ultrasonography results, CTA is useful in adjudicating the findings.

Cerebral angiography

Cerebral angiography remains the gold standard imaging modality for patients with suspected carotid occlusive disease, but its invasive nature and associated morbidity and mortality risk limit its applicability.

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography is a useful adjunct to carotid ultrasonography because it enables physicians to evaluate the flow characteristics of intracerebral vessels. This makes possible the identification of high-grade internal carotid stenosis through examination of the flow patterns of collateral vessels, including the reversal of ophthalmic artery flow.

Management of Carotid Stenosis

Asymptomatic carotid stenosis

Asymptomatic carotid bruits occur in 4% of the US population older than 40 years, and the annual stroke rate in these individuals is 1.5%.

This same population has an annual mortality rate of 4%, primarily from complications of heart disease. The presence of a carotid bruit is, therefore, a better predictor of

arteriosclerotic disease than of stroke. The 2014 AHA/ASA guidelines for management of asymptomatic carotid stenosis include the following:

- Patients with asymptomatic carotid stenosis should be prescribed a statin and aspirin. They should also be screened for conditions that are risk factors for stroke, with appropriate institution of medical therapy and lifestyle modifications.
- Individuals with >50% stenosis should undergo serial annual ultrasonography to identify progression.

It is reasonable to consider *carotid endarterectomy (CEA)* in patients with stenosis >70% if the perioperative complication risk for stroke, MI, and death is <3%. However, the benefit of CEA over intensive medical management is controversial. European guidelines suggest consideration of CEA in patients with ≥60%–99% asymptomatic carotid stenosis who are at increased risk of stroke on maximal medical therapy. CEA is recommended for patients with ≥70%–99% symptomatic stenosis and is suggested for patients with 50%–69% symptomatic stenosis.

- For patients undergoing CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated.
- Prophylactic *carotid artery stenting (CAS)* may be considered in selected patients with stenosis ≥60% on angiography or stenosis ≥70% on ultrasonography, but the benefit of CAS over intensive medical management has not been proved.
- In patients at high risk for complications related to revascularization that could result from either CEA or CAS, the effectiveness of revascularization versus medical therapy is not well established.

Contemporary *intensive medical management* (also called *best medical therapy*), which includes the more widespread and aggressive use of statins, newer antiplatelet agents, and lifestyle modifications (eg, cessation of smoking) as well as improved pharmacologic therapy for diabetes and hypertension, seems to have altered the prognosis of patients receiving medical therapy; outcomes on this regimen may now be equivalent or superior to those of revascularization procedures. Furthermore, because most ischemic strokes due to carotid stenosis are preceded by a TCI, some experts believe that medical management should be the preferred treatment and that physicians should wait until symptoms occur before subjecting a patient to the risks associated with revascularization. The Carotid Revascularization Endarterectomy Versus Stenting Trial-2 (CREST-2) is under way; it will compare outcomes in patients treated with intensive medical management versus those who undergo CEA.

Bonati LH, Kakkos S, Berkefeld J, et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. *Eur Stroke J*. 2021;6(2):I–XLVII.

Safian RD. Asymptomatic carotid stenosis: revascularization. *Prog Cardiovasc Dis.* 2017; 59(6):591–600.

Symptomatic carotid stenosis

Patients with TCI, transient monocular visual loss (TMVL), or previous stroke resulting from carotid stenosis are considered symptomatic. The risk of stroke within 1 year of onset

of symptoms is 8% in patients with TCI; thereafter, the risk is approximately 6% per year, with a 5-year risk of 35%–50%. Current AHA/ASA guidelines for management of symptomatic carotid stenosis are as follows:

- For patients with recent (within the past 6 months) TCI or ischemic stroke and severe (70%–99%) ipsilateral carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is <6% and the patient's life expectancy is >5 years.
- For patients with recent cerebrovascular events and moderate ipsilateral stenosis (50%–69%), CEA is recommended, depending on patient-specific factors such as age, sex, and comorbidities.
- There is no benefit of CEA or CAS in a patient with stenosis <50%.
- Surgery may be performed within 2 weeks of a TCI or stroke.
- CAS may be considered as an alternative to CEA in symptomatic patients at low risk for endovascular intervention complications *and* who have internal carotid artery stenosis >70% as indicated by noninvasive imaging or >50% as indicated by catheter angiography. CAS may also be considered in other selected patients.

Carotid artery stenting versus carotid endarterectomy

The first CREST study randomly assigned patients with asymptomatic or symptomatic carotid disease to CEA or CAS. The primary endpoint of the trial—a composite of any stroke, MI, or death within 30 days of the procedure and ipsilateral stroke during long-term follow-up—was similar in both groups, including the rate of ipsilateral stroke at 31 days to up to 4 years after the procedure. The following are key findings from the study:

- CEA had a greater benefit in older patients (≥70 years).
- CAS was more beneficial in patients <60 years.
- The incidence of stroke and death was higher at 30 days in the CAS group versus the CEA group, but the incidence of MI was significantly lower in the CAS group.
- Despite the higher rate of stroke associated with CAS, no significant differences were found in any quality-of-life measure between the CEA and CAS groups at 1-year follow-up.

Transient monocular visual loss and cardioaortic causes of ischemic stroke

Transient monocular visual loss is usually embolic, originating from either a carotid or a cardiac source. The annual stroke rates among patients with isolated TMVL, retinal infarcts, or TCIs are approximately 2%, 3%, and 8%, respectively. Over a 5-year period, patients with untreated TMVL, retinal infarcts, or TCIs have a 30% risk of MI and an 18% risk of death. A cardiac source of embolization should be excluded for all patients presenting with isolated TMVL.

Transthoracic echocardiography (TTE) can identify multiple potential cardiac causes for embolism, such as atrial fibrillation, rheumatic mitral stenosis, diffuse atherosclerosis, left ventricular aneurysm, or clinical endocarditis. *Transesophageal echocardiography (TEE)* is more sensitive than TTE, except in identifying a left ventricular thrombus. However, because TEE is invasive, imaging typically starts with TTE. If those imaging results are negative but clinical suspicion remains high, the use of TEE would then be indicated. TEE is the best imaging

modality to use to rule out atheromatous plaques in the ascending aorta, a patent foramen ovale, a left atrial appendage clot, or other causes of "cryptogenic" stroke. Other modalities used in the diagnosis of cardioembolic sources of stroke include inpatient telemetry, ambulatory Holter monitoring, loop recorders, and surgically implantable cardiac monitors.

If evidence suggests that a carotid lesion is the cause of the TMVL or if venous stasis retinopathy is present, duplex ultrasonography should be performed to determine whether vessel wall disease or carotid stenosis is present.

When a patient presents with TCI or acute retinal ischemia (including ophthalmic artery occlusion, central retinal artery occlusion, and acute symptomatic branch retinal artery occlusion) that occurred in the previous few days, the clinician should consider immediate referral to a specialized stroke center without additional testing.

The following steps should be taken once the patient is medically stable, or for patients with asymptomatic branch retinal artery occlusion:

- evaluation for the presence of risk factors associated with atherogenesis: hypertension, diabetes, obesity, hyperlipidemia, and smoking
- institution of appropriate medical therapy
- evaluation by appropriate testing for the presence of a cardiac source of emboli
- determination of the possibility of carotid stenosis by using duplex ultrasonography

If ipsilateral carotid stenosis >70% or bilateral carotid stenosis >50% is present or if long-term evidence indicates progressive disease, CEA should be considered—but only if the surgeon's perioperative stroke and death rate is <6%. Otherwise, antiplatelet therapy with aspirin (325 mg/day), aspirin/extended-release dipyridamole combination, or clopidogrel should be initiated. A patient presenting with TCI symptoms who has previously undergone CEA should be evaluated and treated similarly. Special attention should be paid to evaluating patients for the presence of early restenosis and thrombosis.

For further discussion of TCI and transient visual loss, see BCSC Section 5, *Neuro-Ophthalmology.*

Biousse V, Nahab F, Newman NJ. Management of acute retinal ischemia: follow the guidelines! *Ophthalmology.* 2018;125(10):1597–1607.

Katsanos AH, Giannopoulos S, Frogoudaki A, et al. The diagnostic yield of transesophageal echocardiography in patients with cryptogenic cerebral ischaemia: a meta-analysis. *Eur J Neurol.* 2016;23(3):569–579.

Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(12):3754–3832.

Ophthalmic considerations *Giant cell arteritis (GCA),* which may present as TMVL, should always be considered in the differential diagnosis of TMVL and may warrant urgent laboratory investigation in patients ≥50 years. For more on GCA, see BCSC Section 5, *Neuro-Ophthalmology.*

Intracranial Hemorrhage

In the United States, intracranial hemorrhage constitutes approximately 13%–15% of acute cerebrovascular disorders. The most common causes of intracranial hemorrhage are bleeding from aneurysms of the arteries that compose the circle of Willis, bleeding from arterioles damaged by hypertension or arteriosclerosis, and trauma. Although intracranial hemorrhage has many causes, the anatomical location of the bleeding greatly influences the clinical picture. Hemorrhages can be broadly categorized as intracerebral, intraventricular, or subarachnoid.

Intracerebral Hemorrhage

Hypertension is the most common cause of nontraumatic intracerebral hemorrhage. Cerebral amyloid angiopathy is the most common cause of nontraumatic intracerebral hemorrhage in older adults, whereas AVMs are the most common cause in children. Infections resulting from septic emboli, hemorrhagic infarction, brain tumors, coagulopathies, and intrinsic vascular conditions such as moyamoya disease and vasculitis are all associated with intracerebral bleeding.

The pathophysiology of intracerebral bleeding secondary to hypertension appears to be intimal hyperplasia with hyalinosis that results in focal necrosis with pseudoaneurysm formation. When the vessel is exposed to high pressure that cannot be counteracted by the clotting cascade, small leaks can lead to massive hemorrhage. Direct pressure to the brain parenchyma by the expanding clot and from cytotoxic perilesional edema results in direct tissue injury. As the clot expands, the ischemia increases and the cytotoxic edema develops further, raising intracranial pressure; if severe enough, this pressure may lead to herniation. Expansion of the hemorrhage into the intraventricular space occurs in 40%–60% of patients worldwide, greatly increasing morbidity and mortality.

In addition to hypertension, a prospective study showed that age, high alcohol intake, African American race, and, paradoxically, low levels of low-density lipoprotein and triglycerides are associated with increased risk of intracerebral hemorrhage. Most hypertensive hemorrhages occur during routine activity, but some may occur with exertion or intense emotional stress. Symptoms increase gradually over a few minutes to hours. Headache and vomiting occur in approximately 50% of cases. When intraventricular blood is involved, meningismus with stiff neck and nuchal rigidity occur.

Intraventricular Hemorrhage

Worldwide, intraventricular hemorrhage (IVH) accounts for only 3% of intracranial bleeding. IVH typically occurs as a secondary phenomenon when an intracerebral or subarachnoid hemorrhage extends into the ventricles; thus, hypertension is found in nearly half of patients with IVH. Primary IVH is uncommon and is usually due to vascular malformations. Patients with IVH typically present with abrupt-onset headache, nausea, vomiting, and varying degrees of impaired consciousness. Focal neurologic findings are uncommon. The diagnostic test of choice for IVH is a noncontrast head CT. After the CT, MRI or MRA

can be used to identify the anatomical cause of the hemorrhage. Treatment is aimed at stopping the bleeding, reducing hydrocephalus, and managing increased intracranial pressure. Gradual lowering of blood pressure, placement of an intraventricular drain, and treatment of the specific cause (eg, repair of the aneurysm or obliteration of the AVM) should be undertaken.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) accounts for nearly 50% of cases of intracranial hemorrhage. Its incidence increases with age, and it is more common in women. African American and Hispanic individuals have a higher incidence of SAH compared with White individuals. Most SAHs result from *saccular,* or *"berry," aneurysms;* only a minority of cases of SAH are nonaneurysmal. Approximately 85% of congenital saccular aneurysms develop in the anterior part of the circle of Willis. The origin of the posterior communicating artery from the internal carotid artery is the most common site. Such an aneurysm typically presents with headache and third cranial nerve palsy involving the pupil.

Vascular malformations within and on the surface of the brain parenchyma (including capillary telangiectasias, cavernous hemangiomas, venous angiomas, and AVMs) account for approximately 7% of cases of SAH. Capillary telangiectasias and both types of angiomas typically have a low bleeding risk (<0.5%/year). Findings that suggest an AVM as the cause of SAH include a history of previous focal seizures; slow, stepwise progression of focal neurologic signs; and, occasionally, recurrent unilateral throbbing headache resembling migraine. A bruit may be present over the orbit or skull in approximately 40% of patients. SAH usually presents with an abrupt-onset severe headache that is typically described by patients as "the worst headache of my life." The headache occurs in 97% of patients; 30% have symptoms lateralized to the side of the hemorrhage. The combination of vitreous hemorrhage and subarachnoid hemorrhage *(Terson syndrome)* portends a worse prognosis. Maintaining a high index of suspicion and evaluating the patient with noncontrast CT, followed by mandatory lumbar puncture if CT results are negative, are essential in making the diagnosis. Digital subtraction angiography is superior to CT or MRA for the detection of SAH due to aneurysm.

Prognosis and treatment

Aneurysmal SAH carries a high mortality rate: 10% of individuals with an aneurysmal SAH die before they reach the hospital, 25% die within 24 hours, and 45% within 30 days. Prognostic factors include the patient's level of consciousness and neurologic grade on hospital admission, the patient's age, and the amount of hemorrhaged blood visible on the initial head CT. Initial clinical severity may be assessed by a validated metric such as the Hunt and Hess scale, which is the most useful indicator of outcome after acute SAH.

Control and maintenance of BP are mandatory in the treatment of ruptured aneurysms. Surgical intervention is ideally accomplished within 24–72 hours because the likelihood of early rebleeding is high and is associated with a poor outcome. The 2 traditional methods of interventional management are (1) placement of a small clip or ligature *(clipping)* across the neck of the sac; and (2) endovascular coiling. If an aneurysm is judged to be suitable for either technique, an analysis of 3 randomized trials favors endovascular coiling over clipping

in the surgical management of intracranial aneurysms. Patients with large intraparenchymal hematomas or middle cerebral artery aneurysms may have better outcomes with clipping.

Complete obliteration of the aneurysm is recommended, and patients who undergo either type of surgical intervention should have angiography immediately after the surgery to identify any remnants that may require retreatment. If the aneurysm cannot be directly obliterated, surgical ligation of a proximal vessel may be necessary. Complex aneurysms can also be treated with flow-diverting stents, with the shunt placed in the parent blood vessel and going across the neck of the aneurysm. This procedure can be performed along with coiling of the aneurysm. Flow-diverting shunts facilitate gradual thrombosis of the aneurysm and are commonly used for large aneurysms at the proximal portion of the internal carotid artery as well as for intracranial aneurysms, particularly carotid-ophthalmic ones.

The current gold standard of treatment is the surgical excision of a symptomatic AVM. Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy are valuable treatment options for patients with symptomatic AVMs deemed at a high risk for surgical excision; these methods are associated with low morbidity and mortality and have a good occlusion rate. At present, medical therapy is preferred over surgery in patients with unruptured AVMs.

Maher M, Schweizer TA, Macdonald RL. Treatment of spontaneous subarachnoid hemorrhage: guidelines and gaps. *Stroke.* 2020;51(4):1326–1332.

Touzé R, Gravellier B, Rolla-Bigliani C, et al. Occlusion rate and visual complications with flow-diverter stent placed across the ophthalmic artery's origin for carotid-ophthalmic aneurysms: a meta-analysis. *Neurosurgery.* 2020;86(4):455–463.

CHAPTER 8

Pulmonary Diseases

Highlights

- Untreated obstructive sleep apnea is associated with coronary artery disease, congestive heart failure, arrhythmias, refractory hypertension, and type 2 diabetes. It is also associated with various ocular conditions.
- Smoking cessation is the single most efficacious and cost-effective intervention in reducing the risk of chronic obstructive pulmonary disease, heart disease, and stroke. Ophthalmologists should obtain a smoking history from their patients and encourage smoking cessation.
- In 2020, COVID-19 became a worldwide pandemic, with a proportion of infections leading to severe pulmonary disease. The development of vaccines has reduced the risk of severe illness and death. The long-term sequelae on pulmonary functioning from COVID-19 infection are still being studied.

Introduction

The lungs can be affected by numerous pathologic processes, including inflammation (eg, allergic, infectious, autoimmune, toxic), vascular insults, fibrosis, cancer, and changes resulting from cardiac or musculoskeletal problems. Symptoms of lung disease include dyspnea, cough, and wheezing. *Dyspnea* develops when the demand for gas exchange exceeds the capacity of the respiratory system, as in hypoxemia or hypercapnia. Dyspnea may also reflect the increased work of breathing, as occurs in cases of airway obstruction or reduced compliance of the lungs or chest. *Cough* develops when mucus, inflammatory debris, or irritants stimulate the bronchi, causing reflex clearing of expectorant, or when the lung parenchyma is infiltrated with fluid, cells, or fibrosis. *Wheezing* occurs when bronchospasm narrows the large airways and exhaled air is forced through narrowed passages.

The consequences of lung pathology are divided into *obstructive* ventilatory functions and *restrictive* ventilatory functions.

Obstructive Lung Diseases

In patients with obstructive lung disease, changes in the bronchi, bronchioles, and lung parenchyma can cause airway obstruction. Obstructive lung diseases are further categorized as reversible or irreversible, although many patients have some degree of both reversible and irreversible obstructions.

Reversible obstructive diseases are grouped under the term *asthma.* In patients with asthma, the airways are hyperresponsive and develop an inflammatory response with bronchospasm to various stimuli. The specific cause and duration of the bronchospasms vary, however. In some persons, bronchospasms are caused by allergic immunoglobulin E (IgE)–mediated reactions to defined antigens. In others, precipitating factors include exercise, aspirin, sulfites, tartrazine dye, emotional stress, cold air, environmental pollutants, or viral infection. Bronchial smooth muscle constriction, mucosal edema, excess mucus accumulation, and epithelial cell shedding may also contribute to airway obstruction. In many individuals with asthma, however, the cause of abnormal airway reactivity remains unknown. In general, asthma-related airway obstructions are reversible, either spontaneously or with treatment.

Irreversible obstructive disease comprises a group of conditions in which forced expiratory flow is reduced in either a constant or a slowly progressive manner over months or years. Many irreversible obstructive diseases are types of *chronic obstructive pulmonary disease (COPD)*, which is the third leading cause of death in the United States. More information on this disorder is available through the Global Initiative for Chronic Obstructive Lung Disease, which publishes a guide on the diagnosis, classification, and management of COPD (www.goldcopd.org/gold-reports).

Some irreversible obstructive diseases, such as *cystic fibrosis* and *bronchiectasis,* have an identifiable cause (ie, they occur either secondary to recurrent necrotizing bacterial infections or as part of Kartagener syndrome). However, most of these diseases, including emphysema, chronic bronchitis, and peripheral airway disease, cannot be ascribed to specific conditions; rather, they represent an individual response to cigarette smoking and various airborne pollutants.

The pathologic consequences of these abnormal responses vary by disease. *Emphysema* is characterized by pathologic enlargement of the terminal bronchiole air spaces and by destruction of the alveolar connective tissue septa. Bronchitis causes hypertrophied mucous glands in the bronchi, whereas *peripheral airway disease* is distinguished by fibrosis, inflammation, and tortuosity in the small airways only.

Similar to COPD, *obstructive sleep apnea (OSA)* has a pathophysiologic process involving compromised gas exchange that leads to hypoxia and hypercapnia. This breathing disorder is characterized by narrowing of the upper airway, which impairs normal ventilation during sleep. This physical disruption of the upper airway distinguishes OSA from central sleep apnea, which occurs when the brain temporarily ceases transmitting signals to the muscles that control breathing, leading to insufficient ventilation and compromised gas exchange. Currently, the prevalence of OSA in the United States is estimated at 14% for men and 5% for women, with increased prevalence in patients with coronary artery disease, congestive heart failure, arrhythmias, refractory hypertension, type 2 diabetes, and polycystic ovary disease.

When OSA is untreated, the fragmented sleep experienced by affected individuals can lead to daytime sleepiness, cognitive dysfunction, and decreased quality of life. Untreated OSA is also associated with an increased risk of cardiovascular disease, resistant hypertension, coronary artery disease, congestive heart failure, arrhythmias, stroke, and metabolic dysregulation that affects glucose control. The diagnosis of OSA requires polysomnography, a study that records the many biophysical changes that occur during sleep, including

respiratory functions. Treatment of OSA has been shown to improve quality of life, decrease the risk of motor vehicle collisions, and reduce the chronic health consequences associated with the condition.

Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1257–1266.

2020 Focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217–1270.

Restrictive Lung Diseases

Restrictive lung diseases encompass a diverse group of conditions that cause diffuse parenchymal damage. The physiologic consequences of this damage include reductions in total lung volume, diffusion capacity, and vital capacity. Occasionally, patients who have diseases of the chest wall, respiratory muscles, pleura, or spine without parenchymal involvement may have similarly restricted lung volumes.

Among restrictive lung diseases, a *fibrotic* parenchymal response may result from occupational exposure to substances such as asbestos, silica dust, graphite, talc, coal, and tungsten. A *granulomatous* hypersensitivity reaction may develop in response to moldy hay, grains, birds, humidifiers, and cooling systems. Endogenous pulmonary disease may result from collagen vascular diseases, sarcoidosis, eosinophilic granuloma, granulomatosis with polyangiitis (formerly, Wegener granulomatosis), Goodpasture syndrome, alveolar proteinosis, idiopathic pulmonary hemosiderosis, idiopathic pulmonary fibrosis, and other idiopathic parenchymal diseases. Therapeutic agents such as phenytoin, penicillin, gold, methotrexate, and radiation may also cause pulmonary disease. See Table 8-1 for a comparison of obstructive and restrictive lung diseases.

Table 8-1 Obstructive Versus Restrictive Lung Disease

	Obstructive Lung Diseases	Restrictive Lung Diseases
Characterized by	Reduction in airflow	Reduction in lung volume
Symptoms	Shortness of breath; difficulty with exhalation	Difficulty with inhalation
Pulmonary function test	Limitation of maximal airflow rate during forced expiration volume FEV_1/FVC <70%	Decreased total lung capacity while expiratory flow rate is near normal Total lung capacity <70%
Examples	Chronic obstructive pulmonary disease Asthma Cystic fibrosis Bronchiectasis Obstructive sleep apnea	Pulmonary fibrosis Congestive heart failure Sarcoidosis Neuromuscular disorders Obesity

FEV_1 = forced expiratory volume in the first second of expiration; FVC = forced vital capacity (total volume that patient can exhale).

Evaluation

Although all patients with respiratory problems should be under the care of a capable internist or pulmonologist, ophthalmologists and other physicians should be aware of the following key components in the diagnosis and evaluation of patients with pulmonary diseases:

- *Symptoms:* Dyspnea, orthopnea, chronic cough, and chronic sputum production.
- *History:* Occupational exposure to various toxins and irritants, family history, cigarette use.
- *Signs:* Audible wheezing, cyanosis, finger clubbing, forced expiratory time greater than 4 seconds, increased anteroposterior diameter of the chest.
- *Laboratory studies:* Elevated hematocrit level and hypoxia or hypercapnia on arterial blood gas measurement.
- *Chest radiography:* Parenchymal disease, hyperinflation, diaphragmatic flattening, increased retrosternal lucency, and pleural abnormalities.
- *Computed tomography* of the chest: Abnormalities not seen on chest radiographs, such as small areas of adenopathy, pulmonary embolus, small nodules, infiltrative lung disease, and bronchiectasis.
- *Bronchoscopy, transbronchial biopsy,* and *bronchial lavage:* Culture material, cytology material, and pathologic specimens for analysis.
- *Pulmonary function tests:* Measurements of the mechanical and gas exchange functions of the lungs. The *forced expiratory volume in the first second of expiration (FEV_1)* represents the volume exhaled in the first second of exhalation; the *forced vital capacity (FVC)* represents the total volume that the patient can exhale. Both parameters and their serial rate of decline in a patient are objective measures of lung function as well as predictors of comorbidity and mortality from lung cancer and cardiovascular disease. An FEV_1/FVC ratio less than 70% of predicted reference values suggests obstructive disease; total lung capacity less than 70% of predicted values suggests restrictive disease.

Treatment

Treatment of pulmonary disease focuses on 2 major goals. The first goal is to favorably alter the natural history of the disease. The second is to improve the patient's symptoms and functional status and minimize associated problems.

Nonpharmacologic Treatment

Smoking cessation is the single most efficacious and cost-effective intervention in reducing the risk of COPD and slowing its progression. Ophthalmologists should not underestimate the power of even a brief discussion with a patient about the impact of smoking and the beneficial effects of smoking cessation.

Similarly, *avoiding precipitants* of airway obstruction is important in ameliorating asthmatic conditions. In patients with severe pulmonary hypertension and cor pulmonale, use of supplemental oxygen to maintain an arterial oxygen pressure >60 mm Hg confers a modest

reduction in pulmonary hypertension and improves survival rates. However, patients receiving supplemental oxygen must be carefully monitored because such treatment may decrease the body's respiratory drive to eliminate carbon dioxide, aggravating respiratory acidosis and possibly leading to carbon dioxide narcosis. *Breathing exercises* and *postoperative chest physiotherapy* also provide demonstrable short-term improvements in respiratory function.

Noninvasive pressure support ventilation may increase airway pressure, especially in patients with respiratory failure who are expected to quickly respond to medical therapy. For example, continuous positive airway pressure (CPAP) throughout the ventilation cycle improves alveolar oxygen exchange. In CPAP therapy, a tight, well-fitting mask is placed either over the patient's mouth and nose or over just the nose. For patients who require total ventilatory support, intubation and standard ventilation are preferred over the noninvasive method because the mask may slip and effective ventilation may cease.

Currently, CPAP is the most effective treatment for OSA; the positive pressure acts as a pneumatic splint to maintain airway patency. Treatment of OSA with CPAP therapy has been shown to improve daytime sleepiness, health-related quality of life, and mood and attendance at work, as well as reduce the risk of developing cardiovascular disease, refractory hypertension, coronary artery disease, congestive heart failure, arrhythmias, and stroke. Despite these proven benefits, a recent meta-analysis found that CPAP therapy did not reduce the risk of major cardiovascular events (eg, acute coronary events, stroke, or vascular death) or all-cause mortality. In addition, although there are now more than 100 different CPAP mask options to optimize patient comfort and adherence to wearing the masks, consistent use of the device is still low owing to discomfort (ie, some patients still find the mask cumbersome to wear). Additional research is required to optimize the treatment of OSA and avoid its long-term sequelae.

Ophthalmic considerations Several ocular conditions are associated with OSA, including dry eye, floppy eyelid syndrome, glaucoma, papilledema, central serous chorioretinopathy, and nonarteritic anterior ischemic optic neuropathy. Recently, untreated OSA was shown to hinder the response of exudative age-related macular degeneration (AMD) to intravitreal bevacizumab. In contrast, patients with OSA undergoing CPAP treatment have improved AMD response to anti–vascular endothelial growth factor therapy and require notably fewer injections than those with untreated OSA.

Liu PK. Ocular complications of obstructive sleep apnea. *J Clin Med.* 2021;10(15):3422.

Pharmacologic Treatment

Pharmacologic approaches to pulmonary disease include both specific and symptomatic medications. *Specific medications* directly alter the pathophysiologic mechanisms underlying a particular pulmonary disease. Examples include cyclophosphamide for granulomatosis with polyangiitis, corticosteroids for sarcoidosis, and plasmapheresis in combination with immunosuppressive drug therapy for Goodpasture syndrome. *Symptomatic medications* are designed to reduce the obstructive or restrictive components affecting the patient's lung

function, thus improving symptoms and functional status. Medications used to treat bronchospastic airway obstruction include bronchodilators and inhibitors of inflammation as well as antibiotics for infection-precipitated airway closures. *Bronchodilators,* which include theophylline, β-adrenergic agonists, and anticholinergics, act primarily by relaxing the tracheobronchial smooth muscle. *β-Adrenergic agonists* activate bronchial smooth muscle, resulting in bronchodilation. Selective β_2-adrenergics, which have greater bronchodilatory effect and less cardiostimulatory effect, are commonly used, often in metered-dose inhalers (they can also be administered orally or parenterally). These drugs have replaced nonselective β-adrenergic agents such as isoproterenol. The short-acting β_2-agonists include fenoterol, salbutamol (albuterol), and isoetharine, which differ in onset and duration of action. Common long-acting β_2-agonists include formoterol and salmeterol. Salmeterol, a particularly long-acting β_2-adrenergic, is helpful as maintenance treatment for asthma, but should not be used for acute exacerbations. Although epinephrine activates predominantly β-adrenergic receptors in the lungs, it also causes peripheral α-adrenergic stimulation, resulting in vasoconstrictive hypertension and tachycardia. To help control an acute asthma attack, epinephrine is most often administered subcutaneously.

Anticholinergic agents directly relax smooth muscle by competing for acetylcholine at muscarinic receptors. Atropine and similar agents have been replaced by poorly absorbing atropinic congeners such as ipratropium bromide, oxitropium bromide, and tiotropium bromide. These inhalation agents have few systemic and minimal cardiac effects. When combined with submaximal doses of β-adrenergic agonists, they have an additive bronchodilator effect.

Inhibitors of inflammation used to treat pulmonary disease include corticosteroids, leukotriene inhibitors, mast cell stabilizers (cromolyn), and immunosuppressive agents. *Corticosteroids* not only suppress inflammation of the bronchioles but also potentiate the bronchodilator response to β-adrenergic receptors. Inhaled corticosteroids can be used for an extended period to reduce bronchial hyperreactivity; however, they are not used to manage acute attacks. Oral corticosteroids are highly effective in managing acute episodes, but because of the potential adverse effects associated with their use, they should be used only when necessary for serious flare-ups. *Leukotriene inhibitors* suppress the effects of inflammatory mediators. They are especially useful for prophylaxis and long-term maintenance therapy in asthma. *Cromolyn* prevents the release of chemical mediators from mast cells in the presence of IgE antibody and the specific antigen, whereas *immunotherapy* has been helpful for asthma triggered by a defined antigen.

Asthma treatment is tailored to disease severity, with a medication regimen that is sufficient to manage symptoms rapidly and that can later be reduced to the minimal level required to maintain control. The goals of therapy include prevention of symptoms, reduction in frequency and severity of exacerbations, maintenance of normal (or near-normal) pulmonary function, maintenance of normal activity levels, and minimization of medication adverse effects. Maintenance medications include inhaled corticosteroids, cromolyns, leukotriene inhibitors, long-acting β_2-agonists, anticholinergic agents, and oral corticosteroids. Among patients with chronic respiratory failure, appropriately used supplemental oxygen increases survival and has a beneficial effect on pulmonary arterial pressure, polycythemia, exercise capacity, lung mechanics, and mental state. A summary of the National Institutes of Health

2020 updated guidelines for stepwise management of asthma is available (https://www.nhlbi.nih.gov/resources/clinician-guide-2020-focused-updates-asthma-management-guidelines).

Ophthalmic considerations It remains unclear whether use of inhaled corticosteroids increases intraocular pressure (IOP). In a randomized controlled trial involving patients with well-controlled open-angle glaucoma or ocular hypertension receiving either an inhaled steroid regimen or a placebo, there was no clinically significant increase in mean IOP in the steroid group. However, another cross-sectional case-control study did find a probable association between inhaled corticosteroid use and increased IOP. At this time, there is no solid conclusion as to whether inhaled corticosteroid use should raise concern for patients developing increased IOP.

The US Food and Drug Administration has approved the use of sildenafil to slow the progression of pulmonary hypertension and improve patient ability to exercise. Associated adverse ocular events include chromatopsia, cyanopsia, photophobia, and visual disturbance. The incidence of adverse ocular events is low but increases with increased medication dosing.

Moss EB, Buys YM, Low SA, et al. A randomized controlled trial to determine the effect of inhaled corticosteroid on intraocular pressure in open-angle glaucoma and ocular hypertension: the ICOUGH Study. *J Glaucoma*. 2017;26(2):182–186.

Shroff S, Thomas RK, D'Souza G, Nithyanandan S. The effect of inhaled steroids on the intraocular pressure. *Digit J Ophthalmol*. 2018;24(3):6–9.

Pulmonary Aspects of COVID-19

In 2019, a novel coronavirus caused a cluster of atypical pneumonia cases in the city of Wuhan, China. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019. In March 2020, the organization officially declared COVID-19 a global pandemic. The virus that causes COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms typically present at a median of 4 days (range, 3–7 days) after an initial positive polymerase chain reaction test, although some patients remain asymptomatic. (See Chapter 15 for further discussion of COVID-19 symptoms.)

The severity of symptomatic COVID-19 infection ranges from mild to critical, although most cases are not severe. By the end of May 2020, the US Centers for Disease Control and Prevention (CDC) reported that of the 1.3 million people who had been infected with COVID-19 in the United States, 14% had been hospitalized, 2% had been admitted to an intensive care unit, and 5% had died.

Patients with severe COVID-19 disease may be diagnosed as having acute respiratory distress syndrome, and 12% to 24% of hospitalized patients require mechanical ventilation. Other serious and life-threatening complications of infection include cardiac arrhythmias, myocardial injury, heart failure, shock, encephalopathy, thromboembolic complications,

inflammatory complications, and secondary infections. On chest computed tomography (CT), COVID-19 commonly demonstrates ground-glass opacifications with or without consolidation, which is consistent with viral pneumonia (note: CT is not recommended for diagnosis of COVID-19 but is reserved for hospitalized patients during management decision-making). Risk factors for poor prognosis include advanced age, multiple comorbidities, and immunocompromised status. Patients with obstructive or restrictive lung disease or other chronic lung disorder may have a more complicated course and poorer prognosis from COVID-19, although vaccines against COVID-19 have substantially reduced the risk of severe illness and decreased mortality.

As with other viral infections, some patients with COVID-19 recover to full function, whereas others have long-term complications. At this time, the long-term consequences of COVID-19 infection are still being studied. Pulmonary sequelae of the disease may include residual ventilation and blood-gas diffusion abnormalities. Updated information on COVID-19 is available from the US CDC (https://www.cdc.gov/coronavirus/2019-ncov/index.html) and from the European Centre for Disease Prevention and Control (www.ecdc.europa.eu/en/covid-19).

CHAPTER 9

Hematologic Disorders

Highlights

- Alternate-day dosing of iron may yield greater absorption with fewer gastrointestinal adverse effects than a daily regimen in patients with iron deficiency anemia.
- Allogeneic hematopoietic stem cell transplantation (HSCT) may have a cure rate of ≥90% for β-thalassemia when performed in a child with an HLA-identical sibling donor.
- HSCT is potentially curative in sickle cell disease and is strongly recommended for selected pediatric patients.
- Rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors (blood thinners) approved for clinical use.
- Idarucizumab is now available as an antidote for the thrombin inhibitor dabigatran, and andexanet alfa has been approved for reversal of rivaroxaban and apixaban.

Blood Composition

Formed elements—erythrocytes (red blood cells, or RBCs), leukocytes (white blood cells), and platelets—constitute approximately 45% of the total blood volume. The fluid portion, *plasma,* is about 90% water. The remaining 10% of the plasma consists of proteins (albumin, globulin, fibrinogen, and enzymes), lipids, carbohydrates, hormones, vitamins, and salts. If a blood specimen is allowed to clot, the fibrinogen is consumed, and the resultant fluid portion is called *serum.*

Erythropoiesis

All blood cells originate from uncommitted pluripotent stem cells, which give rise to lymphoid stem cells and myeloid stem cells. *Myeloid stem cells* are the precursors of RBCs, granulocytes, monocytes, and platelets. Hormones such as erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor initiate the differentiation of the various cellular elements. The life span of a circulating RBC is approximately 120 days.

Anemia

Anemia is the result of an insufficient quantity of erythrocytes to carry oxygen to the peripheral tissues. It can be classified according to 3 pathophysiologic states: (1) blood loss or nutritional deficiency, (2) underproduction of erythrocytes, and (3) premature destruction of erythrocytes *(hemolysis)*. The normal hemoglobin level in men ranges from 14 to 17 g/dL, while the normal hemoglobin level in women is lower (12–16 g/dL). The higher level in men is due to the erythropoietic effects of androgens.

In the evaluation of a patient with anemia, it is important for the clinician to classify the disorder by reviewing the RBC indexes, including complete blood count, hemoglobin concentration, and erythrocyte count, as well as indexes specifically indicative of RBC size: the mean corpuscular volume (MCV) of erythrocytes and their size distribution (red cell distribution width [RDW]). Reviewing these indexes and observing the morphology on a peripheral blood smear help the clinician to determine whether the anemia is *microcytic* (MCV <80 femtoliter [fL]), *normocytic* (MCV 80–100 fL), or *macrocytic* (MCV >100 fL). In addition to the peripheral blood smear, the *reticulocyte count* gives an indication of erythrocyte production. Patients with normal bone marrow who have lost blood or undergone hemolysis have increased reticulocyte counts, whereas patients with underproduction anemia have low reticulocyte counts for their degree of anemia.

Anemia Due to Blood Loss or Nutritional Deficiency

Iron deficiency anemia

Iron deficiency anemia remains by far the most common type of anemia, affecting nearly 1 billion people worldwide. It is also the most common nutritional deficiency in the world. Iron deficiency anemia is generally defined as a serum ferritin concentration <15 μg/L or a transferrin saturation <16%; the gold standard for diagnosis is the absence of stainable iron in the bone marrow.

In low-income countries, iron deficiency is typically caused by poor intake and/or parasitic infections, whereas in high-income countries, chronic blood loss, vegetarian or vegan diet, and poor absorption are more common causes. Absorption can be affected by inflammatory bowel disease, celiac sprue, and *Helicobacter pylori* infection. Bariatric surgery is an increasingly common cause of iron deficiency.

Iron deficiency anemia is also characterized by low hepcidin levels. *Hepcidin,* a peptide hormone produced by the liver, inhibits iron transport across the intestinal mucosa, thereby preventing excess iron absorption and maintaining normal iron levels within the body. Hepcidin also inhibits the transport of iron out of macrophages and enterocytes, that is, the site of iron storage and transport. Every adult with iron deficiency anemia should be suspected to be bleeding until proved otherwise. Menstrual blood loss in women plays a major role, as does gastrointestinal bleeding in both men and women. Aspirin can cause gastrointestinal bleeding.

Patients with mild iron deficiency anemia may experience fatigue, malaise, irritability, decreased exercise tolerance, restless legs syndrome, and headaches before symptoms

of overt anemia occur. Patients with iron deficiency anemia typically have normal findings on physical examination. However, in severe cases, abnormal findings such as facial pallor, glossitis, stomatitis, koilonychia (spoon nails), and conjunctival pallor may be present. Occasionally, patients with severe iron deficiency anemia exhibit pica, a tendency to eat ice, clay, starch, paper, or crunchy materials.

Once the etiology of iron deficiency anemia has been identified, it may be treated with oral ferrous sulfate, which is the least expensive preparation for treating this condition. It is typically administered at a dosage of 325 mg 3 times daily. However, recent data suggest that an alternate-day dosing regimen may yield greater absorption of iron because of its favorable effect on hepcidin levels, and it also has fewer gastrointestinal adverse effects. Parenteral iron preparations are indicated for patients who are unable to absorb oral iron, are intolerant of its adverse effects, are on dialysis, or have iron deficiency due to blood loss from inflammatory bowel disease.

Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol.* 2017;4(11):e524–e533.

Vitamin B_{12} deficiency

Vitamin B_{12} is available in all foods of animal origin and often in fortified cereals and nutritional yeast. Absorption of vitamin B_{12} forms a complex with intrinsic factor (produced by gastroparietal cells). This complex is absorbed in the terminal ileum and stored in the liver. It takes 3 years to deplete the reserves of vitamin B_{12} in the liver. Vegetarians and vegans, patients with a history of abdominal surgery or gastrectomy/bariatric surgery, individuals with parasitic (tapeworm) infestation, and those with pancreatic disease are at increased risk for vitamin B_{12} deficiency. *Pernicious anemia* is an autoimmune disease in which atrophic gastritis and subsequent intrinsic factor deficiency lead to impaired vitamin B_{12} absorption. *Megaloblastic anemia* is a type of macrocytic anemia resulting from inhibition of DNA synthesis in RBC precursors in the marrow, leading to reduced cell division.

When B_{12} levels are in the low-normal range, the physician should assess levels of serum cobalamin B_{12}, folate, homocysteine, and methylmalonic acid (a more sensitive and specific test for diagnosing vitamin B_{12} deficiency). Often, leukopenia and thrombocytopenia accompany the anemia. Even in the absence of hematologic changes, vitamin B_{12} deficiency can cause a neurologic syndrome; peripheral nerves are affected first, while balance problems and alteration of cerebral function (eg, dementia, neuropsychiatric changes) occur in more severe cases. Parenteral B_{12} is used for treatment of pernicious anemia; otherwise, daily oral B_{12} is effective, less expensive, and less cumbersome than parenteral B_{12}.

Ophthalmic considerations Vitamin B_{12} deficiency may cause bilateral optic neuropathy presenting with central acuity loss and cecocentral scotomas on visual field testing.

Folate deficiency

Folate deficiency (also called *folic acid deficiency*) is another cause of megaloblastic macrocytic anemia. The most common etiology of the deficiency is inadequate dietary intake of folate due to generalized malnutrition or poor nutrition associated with alcohol dependence. Other causes of folate deficiency include

- malabsorption (celiac disease or tropical sprue, zinc deficiency)
- impaired metabolism (alcoholism, folate inhibitor drugs such as methotrexate and trimethoprim)
- increased requirements (hemolytic anemia, pregnancy, lactation, infection, malignancy)
- increased excretion (dialysis, subsequent to vitamin B_{12} deficiency)

It is important to exclude vitamin B_{12} deficiency in patients with presumed folate deficiency; although treatment with folic acid can correct anemia in patients with vitamin B_{12} deficiency, it does not reverse the neuropsychiatric symptoms that can occur in severe B_{12} deficiency. Patients with folate deficiency may also develop neuropsychiatric symptoms that overlap with vitamin B_{12} deficiency. Once vitamin B_{12} deficiency is excluded, a therapeutic trial of folic acid in patients with presumed folate deficiency may be the most cost-effective way of establishing the diagnosis.

Anemia Due to Defective Hemoglobin Synthesis (Hemoglobinopathies)

Thalassemia

The thalassemias, a group of hereditary anemias that occur most frequently in persons of South Asian, Italian, Greek, Middle Eastern, and African descent, are characterized by a reduced rate of synthesis of hemoglobin polypeptide chains alpha or beta. This decreased synthesis leads, in turn, to reduced hemoglobin and a hypochromic microcytic anemia. *α-Thalassemia* is due to a gene deletion that reduces synthesis of alpha hemoglobin chains. Homozygous α-thalassemia leads to hydrops fetalis, which usually results in intrauterine or perinatal death. *β-Thalassemia* is caused by a point mutation rather than a deletion. In the absence of beta chains, the excess of alpha chains leads to instability in the RBC and hemolysis. The bone marrow becomes hyperplastic, which may lead to bone deformities and fractures in severe cases.

Management includes transfusion and iron chelation to minimize iron overload. Advances in transfusion and institution of regular chelation therapy with better-tolerated iron-chelating agents—as well as earlier recognition and treatment of iron-induced organ injury—have markedly improved survival rates. Until recently, *allogeneic hematopoietic stem cell transplantation* (*HSCT,* also called *bone marrow transplantation*) was the only potentially curative therapy available for thalassemia. Prognostic factors associated with a good outcome for HSCT are young age of patient, availability of an HLA-identical sibling donor without thalassemia, and matched sibling bone marrow—or umbilical cord blood–derived transplant stem cells. The prognosis for HSCT is also correlated with the severity and duration of iron overload. Thus, the importance of iron chelation performed on a regular basis cannot be overemphasized. The likelihood of cure in optimal patients exceeds 90%, with a 4% risk of transplant-related mortality.

Splenectomy is an option for some patients with hypersplenism and splenic complications such as splenic infarction or splenic vein thrombosis and may reduce the need for transfusions. The effect of splenectomy, however, may be transient, and its benefits must be weighed against the risk of infection after the procedure.

Recently, betibeglogene autotemcel gene therapy (beti-cel; sold as Zynteglo) was approved by the US Food and Drug Administration (FDA) for the treatment of adult and pediatric patients with β-thalassemia who require transfusions of RBCs regularly. Although it had previously received conditional approval in Europe, the manufacturer has withdrawn it from the European market. The patient's own $CD34^+$ hematopoietic stem cells are harvested, transfected with a BB305 lentiviral vector, and reintroduced into the patient. The genetically modified cells enable production of beta-globin; this treatment has shown promise in reducing or eliminating the need for blood transfusions and iron chelation.

Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-β^0/β^0 genotype β-thalassemia. *N Engl J Med*. 2022;386(5):415–427.

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Sickle cell disease

Sickle cell disease (SCD), or *sickle cell anemia,* is an autosomal recessive disorder caused by an amino acid substitution on the beta chain, which produces an abnormal form of hemoglobin *(hemoglobin S)* that leads, in turn, to chronic hemolytic anemia. Hemoglobin S, which appears several months after birth, damages the RBC membrane, resulting in malformed sickle-shaped cells. Couples at risk of having a child with SCD can be tested for sickle cell trait. While most common in Black individuals, other ethnic groups can also be affected. One out of 400 Black persons born in the United States, 1 out of 250 Black persons born in the West Indies, and 1 out of 4000 born in France have SCD. Every year, approximately 200,000 children are born in Africa with SCD. Chronic hemolytic anemia can result in jaundice, gallstones, poorly healing ulcers over the lower tibia, and splenomegaly (which disappears after a few years because of repeated splenic infarction).

In addition to causing hemolytic anemia, SCD has systemic multiorgan manifestations. It is characterized by acute, painful episodes caused by the sickling of RBCs *(vaso-occlusive crisis);* these episodes can be precipitated by infection, dehydration, and/or hypoxia. Vascular occlusion can lead to necrosis of bone and to infection. Hematuria can be caused by infarction of the renal papillae. Sickle cell retinopathy can lead to vision loss in severe cases.

With improved supportive care, an affected person now has an average life expectancy into the 50s or 60s. Diagnosis is made with a screening test for sickle cell hemoglobin and confirmed by hemoglobin electrophoresis. SCD requires lifelong routine medical care, which includes regular updating of vaccinations; ophthalmologic examinations performed at least annually; screening for hypertension, proteinuria, and pulmonary hypertension; and treatment for infections as they arise. Patients are sometimes given folic acid supplements, as they may be at risk of folate deficiency due to increased erythropoiesis.

There are several FDA-approved medications for sickle disease. Hydroxyurea decreases mortality, and crizanlizumab (a monoclonal antibody against P-selectin adhesion molecule) and L-glutamine have been shown to reduce episodes of painful vaso-occlusive crisis. Voxelotor increases hemoglobin levels in patients with SCD. Finally, CRISPR-Cas9 gene editing shows promise in the treatment of SCD and β-thalassemia but requires further clinical research.

HSCT from an HLA-identical sibling is a potentially curative option in the treatment of SCD. Current data from the Center for International Blood and Bone Marrow Transplant Research and from European Blood and Marrow Transplant registries show an overall survival of 91% and 95%, respectively, after HSCT, as well as improved quality of life. However, HSCT can also be associated with an increased risk of mortality, debilitating chronic graft-vs-host disease, and infertility. If an HLA-matched sibling donor is available, HSCT is recommended for individuals younger than 17 years with severe symptoms of SCD that are unresponsive to medical therapy. Vaccination against SARS-CoV-2 is recommended in these patients, although antibody response may be limited.

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Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *N Engl J Med.* 2021;384(3):252–260.
Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of LentiGlobin for sickle cell disease. *N Engl J Med.* 2022;386(7):617–628.

Anemia Due to Destruction of Red Blood Cells

Hemolytic anemia is defined as a condition in which the life span of RBCs is shortened by premature destruction. In response to hemolysis, the kidneys increase synthesis of erythropoietin, stimulating production of RBC precursors and a subsequent rise in reticulocyte count. Peripheral blood smear evaluation may show a pattern of red cell destruction (evidenced by fragmented RBCs, called *schistocytes*) that reveals a potentially life-threatening disease process such as thrombotic microangiopathy associated with thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.

The causes of hemolytic anemia are numerous and include acquired conditions as well as genetic conditions. Hemolytic anemia may be severe and life-threatening or mild and chronic. Given the numerous etiologies, it is useful to conceptualize the mechanisms of hemolysis as being either *intracorpuscular* (intrinsic defects of RBCs that lead to premature destruction) or *extracorpuscular* (in which RBCs are rendered susceptible to lysis by extrinsic factors).

Intracorpuscular defects

Intracorpuscular defects may be caused by hemoglobinopathies, genetic membrane or cytoskeletal defects, acquired membrane disorders, or intrinsic metabolic abnormalities, such as the following:

- *Hereditary membrane disorders.* Hereditary spherocytosis is the most common type.
- *Acquired membrane disorders.* Paroxysmal nocturnal hemoglobinuria (PNH) manifests clinically with intravascular hemolysis, nocturnal pink or red urine, and a

variable degree of jaundice and fatigue. Diagnosis of PNH is made by flow cytometry, which may incorporate fluorescent aerolysin (FLAER) assay.

- *Metabolic disorders.* Glucose-6-phosphate dehydrogenase (G6PD) deficiency (X-linked inheritance) and pyruvate kinase deficiency increase the susceptibility of RBCs to oxidative stress and damage.

Extracorpuscular causes

Antibody-mediated destruction leading to anemia *(Coombs-positive hemolytic anemia)* is caused by autoantibodies directed at RBC surface antigens. The condition may be assessed by direct antiglobulin testing (direct Coombs testing) for the presence of anti-IgG or anti-C3d. Other causes of antibody-mediated destruction include drug-induced autoimmune hemolytic anemia, autoimmune disease (systemic lupus erythematosus [SLE]), lymphoproliferative disorders, and transfusion-related hemolysis.

Other extracorpuscular factors leading to accelerated RBC destruction include hypersplenism with increased trapping; pathogens that affect RBCs such as malaria, babesiosis, bartonellosis, and clostridial sepsis; mechanical heart valves; platelet microthrombi, as in thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome; and fibrin strands in blood vessels that shear the RBCs, as in disseminated intravascular coagulation. In addition, exposure to drugs that cause nonimmune (oxidative stress) destruction; trauma; and, less commonly, toxins such as snake venom, insect bites, and copper poisoning in Wilson disease are extrinsic causes of hemolytic anemia.

Evaluation and management

Hemolytic anemia may be suspected in a patient who has rapid-onset anemia in the absence of blood loss, dark urine, and jaundice, along with laboratory confirmation of hemolysis. A detailed history may reveal a recent transfusion, initiation of a new drug, or a family history of a hemoglobinopathy or other genetic disorder. Examination of the peripheral smear and flow cytometry may provide the diagnosis. Treatment of hemolytic anemia depends on the underlying etiology, but regardless of cause, folic acid supplementation is necessary.

Robertson JJ, Brem E, Koyfman A. The acute hemolytic anemias: the importance of early diagnosis and management. *J Emerg Med.* 2017;53(2):202–211.

Anemia Due to Inflammation and Chronic Disease

Inflammatory anemia can occur in chronic conditions such as chronic infections (eg, tuberculosis, osteomyelitis), malignancies, autoimmune collagen vascular diseases, and liver disease. Chronic renal failure can also cause a more severe type of anemia, primarily due to the decrease in erythropoietin production.

Anemia Due to Bone Marrow Disorders

Aplastic anemia

Aplastic anemia refers to anemia with pancytopenia associated with varying degrees of bone marrow hypoplasia or aplasia. The causes are diverse, and the condition has a very

high mortality if left untreated. The loss of hematopoietic stem cells in aplastic anemia may be caused by direct toxic injury by drugs, chemicals, ionizing radiation, autoimmune processes, or infectious agents, as well as by clonal and genetic abnormalities. Bone marrow aspiration and biopsy are required to confirm the diagnosis and exclude other conditions that cause pancytopenia, such as megaloblastic anemia and bone marrow infiltration. Affected patients can develop retinal hemorrhages, cotton-wool spots, macular edema, and optic disc edema. The treatment options vary depending on the underlying cause; they can include blood transfusions, HSCT, immunosuppression, and bone marrow stimulants.

Sideroblastic anemia

If iron is not incorporated properly into the heme molecule, hemoglobin synthesis is reduced; this condition is called *sideroblastic anemia (SA).* Diagnosis of SA is made primarily on the basis of bone marrow examination with Prussian blue stain. Iron accumulation in SA, particularly in the mitochondria, leads to development of *ring sideroblasts,* so named because of the iron-laden mitochondria that surround the nucleus of the defective erythroblasts. SA can be caused by a genetic disorder, or it can develop secondary to a myelodysplastic syndrome (refractory anemia with ring sideroblasts) that can progress to acute myelogenous leukemia or other hematologic malignancies. Other causes of SA are usually acquired and include chronic alcoholism and lead poisoning. Treatment includes pyridoxine (vitamin B_6), iron-chelating agents such as deferoxamine, and HSCT.

Disorders of Hemostasis

Disorders of hemostasis may be caused by defects in platelet number or function or by problems in formation of a fibrin clot (coagulation). Figure 9-1 is a simplified illustration of the hemostatic process and the manifestations associated with specific abnormalities. For the purpose of laboratory test interpretation, the coagulation cascade can be divided into *intrinsic* and *extrinsic* pathways, although some factors act on both pathways.

Hemostasis is initiated by damage to a blood vessel wall. This event triggers constriction of the vessel, followed by accumulation and adherence of platelets at the site of injury. Coagulation factors in the blood are activated, leading to formation of a fibrin clot. Slow fibrinolysis ensues, dissolving the clot while the damage is repaired. Circulating inhibitors are also present, modulating the process by inactivating coagulation factors to prevent widespread clotting. Normal endothelium plays a critical role in naturally anticoagulating blood by preventing fibrin accumulation. The following physiologic antithrombotic components can produce this effect:

- antithrombin (inactivates thrombin)
- protein C and/or protein S (natural anticoagulant, destroys factors Va and VIIa)
- tissue factor pathway inhibitor
- the fibrinolytic system

Inherited deficiencies of antithrombin, protein C, or protein S are associated with a lifelong thrombotic tendency, but tissue factor pathway inhibitor deficiency is not.

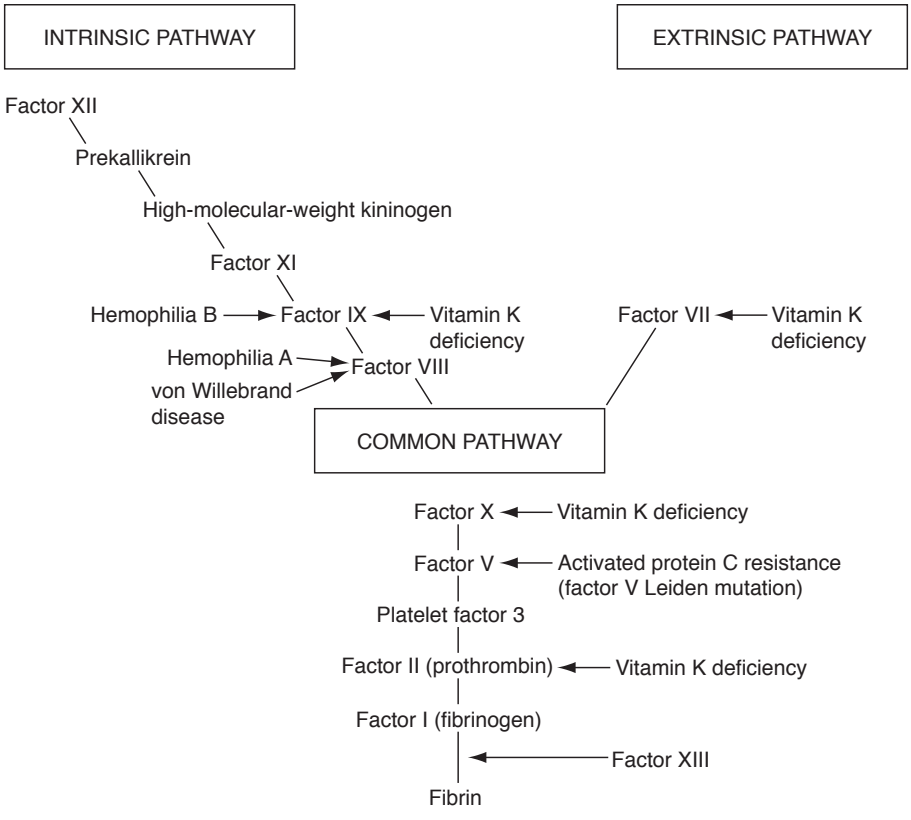

Figure 9-1 Blood-clotting pathways and associated disease states.

Laboratory Evaluation of Hemostasis and Blood Coagulation

Various techniques are used to assess the status of a patient's hemostatic mechanisms. Following are some of the most common tests:

- *Platelet count.* Minor bleeding may occur at platelet counts below 50,000/μL. Abnormal bleeding at higher platelet counts suggests abnormal platelet function. Below 20,000/μL, spontaneous bleeding may be serious.
- *Tests of platelet function.*
  - *Bleeding time.* This was the first test of in vivo platelet function. However, because it is operator-dependent, insensitive, time-consuming, and poorly reproducible, it has largely been replaced by platelet function assays.
  - *Platelet function analyzer*. This rapid and simple test measures the ability of activated platelets in a high-shear environment to occlude an aperture.
  - *Platelet aggregometry.* Various techniques include impedance whole blood, light transmission, and the VerifyNow assay. Light transmission aggregometry is the current gold standard test for measuring platelet function and inhibition.
  - *Activated partial thromboplastin time (aPTT).* The aPTT test incorporates factors I, II, V, VIII, IX, X, XI, and XII; prekallikrein; and high-molecular-weight

kininogen. The aPTT test is most commonly used to measure the effect of heparin therapy. Platelet abnormalities do not affect the result of this test.

- *Prothrombin time (PT).* The PT test measures the integrity of factors I, II, V, VII, and X. It requires a 30% concentration of the vitamin K–dependent factors II, VII, and X (but not factor IX, a part of the intrinsic pathway) and therefore is prolonged in conditions affecting these factors (see Disorders of Blood Coagulation later in this chapter). The PT test is most commonly used to monitor anticoagulant therapy. The action of heparin may slightly prolong PT.

The *international normalized ratio (INR)* was developed to address variation in test results among and within laboratories. The INR modifies the standard PT ratio (patient PT to control PT) to reflect the particular thromboplastin reagent used by a laboratory. The resulting reported INR value is an expression of the ratio of the patient's PT to the laboratory's mean normal PT. Anticoagulation therapy can then be tailored to the clinical problem being treated; for example, the recommended INR value for prevention or treatment of deep venous thrombosis is 2.0–3.0; for tissue replacement valves, 2.0–3.0; and for mechanical replacement valves, 2.5–3.5.

Genetic testing in the form of a DNA assay is also available to determine the correct warfarin dose for an individual patient, especially in cases in which resistance to the drug is suspected. This knowledge has substantially reduced the risk of bleeding and clotting events.

Clinical Manifestations of Hemostatic Abnormalities

Hemorrhage resulting from hemostatic derangement must be differentiated from hemorrhage caused by localized processes. The presence of generalized or recurrent bleeding suggests abnormal hemostasis. *Petechiae* (small capillary hemorrhages of the skin and mucous membranes), *purpura* (<1 cm), and *ecchymoses* (≥1 cm) are typical of platelet disorders and vasculitis. Subcutaneous hematomas and hemarthroses characterize coagulation abnormalities. Bleeding due to trauma may be massive and life-threatening in coagulation disorders, whereas bleeding is more likely to be slow and prolonged when platelet function is impaired.

Vascular Disorders

A number of inherited and acquired disorders of blood vessels and their supporting connective tissues result in pathologic bleeding. *Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)* is an autosomal dominant condition characterized by localized dilatation of capillaries and telangiectasias (actually small arteriovenous malformations) of the skin and mucous membranes. The lesions increase in size and number over a period of decades, often leading to profuse bleeding.

Several heritable connective tissue disorders that affect the blood vessels are associated with hemorrhage. *Ehlers-Danlos syndrome* is characterized by hyperplastic fragile skin and hyperextensible joints; it is dominantly inherited. In *osteogenesis imperfecta,* also a dominant disorder, bone fractures and otosclerosis (leading to deafness) are common.

In both conditions, easy bruising and hematomas are common. *Pseudoxanthoma elasticum,* a recessive disorder, is much rarer but is often complicated by gastrointestinal hemorrhage. *Marfan syndrome* is sometimes associated with mild bleeding as well as with aortic dissection.

Scurvy, caused by severe ascorbic acid deficiency, is associated with marked vascular fragility and hemorrhagic manifestations resulting from abnormal synthesis of collagen. In addition to the classic findings of perifollicular petechiae and gingival bleeding, intradermal, intramuscular, and subperiosteal hemorrhages are common. *Amyloidosis* is another acquired disorder in which petechiae and purpura are common.

Ophthalmic considerations All of the heritable connective tissue disorders have associated ocular findings. Conjunctival lesions occur in hereditary hemorrhagic telangiectasia. Blue sclerae are typical of osteogenesis imperfecta. Ocular manifestations of Ehlers-Danlos syndrome include microcornea, myopia, and angioid streaks; retinal detachment and ectopia lentis have also been reported. Angioid streaks also occur in patients with pseudoxanthoma elasticum. Fifty percent of patients with Marfan syndrome have ectopia lentis; severe myopia and retinal detachment are common.

Platelet Disorders

By far the most common cause of abnormal bleeding, platelet disorders may result from an insufficient number of platelets, inadequate functioning, or both. Mild derangement of platelet function may be asymptomatic or may cause minor bruising, menorrhagia, or bleeding after surgery. More severe dysfunction leads to petechiae, purpura, ecchymoses, and gastrointestinal bleeding and other types of serious bleeding.

Thrombocytopenia

The number of platelets may be reduced by decreased production, increased destruction, or abnormal distribution. Production may be suppressed by many factors, including radiation, drugs, chemotherapy, alcohol use, malignant invasion of the bone marrow, aplastic anemia, and vitamin B_{12} or folic acid deficiency.

Thrombocytopenia due to immune destruction *Idiopathic thrombocytopenic purpura (ITP)* is the result of platelet injury by antiplatelet antibodies. The International Working Group on ITP classifies it into 3 categories: primary ITP; secondary ITP associated with other conditions such as SLE, HIV infection, malignancy, and hepatitis C; and drug-induced thrombocytopenia. The acute form of ITP usually occurs in children and young adults, often following a viral illness, and commonly undergoes spontaneous remission. Chronic ITP is more common in adults and is characterized by mild manifestations; spontaneous remission is uncommon.

Initial treatment consists of systemic corticosteroid therapy. Patients with ITP who do not respond to corticosteroid therapy, who are bleeding and require rapid increase in platelet count, or who require surgical intervention may benefit from intravenous immunoglobulin.

Alternatively, anti-D immunoglobulin may be administered to Rh-positive individuals. Rituximab or splenectomy is often used for ITP refractory to corticosteroids and intravenous immunoglobulin. Because spontaneous remission may occur, clinicians often delay splenectomy for at least 6 months. Thrombopoietin receptor agonists (TPO-RAs) such as romiplostim, eltrombopag, or avatrombopag or immunosuppressive agents such as azathioprine, cyclosporine, or mycophenolate mofetil may also be of benefit. Fostamatinib is a kinase inhibitor approved by the FDA and the European Medicines Agency (EMA) for the treatment of chronic ITP. Splenectomy, however, has been reported to provide the highest durable remission rate and, in balance, still appears to be the favored second-line treatment over rituximab and TPO-RAs, except in patients who are poor surgical candidates or those who prefer a nonsurgical approach.

A neonatal form of the disorder occurs in babies born to women with ITP; this form results from transplacental passage of antiplatelet antibodies. Recovery follows physiologic clearance of the antibodies from the child's circulation.

Drug-induced thrombocytopenia is common. Many drugs and other substances, including quinine, quinidine, digitalis, procainamide, thiazide-type diuretics, sulfonamides, phenytoin, aspirin, penicillin, heparin, and gold compounds, have been implicated as causes of immunologic platelet destruction. Discontinuation of the offending substance should result in platelet recovery.

Nonimmunologic thrombocytopenia Types of nonimmunologic thrombocytopenia include thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and the disseminated intravascular coagulation syndrome (see the section "Disseminated intravascular coagulation" later in the chapter).

Thrombotic thrombocytopenic purpura (TTP) is caused by an inherited or acquired deficiency of the von Willebrand factor–cleaving protease ADAMTS13. It is characterized by thrombotic microangiopathy and hemolytic anemia. Fever, neurologic symptoms, microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and renal dysfunction occur, often with subacute onset. Death occurs in days to weeks in the majority of untreated cases. However, early treatment with exchange plasmapheresis has improved the survival rate to over 80%, especially when rituximab is given as part of initial therapy. Caplacizumab is an FDA-approved option.

Despite significant thrombocytopenia, bleeding is relatively uncommon, and platelet transfusions are usually unnecessary. Platelet transfusion may be indicated in patients with severe bleeding or in those who will undergo an invasive procedure. Refractory cases may be treated with antiplatelet drugs, corticosteroids, and immunosuppressive agents. Eculizumab can be used for complement-mediated TTP.

Hemolytic-uremic syndrome (HUS) is similar in pathophysiology to TTP in that both are associated with MAHA, thrombocytopenia, and renal involvement. The most common cause of HUS, especially among children, is Shiga toxin–producing *Escherichia coli* (STEC), which accounts for 90% of cases of HUS. TTP and HUS are similar in clinical appearance, and laboratory confirmation of low ADAMTS13 activity (<10% in patients with TTP) may take several days; these factors complicate the decision whether to initiate plasma exchange or anticomplement therapy (eculizumab) urgently. The abnormal

distribution of platelets is most commonly caused by splenic sequestration. Patients with severely depressed platelet counts probably also have accelerated platelet destruction in the spleen.

Thrombocytosis and essential thrombocythemia

Thrombocytosis is defined as a platelet count exceeding 450,000. *Essential thrombocythemia (ET),* also called *primary thrombocytosis/thrombocytopenia,* refers to an excess of platelets due to a primary bone marrow clonal disorder. *Thrombocytosis,* also called *reactive thrombocytosis,* is secondary to other conditions such as inflammatory disorders. Management of reactive thrombocytosis is aimed at treating the underlying cause such as infection, inflammation (eg, giant cell arteritis), trauma, iron deficiency, congestive heart failure, renal failure, and pancreatitis. In contrast, ET is a clonal myeloproliferative disorder akin to neoplastic disease. Severe autonomous increase in platelet counts may also be caused by other myeloproliferative disorders such as polycythemia vera, primary myelofibrosis with myeloid metaplasia, chronic myeloid leukemia, and myelodysplastic syndromes.

The prevalence of ET is estimated to be 30/100,000 in the general population worldwide, with a nearly 2:1 ratio of men to women. Regardless of etiology, severe thrombocytosis can cause both thrombotic and hemorrhagic events. However, thrombohemorrhagic complications are much more common in ET and in other clonal myeloproliferative disorders than with thrombocytosis generally and include arterial and venous thromboses, cerebrovascular accident, myocardial infarction, and deep venous thrombosis. Hemorrhagic events include ecchymoses, subcutaneous hematomas, epistaxis, and gingival bleeding. Approximately 36% of patients, however, are asymptomatic. There is a 2%–5% long-term risk of leukemic transformation into acute myeloid leukemia.

Treatment is centered on inhibition of platelet aggregation, especially in patients at high risk of thrombotic events, as well as cytoreduction. Aspirin and other antiplatelet agents such as ticlopidine and clopidogrel inhibit aggregation. Hydroxyurea and interferon alfa reduce platelet counts by bone marrow inhibition. Anagrelide, a phosphodiesterase inhibitor, has both platelet antiaggregating and cytoreductive properties.

Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2020;95(12):1599–1613.

Ophthalmic considerations Ocular manifestations of thrombocytosis include orbital hematopoiesis, subconjunctival hemorrhage, retinal hemorrhages, cotton-wool spots, retinal ischemia, retinal vein occlusion, optic nerve ischemia, and proliferative retinopathy. See BCSC Section 5, *Neuro-Ophthalmology,* and Section 12, *Retina and Vitreous,* for discussion of many of these conditions.

Platelet dysfunction

Patients with platelet dysfunction usually come to the physician's attention because of easy bruising, epistaxis, menorrhagia, or excessive bleeding after surgery or dental work. Unlike patients with marked thrombocytopenia, patients with platelet dysfunction rarely have petechiae.

Hereditary disorders of platelet function are rare. Much more important clinically are the acquired forms, most commonly caused by drugs. The list of causative agents is very long. Taking a single aspirin tablet irreversibly inhibits platelet aggregation for the life span of the circulating platelets present, causing a modest prolongation of bleeding time for at least 48–72 hours following ingestion. This reaction has remarkably little effect in otherwise healthy individuals, although intraoperative blood loss may be slightly increased. However, bleeding may be significant in patients with hemophilia, severe thrombocytopenia, or uremia and in those on warfarin or heparin therapy.

Nonsteroidal anti-inflammatory drugs cause reversible inhibition of platelet function in the presence of the drug; the effect disappears as the drug is cleared from the blood. Other commonly used drugs that may affect platelet function include ethanol, tricyclic antidepressants, and antihistamines.

In addition to uremia, clinical conditions associated with abnormal platelet function include liver disease, multiple myeloma, SLE, chronic lymphocytic leukemia, and Hermansky-Pudlak syndrome (an autosomal recessive form of oculocutaneous albinism).

Disorders of Blood Coagulation

Hereditary coagulation disorders

The various types of inherited coagulation abnormalities involve all of the coagulation factors except factors III and IV. The most severe of these abnormalities is factor VIII deficiency, called *hemophilia A,* or *classical hemophilia.* Factor IX deficiency is called *hemophilia B.* Both types have X-linked inheritance, and both are treated with infusions of the missing factor. Typical manifestations of hemophilia A include severe and protracted bleeding, after even minor trauma, and spontaneous bleeding into joints *(hemarthroses),* the central nervous system, and the abdominal cavity.

Treatment of hemophilia A involves infusion of factor VIII. With the availability of recombinant factor VIII, the risk of transmission of hepatitis B and C and HIV has now been mostly eliminated. However, approximately 5%–10% of patients with hemophilia A develop inhibiting antibodies, presumably as the result of sensitization following administration of factor VIII. These inhibitors bind to the infused factor VIII and render it ineffective; consequently, the patient will need bypassing agents such as recombinant factor VIIa or an anti-inhibitor coagulant complex. (Antibodies inhibiting coagulation can also develop in healthy older patients, in nonhemophilic patients after drug reactions, and in those with heritable connective tissue disorders. Clinical manifestations range from mild bleeding to full-blown hemophilia that correlates with level of factor deficiency. The aPTT is prolonged, while the PT is normal.) For patients with inhibitors, treatment consists of various regimens of coagulation factor replacement and immunosuppression in an attempt to eliminate the inhibitor. However, during episodes of bleeding or as prophylaxis before surgery, patients with high titers of inhibitor should receive recombinant factor VIIa or an anti-inhibitor coagulant complex as first-line therapy.

Emicizumab, a monoclonal antibody that binds factor IXa and supplants the need for factor VIIIa as a cofactor for factor X activation, was recently approved by the FDA and the European Commission for patients with hemophilia A, with or without factor VIII

inhibitors. An investigational monoclonal antibody, *concizumab,* which inhibits the tissue factor pathway, is now in clinical trials. Gene therapy is early in development, but there have been encouraging results.

von Willebrand disease (vWD) is the most common inherited bleeding disorder: low levels of von Willebrand factor (vWF) are found in 1% of the population. The 2 main functions of vWF are stabilizing factor VIII to prevent degradation and promoting platelet adhesion. There are 3 major types of vWD. *Type 1* is autosomal dominant and accounts for 75% of cases. *Type 2* (15%–20% of cases) has 4 subtypes and is predominantly autosomal dominant. *Type 3* (5%) is autosomal recessive. Type 1 manifests with mild mucocutaneous bleeding, and most forms of type 2 are associated with mild to moderate bleeding. In contrast, the recessively inherited forms are associated with very low levels of factor VIII and severe bleeding. A form of vWD also occurs in patients with aortic valve stenosis and in some patients with thrombocythemia. Desmopressin, a synthetic form of vasopressin (antidiuretic hormone), may be used for episodes of bleeding. It may also be administered preoperatively to reduce risk of surgical bleeding. Plasma-derived vWF concentrates, recombinant vWF, and combined vWF/factor VIII concentrates are available for patients who cannot tolerate or do not respond adequately to desmopressin or who need prolonged treatment.

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Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet.* 2021;397(10274): 630–640.

Nathwani AC. Gene therapy for hemophilia. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):1–8.

Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med.* 2017;377(9):809–818.

Acquired coagulation disorders

Vitamin K deficiency Vitamin K is required for the production of factors II (prothrombin), VII, IX, and X in the liver. Normal diets contain large amounts of vitamin K, which is also synthesized by intestinal flora. Causes of vitamin K deficiency include biliary obstruction and various malabsorption syndromes (including tropical sprue, cystic fibrosis, and celiac disease), in which intestinal absorption of vitamin K is reduced. Suppression of endogenous gastrointestinal flora, seen commonly in hospitalized patients on prolonged broad-spectrum antibiotic therapy, decreases intestinal production of vitamin K. However, clinical deficiency occurs only if dietary intake is also diminished. Nutritional deficiency is unusual but may occur with prolonged parenteral nutrition. Laboratory evaluation reveals prolongation of both PT and, later in the course of the disease, aPTT. Most forms of vitamin K deficiency respond to subcutaneous or intramuscular administration of 20 mg of vitamin K_1; coagulation defects normalize within 24 hours. Vitamin K_1 should not be given intravenously because of the risk of sudden death from an anaphylactoid reaction.

One special form of vitamin K deficiency is *hemorrhagic disease of the newborn,* which is the result of a normal mild deficiency of vitamin K–dependent factors during the first 5 days of life and the absence of the vitamin in maternal milk. This condition is now rare

in developed countries because of the routine administration of vitamin K to newborns. (See also the section Antiphospholipid Syndrome in Chapter 10.)

Liver disease Hemostatic abnormalities of all types may be associated with disease of the liver, the site of production of all the coagulation factors except factor VIII and factor XIII A-subunit. As liver dysfunction develops, levels of the vitamin K–dependent factors decrease first, followed by those of factors V, XI, and XII; both PT and aPTT are prolonged. Thrombocytopenia, primarily the result of hypersplenism, and a prolonged bleeding time due to platelet dysfunction are common. In addition, intravascular coagulation and fibrinolysis are often present, further complicating the clinical picture.

Mild hemorrhagic symptoms are common in patients with significant liver disease. Severe bleeding is usually gastrointestinal in origin, arising from peptic ulcers, gastritis, or esophageal varices. Treatment is difficult at best and consists of blood and coagulation factor replacement. Local measures, such as vasopressin infusion or balloon tamponade of bleeding varices, can sometimes control potentially catastrophic bleeding.

Disseminated intravascular coagulation *Disseminated intravascular coagulation (DIC)* is a complex syndrome involving widespread activation of the coagulation and fibrinolytic systems in the general circulation. The syndrome is a secondary process, triggered by exposure of procoagulants to the bloodstream, which activates the coagulation cascade, leading to the formation of fibrin and fibrin degradation products (fibrin split products), which results in occlusion of the microcirculation as well as various forms of organ failure and, occasionally, thrombosis of larger vessels. Subsequently, utilization and consumption of the coagulation factors and platelets produce bleeding. Laboratory findings may vary but usually include thrombocytopenia, hypofibrinogenemia, and elevated levels of fibrin split products. PT and aPTT are usually, but not invariably, prolonged.

Clinically, 2 forms of DIC are recognized. *Acute DIC* is characterized by the abrupt onset of severe, generalized bleeding. The most common causes are obstetric complications (most notably abruptio placentae and amniotic fluid embolism), septicemia, shock, massive trauma, malignancy (especially acute promyelocytic leukemia), ABO incompatibility, and major surgical procedures. Bleeding, thrombocytopenia, prolonged PT/aPTT, reduced procoagulant factors, low plasma fibrinogen, and reduced levels of coagulation inhibitors are characteristics of acute DIC. Treatment, other than specific measures aimed at the underlying disease, is controversial. Among the modalities used are heparinization and replacement of blood, platelets, and fibrinogen.

Chronic DIC is associated with disseminated solid-tumor neoplasms (pancreatic, ovarian, gastric, or brain) and autoimmune diseases. Laboratory values range from normal to moderately abnormal; levels of coagulation factors may even be elevated (high plasma fibrinogen). Bleeding and thrombosis (especially lower extremity deep venous thrombosis and pulmonary embolism) may occur, but the syndrome remains undiagnosed in most patients unless renal failure results from intravascular coagulation in the kidney. Many patients with chronic DIC do not require specific therapy for the coagulopathy because it is not severe enough to present a major risk of bleeding or thrombosis. On occasion, chronic DIC may convert to the acute form.

Thrombotic disorders

The hypercoagulable states encompass a group of inherited and acquired thrombotic disorders that increase the risk of thrombosis *(thrombophilia)*. The *primary hypercoagulable states* are caused by abnormalities of specific coagulation proteins resulting from inherited mutations in one of the antithrombotic factors. The trigger for a thrombotic event is often the development of an acquired secondary hypercoagulable state superimposed on an inherited state of hypercoagulability. The *secondary hypercoagulable states* lead to a thrombotic tendency by means of complex and often multifactorial mechanisms.

Primary Hypercoagulable States

Activated protein C resistance (factor V Leiden mutation)

Factor V is a procoagulant factor that amplifies thrombin production. Most patients with activated protein C (APC) resistance harbor a single specific point mutation in the factor V gene, termed *factor V Leiden,* which renders both forms of factor V (active and inactive) insensitive to APC proteolysis. This mutation occurs with remarkable frequency (3%–7%) in healthy White populations but appears to be far less prevalent or even absent in certain Black and Asian populations. The major clinical manifestation of the heterozygous form is deep venous thrombosis or pulmonary embolism, for which there is a lifetime risk of 5% in the general population but up to 20% in families with history of thrombophilia. Asymptomatic heterozygotes with no history of thromboembolic events do not need to be routinely screened for other thrombophilias or treated with anticoagulants except in high-risk situations such as surgery or pregnancy.

Kujovich JL. Factor V Leiden thrombophilia. May 14, 1999; updated January 4, 2018. *GeneReviews*. Accessed September 2, 2022. www.ncbi.nlm.nih.gov/books/NBK1368

Prothrombin G20210A gene mutation

The G20210A mutation in the prothrombin gene has been associated with elevated plasma levels of prothrombin. It is second only to factor V Leiden as a genetic risk factor for venous thrombosis and is also a risk factor for premature cardiovascular disease. It is much more common among White populations than in other populations. The risk of venous thromboembolism (VTE) increases 20-fold when both prothrombin G20210A and factor V Leiden mutation are present in the same individual.

Antithrombin deficiency

Antithrombin deficiency is rare. It leads to increased thrombin generation and, hence, fibrin accumulation with a lifelong propensity for thrombosis. A meta-analysis of case control and cohort studies showed a 16-fold increased risk of VTE in patients with antithrombin deficiency. This mutation may be acquired or hereditary.

Protein C deficiency

Protein C deficiency is also rare, affecting between 0.2% and 0.5% of the general population. This disorder leads to unregulated fibrin generation due to impaired inactivation

of factors VIIIa and Va. The risk of VTE in patients who have protein C deficiency is increased 7-fold compared to that of persons without this deficiency.

Protein S deficiency

Protein S is the principal cofactor of APC; therefore, its deficiency mimics that of protein C. The prevalence of this condition in patients presenting with VTE is approximately 1%, and patients with protein S deficiency have 5 times the risk of developing VTE than those without this deficiency.

Screening for inherited thrombophilia

Screening for these conditions in the unselected general population is not recommended because of the low prevalence, low and variable penetrance among carriers, and lack of safe and cost-effective prophylaxis. Screening would be appropriate in the following groups:

- pedigrees that include multiple first-degree relatives with inherited thrombophilia and VTE onset before age 50
- family members of probands with symptomatic thrombophilia, particularly those who have protein C, protein S, or antithrombin deficiency
- women who plan to use oral contraceptives or hormone replacement therapy and have a family history of VTE with thrombophilia

Screening for methylenetetrahydrofolate reductase gene *(MTHFR)* variants, assaying homocysteine levels, or seeking plasminogen activator/promoter variants is not recommended, as there is no evidence that risk for blood clots is significantly higher or that prophylactic anticoagulation reduces risk.

Bravo-Pérez C, Vicente V, Corral J. Management of antithrombin deficiency: an update for clinicians. *Expert Rev Hematol.* 2019;12(6):397–405.

Hyperhomocysteinemia

Hyperhomocysteinemia, which is caused by elevated blood levels of homocysteine, leads to severe neurologic developmental abnormalities in the homozygous state. Adults with the heterozygous state may have only thrombotic tendencies. Acquired causes of hyperhomocysteinemia in adults commonly involve nutritional deficiencies of pyridoxine, vitamin B_{12}, and folate, all of which are cofactors in homocysteine metabolism. High blood concentration of homocysteine constitutes an independent risk factor for both venous and arterial thrombosis; in contrast, all of the other primary hypercoagulable states are associated only with venous thromboembolic complications, usually involving the lower extremities. The initial treatment of acute venous thrombosis in these patients does not differ from that in patients without genetic defects.

Ophthalmic considerations Primary hypercoagulable states, particularly factor V Leiden mutation and subsequent APC resistance, are risk factors for central and branch retinal vein occlusion, particularly in young patients.

Secondary Hypercoagulable States

Malignancy may stimulate thrombosis directly by elaborating procoagulant substances that initiate chronic DIC. This process appears to be most prominent in patients with pancreatic cancer, adenocarcinoma of the gastrointestinal tract or lung, or ovarian cancer. *Myeloproliferative disorders* (see the earlier section "Thrombocytosis and essential thrombocythemia") are major causes of thrombosis and paradoxical bleeding, as is *paroxysmal nocturnal hemoglobinuria,* a related stem cell disorder.

Antiphospholipid syndrome is characterized by both venous and arterial thrombosis, including recurrent spontaneous abortions, deep venous thrombosis, and thrombotic events involving the cerebrovascular arteries. Evaluation of patients with this syndrome includes tests for anticardiolipin antibodies and lupus anticoagulants. See the section Antiphospholipid Syndrome in Chapter 10 for additional discussion.

Hypercoagulability associated with pregnancy involves a progressive state of DIC throughout the course of pregnancy, activated in the uteroplacental circulation. Oral contraceptives induce similar changes. The postoperative state and trauma are significant causes of venous thrombosis.

Ophthalmic considerations Ophthalmic complications of antiphospholipid syndrome include retinal vein and artery occlusion, retinal vasculitis, choroidal infarction, and nonarteritic anterior ischemic optic neuropathy.

Therapeutic anticoagulation

Many clinical situations require intentional disruption of the hemostatic process. The effect of aspirin on platelet function has already been discussed.

Unfractionated heparin (UFH) is a mucopolysaccharide that binds antithrombin III, potentiating its effects and inhibiting the formation of thrombin. It is given intravenously or subcutaneously, and therapy is assessed by measuring the aPTT. Aspirin should not be given to patients receiving heparin because the resultant platelet dysfunction may provoke bleeding. *Low-molecular-weight (LMW) heparins* are another type of parenteral anticoagulant. LMW heparins have a number of advantages over UFH, including greater bioavailability when given by subcutaneous injection and longer duration of anticoagulant effect, permitting once- or twice-daily administration. The dose is highly correlated with body weight, allowing administration of a fixed dose, and laboratory monitoring is not necessary. In addition, the risk of heparin-induced thrombocytopenia is lower.

Fondaparinux, which binds to antithrombin, is a synthetic anticoagulant that is very similar to UFH and LMW heparin. It exclusively catalyzes antithrombin inhibition of factor Xa. Because it is eliminated in the kidney, it should be used cautiously in patients with renal disease.

Direct parenteral thrombin inhibitors, such as argatroban and bivalirudin, are utilized during percutaneous coronary intervention and for the treatment of heparin-induced thrombocytopenia.

There are 2 groups of *direct oral anticoagulants: factor Xa inhibitors* (eg, rivaroxaban, apixaban, and edoxaban) and *direct thrombin inhibitors* (eg, dabigatran, lepirudin,

desirudin, bivalirudin and argatroban). These are fixed-dose oral agents that, unlike vitamin K antagonists, do not require routine laboratory monitoring or dose adjustments. Another advantage is that they reach their peak efficacy in 1–4 hours after ingestion; therefore, a period of bridging therapy is not required when switching from the initial treatment (eg, heparin) to these agents. Furthermore, unlike heparin and vitamin K antagonists, these drugs bind to circulating as well as clot-bound thrombin or factor Xa. Until recently, the major disadvantage of these drugs was that no antidotes were readily available in case of bleeding events. However, idarucizumab, a dabigatran-specific Fab fragment, is now available to reverse the effect of dabigatran, and andexanet alfa (a recombinant factor Xa decoy molecule) will reverse the effects of rivaroxaban and apixaban. Ciraparantag, which can potentially inhibit the anticoagulant effect of factor Xa inhibitors, is under investigation but is not yet FDA approved.

The orally administered *warfarin derivatives,* of which warfarin sodium is the most widely used, inhibit the production of normal vitamin K–dependent coagulation factors (II, VII, IX, and X). Therapeutic effect is assessed by measuring the patient's international normalized ratio (INR). One critical issue is the long list of commonly used drugs that interact with warfarin. These interactions may cause an unintended increase or decrease in the INR, depending on the drug.

Heparin and the warfarin derivatives are used to prevent the formation of new thrombi and the propagation of existing thrombi, but neither affects the original clot. *Thrombolytic agents* such as streptokinase, urokinase, and tissue plasminogen activator (tPA) are sometimes indicated to lyse existing thrombi, as in the very early stages of myocardial infarction and in the early treatment of thrombotic stroke.

See also Chapter 6, Table 6-1 (for oral antithrombotic drugs) and Table 6-2 (for subcutaneous or intravenous antithrombotic drugs), for lists of these drugs, their classifications, and their mechanisms of action.

Kaide CG, Gulseth MP. Current strategies for the management of bleeding associated with direct oral anticoagulants and a review of investigational reversal agents. *J Emerg Med.* 2020;58(2):217–233.

Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med.* 2017;377(5):431–441.

CHAPTER 10

Rheumatic Disorders

Highlights

- Rheumatic disorders are often associated with ocular manifestations. The initial manifestation of spondyloarthritis may be anterior uveitis.
- Children with the oligoarticular form of juvenile idiopathic arthritis should be periodically screened for uveitis, which is often asymptomatic.
- When atypical ocular vaso-occlusive disease occurs in a patient younger than 50 years, the clinician should consider antiphospholipid syndrome.
- New biologic agents target cytokines through various mechanisms: inhibiting tumor necrosis factor (TNF) α, blocking interleukin receptors, modifying T-cell or B-cell activity, or inhibiting the Janus kinase enzyme involved in mediating inflammation.
- Various ocular adverse effects, including optic neuritis and uveitis, may be associated with the use of anti–TNF-α agents.

Introduction

Rheumatic disorders are a heterogeneous collection of autoimmune and inflammatory diseases that include rheumatoid arthritis, spondyloarthritis, connective tissue diseases, and vasculitides. Ocular involvement is common in autoimmune diseases, but its prevalence and manifestations vary among the different disorders. Ophthalmologists should be familiar with these conditions, their potential for ocular involvement, and the pharmacotherapy used. If a patient has been diagnosed with a rheumatic disorder, it is important for the ophthalmologist and the rheumatologist to communicate and coordinate management. Treatment of rheumatic diseases commonly involves systemic anti-inflammatory and immunosuppressive therapies, some of which have ocular adverse effects. Drug therapy is discussed at the end of this chapter.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common rheumatic disorder, affecting approximately 1% of adults worldwide, and is twice as likely to occur in women than in men. RA is classically a progressive, symmetric, and deforming peripheral polyarthritis characterized by synovial inflammation, hypertrophy, and autoantibody production. Although it can involve any joint, RA primarily affects the small joints of the hands and feet. Typically, affected joints are swollen and tender, with decreased range of motion and deformity from bone and cartilage destruction.

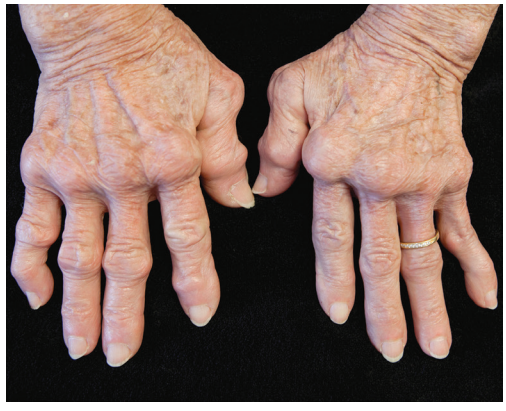

Figure 10-1 Rheumatoid arthritis showing characteristic ulnar deviation, swollen joints, and swan-neck deformities. *(Courtesy of Darin K. Bowers, MD.)*

Hand deformities (Fig 10-1) include nodules, ulnar deviation, Boutonnière deformity (abnormally flexed proximal interphalangeal [PIP] joint and extended distal interphalangeal [DIP] joint), and swan-neck deformity (abnormally hyperextended PIP and flexed DIP). Early diagnosis and treatment are critical in controlling joint damage and associated disability. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) continue to use the same classification criteria developed in 2010.

Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569–2581.

Extra-articular Manifestations

Extra-articular involvement, an indicator of disease severity, occurs in approximately 40% of RA patients during the course of the illness. Risk factors for systemic involvement include the presence of rheumatoid factor (RF), anti–cyclic citrullinated peptide (CCP) antibodies, and smoking. RA can affect almost all systems; manifestations include the following:

- subcutaneous rheumatoid nodules (in approximately 25% of patients)
- anemia of chronic disease (common in RA patients)
- increased risk of lymphoma
- Felty syndrome (seropositive RA, neutropenia, and splenomegaly)
- osteopenia and a higher risk of fractures
- pleural effusions, pulmonary nodules, and interstitial fibrosis
- cardiac disease (coronary artery disease, pericarditis and effusions, valvular disease from rheumatoid nodules, and cardiomyopathy from secondary amyloid deposition)
- peripheral vascular disease and vasculitis (small- to medium-sized vessels)
- carpal tunnel syndrome (from synovitis, compressive myelopathy, or radiculopathy)
- muscle weakness (primary or drug-induced myopathy)

Ocular involvement may include dry eye; scleritis; episcleritis; and corneal inflammation, melting, and infection. The ocular manifestations of RA are discussed in BCSC Section 8, *External Disease and Cornea*.

Laboratory Testing

Serologic testing is important in the workup and diagnosis of RA. *RF* is present in 70%–80% of patients with RA. However, it has limited specificity for the disease, because it can be positive in up to 10% of unaffected individuals and in approximately one-third of patients with systemic lupus erythematosus (SLE). *Anti–citrullinated peptide antibody (ACPA)* testing, specifically *anti-CCP* and *anti–mutated citrullinated vimentin (MCV),* is as sensitive as RF but has a higher specificity for RA (>95%). Nevertheless, in up to 50% of RA patients, the results of both ACPA and RF testing are negative. *Erythrocyte sedimentation rate (ESR)* and *C-reactive protein (CRP)* levels are usually elevated. *Antinuclear antibody (ANA)* testing is nonspecific, because only 30% of patients with RA test positive, but it can help exclude other diseases, such as SLE. Various protein biomarkers and genetic testing are being investigated as potential tools in diagnosing and managing RA.

Treatment

Treatment of RA involves an integrated approach, incorporating medications and nondrug therapies. Nonpharmacologic interventions include dietary counseling, exercise, physical therapy, smoking cessation, lipid control (to reduce the associated cardiovascular risks), and immunizations (to reduce the risk of infection linked with the use of immunosuppressive agents).

The ultimate goal of pharmacologic treatment (discussed in detail at the end of this chapter) is disease remission. Early diagnosis and treatment are imperative in preventing or delaying the long-term effects of disease progression. Treatment with *disease-modifying antirheumatic drugs (DMARDs)* should be started within 3 months of symptom onset.

DMARDs, which are divided into nonbiologic and biologic agents, have been shown to slow disease progression, reduce potential joint destruction, and maintain joint function while also limiting the need for long-term corticosteroid use. In addition to their anti-inflammatory effect, these drugs reduce the body's heightened autoimmune reaction. Thus, before DMARDs are initiated, the clinician should consider screening for preexisting infectious conditions such as hepatitis B and C and tuberculosis. Among *nonbiologic agents,* methotrexate is generally the first-line treatment, but other options are available. *Biologic agents,* developed through genetic engineering, are modified proteins that can target cytokines. The largest group of currently available biologic agents consists of tumor necrosis factor (TNF)-α inhibitors. Other biologics act by blocking interleukin (IL)-1 or IL-6 receptors or in modifying T-cell or B-cell activity. The mechanism of action of one emerging group of DMARDs, which are technically small-molecule drugs as opposed to true biologic agents, is the inhibition of the Janus kinase (JAK) enzyme involved in mediating inflammation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are sometimes used in combination with DMARDs. Limited-course *glucocorticoids* are sometimes necessary for controlling the acute stages of inflammation while waiting for the full effect of DMARD treatment.

Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2021;73(7):924–939.

Spondyloarthritis

Spondyloarthritis (SpA) represents a spectrum of human leukocyte antigen B27 (HLA-B27)–related rheumatic diseases that have a predilection for axial (spinal and sacroiliac joint) inflammation. The predominant symptom is low back pain, but a small subset of patients lack axial symptoms and have primary peripheral disease characterized by pain and swelling in the arms and legs. Men are affected 2–3 times more often than women. Among these diseases are ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and enteropathic arthropathies linked to inflammatory bowel disease (ulcerative colitis and Crohn disease). Syndromes that do not clearly fall into 1 of these categories and show no radiographic evidence of sacroiliitis are sometimes referred to as *nonradiographic axial spondyloarthritis.* What distinguishes SpA, in general, from other forms of arthritis is its tendency to cause inflammation in the ligaments and tendons that insert onto bone *(enthesitis);* the heel or Achilles tendon is a common target. Other features include asymmetric oligoarthritis and inflammation of fingers or toes *(dactylitis),* giving the appearance of "sausage digits." Axial radiographs or magnetic resonance imaging (MRI) of the sacroiliac joints can be helpful, although abnormalities are not always present early in the course of the disease.

Spondyloarthritis may occur in childhood, although it is rare before the second decade of life. The *juvenile-onset spondyloarthropathies* are generally classified as a type of juvenile idiopathic arthritis known as *enthesitis-related arthritis.* Because the radiographic findings are similar, SpA is sometimes misdiagnosed as the result of trauma. As in adults, most young patients are HLA-B27 positive, and males seem to be affected more often than females. These patients may develop acute uveitis characteristic of HLA-B27–associated uveitis.

Ophthalmologists should be familiar with these diseases because acute recurrent HLA-B27–associated anterior uveitis may be the presenting feature of SpA (see "Ophthalmic considerations" at the end of this section). With appropriate referral of patients with suspected SpA, early disease can be recognized and treated to limit future morbidity. See BCSC Section 9, *Uveitis and Ocular Inflammation,* for further discussion of the ophthalmic manifestations.

Ritchlin C, Adamopoulos IE. Axial spondyloarthritis: new advances in diagnosis and management. *BMJ.* 2021;372:m4447.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is the most common type of axial SpA. The cause is unknown, but the strong association with HLA-B27 (positive in up to 90% of patients with AS) suggests a genetic predisposition. The disease occurs most commonly in young men. Low back pain with limitation in spinal mobility is typical; complete spinal fusion may develop in later stages. Peripheral arthritis may also be present, most frequently affecting the ankles, hips, and knees. Extra-articular features of AS include a higher risk of cardiovascular disease, venous thromboembolism, stroke, and restrictive pulmonary disease.

NSAIDs are often the first-line treatment and are very effective, with 70%–80% of patients reporting significant improvement in symptoms. TNF-α and IL-17 inhibitors are effective as second- and third-line treatments, respectively; most clinicians consider their use after

the failure of 2 separate NSAID trials. Nonbiologic DMARDs (eg, sulfasalazine or methotrexate) tend to work better for peripheral arthritis than for primary axial disease. Local glucocorticoid injection is helpful in some patients.

Reactive Arthritis

Reactive arthritis is an unusual form of SpA that occurs after an infection, usually originating in the gastrointestinal (GI) or genitourinary system, and most commonly affects young adults, both men and women. The infectious organisms associated with this disease include *Chlamydia trachomatis* in the genitourinary tract and *Salmonella, Shigella, Yersinia,* or *Campylobacter* in the GI tract. Other microbes, including *Escherichia coli, Clostridioides (Clostridium) difficile,* and *Chlamydia pneumoniae* have recently been added to the list of causative agents. HLA-B27 and genetics appear to be involved in susceptibility to developing reactive arthritis after an infection.

The arthritic symptoms typically have their onset from days to weeks after the antecedent infection. The arthritis is aseptic because no microbes have been identified in the joints. Joint involvement is typically asymmetric and episodic, primarily affecting the knees and ankles. In addition to a preceding urethritis or diarrhea, extra-articular findings may include enthesitis (often of the knees and ankles), dactylitis ("sausage digits"), and sacroiliitis. Oral ulceration, nail pitting, and the skin eruptions of keratoderma blennorrhagicum (Fig 10-2) and erythema nodosum (Fig 10-3) can also occur. Ocular findings are present in up to 40% of patients (see "Ophthalmic considerations" at the end of this section).

The disease is often episodic, and most patients go into remission within 2 years. Any underlying infection should be treated with appropriate antibiotics. In most patients, NSAIDs are effective in managing inflammation. For refractory symptoms, glucocorticoid injection into inflamed joints or, more rarely, the use of biologic agents is sometimes necessary.

Enteropathic Arthritis

Spondyloarthritis may occur in association with *inflammatory bowel disease (IBD),* of which ulcerative colitis and Crohn disease represent the majority of cases. Males and

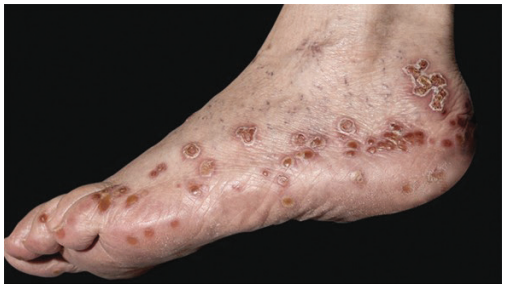

Figure 10-2 Keratoderma blennorrhagicum demonstrating hyperkeratotic lesions of the foot. The condition can also affect the scalp, trunk, and palms of the hands. The rash can resemble psoriasis. *(From Wolff K, Johnson RA, Saavedra AP.* Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. *7th ed. Copyright © 2013. Courtesy of Klaus Wolff, MD.)*

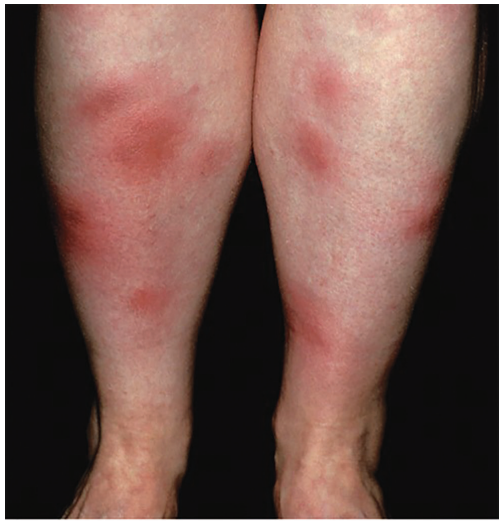

Figure 10-3 Erythema nodosum characterized by tender nodular eruptions, often involving the extensor surface of the legs below the knees. *(From Wolff K, Johnson RA, Saavedra AP.* Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. *7th ed. Copyright © 2013. Courtesy of Klaus Wolff, MD.)*

females are equally affected, although spondylitis is more common in men, and its onset can be from childhood to adulthood. *Ulcerative colitis* is characterized by inflammation of the GI mucosa with diffuse involvement of the colon. *Crohn disease,* also known as *regional enteritis, granulomatous ileocolitis,* or *granulomatous colitis,* is a focal granulomatous disease that can affect both the large and small intestines. Symptoms of both ulcerative colitis and Crohn disease include diarrhea (with or without bleeding) and cramping abdominal pain. Arthritis tends to occur more frequently in patients with large-bowel involvement or with extraenteric findings such as erythema nodosum (see Fig 10-3), stomatitis, or uveitis. HLA-B27 prevalence is as high as 75% in patients with axial involvement and is somewhat lower in those with primarily peripheral disease.

Radiographic findings of axial involvement are similar to those of AS but are of limited value in diagnosing early disease. MRI may also be helpful in demonstrating abnormal axial and sacroiliac findings in symptomatic patients. Elevated acute phase reactants, including ESR and CRP, often indicate heightened GI inflammation but have limited benefit in assessing peripheral arthritis or spondylitis activity.

Psoriatic Arthritis

The skin disease psoriasis can be associated with SpA. Psoriatic arthritis has various presentations, including oligoarthritis (up to 4 joints), distal polyarthritis (more than 4 joints), and a more destructive type of arthritis known as *arthritis mutilans.* The prevalence of HLA-B27 is higher in these patients than in the general population (30% vs 6%), although not as high as in AS (up to 90%). The course of the disease varies, but it is often similar to the progression seen with RA. More than half of individuals who have the disease for more than 10 years develop deforming arthritis in 5 or more joints. Although methotrexate is sometimes initially used for treatment, various biologics and apremilast (a selective phosphodiesterase-4 inhibitor) have shown benefit. More recently, the JAK-1 inhibitor upadacitinib has been added to the list of effective treatments.

Ophthalmic considerations Of all the known immune disorders in North America and Europe, SpA, including the subtypes reviewed here, has the strongest association with uveitis. A small percentage of patients presenting with idiopathic acute anterior uveitis have undiagnosed SpA. Up to 40% of patients with either AS or reactive arthritis develop the typical manifestations of acute nongranulomatous iridocyclitis, which can be recurrent and bilateral. Ocular involvement tends not to correlate with the activity of the joint disease.

Culture-negative bilateral conjunctivitis, which is typically self-limited, is also a common manifestation of reactive arthritis. IBD is more frequently associated with episcleritis. Uveitis presents in up to 3% of patients with IBD, is significantly more common in females, and is not linked to the activity of the underlying disease. Ocular involvement with psoriatic arthritis is similar to that of other types of SpA, although the uveitis can be more insidious, posterior, and bilateral. See BCSC Section 9, *Uveitis and Ocular Inflammation,* for additional discussion.

Juvenile Idiopathic Arthritis

The term *juvenile idiopathic arthritis (JIA)* has replaced the older name, juvenile rheumatoid arthritis, because the disease has no direct relationship with adult-onset RA. Girls are affected more often than boys by a 3:1 ratio. The age at onset tends to be younger for girls (1–4 years) than for boys (8–10 years), and JIA is somewhat less common in African American and Asian populations than in White populations. As with many other autoimmune disorders, the pathogenesis of JIA is unclear.

Classification of JIA has always been challenging. The International League of Associations for Rheumatology divides JIA into the 7 categories shown in Table 10-1. Ocular involvement is most common in the oligoarticular group and least common in the systemic group. Patients with oligoarticular or polyarticular (especially RF-negative) disease should be periodically screened for ocular involvement because it is often asymptomatic. Furthermore, ANA positivity in patients with oligoarticular, polyarticular, or psoriatic arthritis is associated with an increased risk of developing uveitis. Other JIA-associated ocular sequelae include cataracts, glaucoma, and band keratopathy.

Systemic JIA may present with variable onset of intermittent fever, arthritis, macular rash, lymphadenopathy, hepatosplenomegaly, pericarditis, and pulmonary effusions. Laboratory findings of elevated ESR and CRP level and thrombocytosis are typical; ANA and RF are rarely present. The arthritis can involve any number of joints. Ocular involvement is not typical for this form of JIA.

Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res (Hoboken).* 2019;71(6):703–716.

Table 10-1 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA) and Recommended Frequency of Ocular Examination

Subtype	Percentage of JIA Cases	Sex	Percentage of JIA Patients With Uveitis	Ocular Examination Interval, Months	
				ANA+	ANA–
Oligoarticular	40–50	F > M	Approx. 30	3	6–12
RF-negative, polyarticular	20–25	F > M	Approx. 10	3	6–12
RF-positive, polyarticular	5	F > M	<1	6–12	6–12
Psoriatic	5–10	F > M	Approx. 10	3	6–12
Enthesitis-related	5–10	M > F	Approx. 10	6–12	6–12
Systemic	5–10	F = M	<1	6–12	6–12
Undifferentiated	10–15	–	Unknown	6–12	6–12

ANA = antinuclear antibody; approx. = approximately; F = female; M = male; RF = rheumatoid factor.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease of undetermined cause that presents with a wide range of clinical manifestations and can involve any organ. It is characterized by remissions and relapses, from mild to severe. The disease is estimated to affect 240 per 100,000 people in the United States, with reduced rates in Europe and the lowest prevalence in Africa and Australia. Women are affected far more frequently than men, and the median age at onset is between 35 and 50 years. Individuals of African, Asian, and Native American heritage are more likely than White individuals to develop SLE. It is associated with B-cell hyperactivity, hypergammaglobulinemia, and a plethora of autoantibodies. These include ANA as well as antibodies to DNA and cytoplasmic components. SLE has classically been considered an immune complex disease that leads to an inflammatory response and tissue damage.

Clinical Findings

Patients may present with single-organ involvement, such as nephritis, or with multisystem disease. The characteristic cutaneous manifestation of SLE is the *butterfly rash* (or *malar rash*) across the nose and cheeks, which appears in 70%–80% of patients (Fig 10-4). Other cutaneous manifestations include discoid lesions, which often lead to scarring, and alopecia. Mucosal lesions, usually painless oral or nasal ulcers, are present in up to 40% of patients. Acute or chronic photosensitivity occurs in many patients.

Approximately 90% of patients with SLE experience articular disease, as either polyarthralgia or nondeforming migratory polyarthritis. Constitutional symptoms, such as fatigue, fever, myalgia, and weight loss, are common. Renal disease affects approximately 50% of patients; it can present with a range of manifestations from hematuria, proteinuria, and nephrotic syndrome to fulminant glomerulonephritis and renal failure.

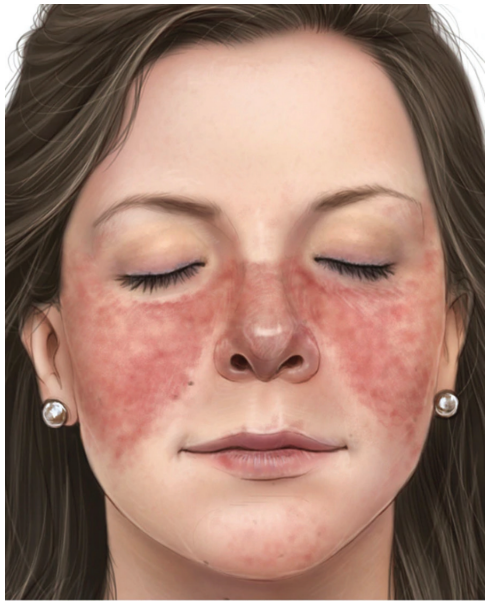

Figure 10-4 Malar (butterfly) rash in a patient with systemic lupus erythematosus. *(Used with permission from Mayo Foundation for Medical Education and Research. All rights reserved.)*

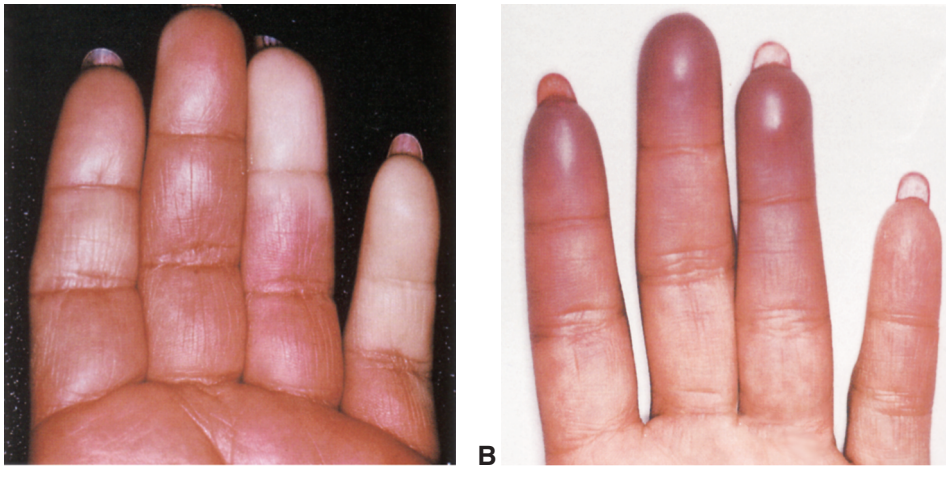

Figure 10-5 Raynaud phenomenon. **A,** Sharply demarcated pallor resulting from the closure of digital arteries. **B,** Digital cyanosis of the fingertips in a patient with primary Raynaud phenomenon. *(Reproduced with permission from Wigley FM. Clinical practice. Raynaud's phenomenon.* N Engl J Med. *2002;347(13):1001. Copyright © 2002 Massachusetts Medical Society.)*

Raynaud phenomenon occurs in up to 50% of patients with SLE (Fig 10-5). Anemia of chronic disease is common, along with a reduction in leukocytes and platelets. The rate of coronary artery disease is significantly greater in SLE patients than in unaffected individuals. Other, less common cardiac manifestations include pericarditis, myocarditis, and Libman-Sacks endocarditis. Valvular disease has been reported in more than 50% of patients.

Thromboembolism is more common in SLE, especially in the presence of antiphospholipid antibodies and lupus anticoagulant. Pulmonary involvement includes pleuritis, interstitial lung disease, and pulmonary hypertension. GI manifestations are varied and include dysphagia, esophagitis, hepatitis, and pancreatitis (GI symptoms are sometimes related to medications). Central nervous system (CNS) involvement occurs in more than one-third of patients, and symptoms are typically transient. The most common presentations of neurologic lupus are headache, cognitive impairment, seizures, psychosis, and peripheral neuropathy.

Ophthalmic considerations Ocular involvement in SLE is present in up to a third of patients and may correlate with systemic disease activity. The most common ocular manifestation of SLE is keratoconjunctivitis sicca from secondary Sjögren syndrome. Other manifestations include discoid cutaneous lesions of the eyelids as well as retinal or choroidal microvascular lesions. Cotton-wool spots, hemorrhages, vascular occlusions, and neovascularization may be present. The inflammatory vasculopathy of SLE should be distinguished from vascular damage caused by secondary problems such as hypertension from renal disease or occlusions due to embolic disease or antiphospholipid antibodies. Typical anterior or intermediate uveitis is not a common feature of SLE. Neuro-ophthalmic involvement in SLE includes cranial nerve palsies, lupus optic neuropathy, and central retrochiasmal disorders of vision. Orbital inflammation has rarely been reported. Cerebral disorders of vision include hallucinations, visual field defects, and cortical blindness. (See also BCSC Section 9, *Uveitis and Ocular Inflammation,* and Section 12, *Retina and Vitreous.*)

Dammacco R. Systemic lupus erythematosus and ocular involvement: an overview. *Clin Exp Med*. 2018;18(2):135–149.

Diagnosis

The diagnosis of SLE can be challenging because of myriad variable signs and symptoms and requires the exclusion of other diseases in the workup. Table 10-2 lists the 2019 SLE classification criteria developed jointly by EULAR and the ACR. Although the classification system was intended primarily for research purposes, clinicians have found it useful in diagnosing and documenting the disease. The classification uses an ANA titer ≥1:80 as the entry criterion; additive criteria are grouped in 7 clinical and 3 immunologic domains and are weighted from 2 to 10. SLE classification requires ≥10 points and must include at least 1 clinical criterion. This classification has a sensitivity of 96% and a specificity of 93%.

Treatment

The treatment of SLE depends on disease severity. SLE can have a varied clinical course, ranging from a relatively benign illness to fulminant organ failure and death. Most patients have a relapsing and remitting course that requires frequent titration of medications.

Table 10-2 Classification Criteria for Systemic Lupus Erythematosus (SLE)

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE.
If present, apply additive criteria.

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least 1 occasion is sufficient.
SLE classification requires at least 1 clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest-weighted criterion is counted toward the total score.[a]

Clinical Domains and Criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g/24 h	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10

Immunology Domains and Criteria	Weight
Antiphospholipid antibodies	
Anticardiolipin antibodies OR Anti-β_2GPI antibodies OR Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody[b] OR Anti-Smith antibody	6

Total score

↓

Classify as SLE with a score of 10 or more if entry criterion fulfilled.

Anti-β_2GPI = anti–β_2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA; HEp-2 = human epidermoid cancer cell 2.

[a] Additional criteria within the same domain will not be counted.

[b] In an assay with ≥90% specificity against relevant disease controls.

Modified with permission from Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71(9):1400–1412. Fig 2.

Nonpharmacologic measures include sun protection to address photosensitivity, smoking cessation to reduce cardiovascular risks, and immunizations to decrease infection risk (if immunosuppressive agents are used). The most commonly prescribed medication is hydroxychloroquine. Alternatively, treatment may include NSAIDs, glucocorticoids (preferably low dose and short term), and immunosuppressive drugs. If antiphospholipid antibodies are present, low-dose aspirin appears to reduce the risk of thrombosis. Anifrolumab, a type I interferon receptor antagonist recently approved by the US Food and Drug Administration (FDA), has shown benefit in patients with moderate to severe SLE in whom at least 1 other first-line treatment failed.

Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736–745.

Sarcoidosis

Sarcoidosis is a multisystem disease of unknown cause in which noncaseating granulomas are present in affected tissues. The disease occurs primarily in young adults. Although any organ can be affected, there is a tendency for hilar adenopathy and pulmonary infiltrates, as well as joint and skin involvement. Common signs and symptoms include cough, fever, weight loss, dyspnea, arthralgias, and erythema nodosum (see Fig 10-3).

Clinical Findings

Pulmonary findings are the most typical (present in approximately 30% of patients), while extrapulmonary manifestations vary widely by ethnicity and sex. The skin, liver, and eye tend to be involved more commonly in African American individuals than in White individuals. Skin and ocular manifestations occur more frequently in females than in males, while the incidence of cardiac involvement is higher in males. Cutaneous findings vary and include papules, plaques, and nodules, such as the painful nodules of erythema nodosum. Arthropathy occurs in 10%–15% of affected individuals. It tends to be acute rather than chronic and can be mistakenly diagnosed as reactive arthritis.

Ophthalmic considerations An ophthalmologic examination is an important part of the workup of any patient suspected of having sarcoidosis. Ocular manifestations occur in approximately 25% of patients with sarcoidosis and are the presenting symptom in 5% of cases. Eye involvement can include any periocular structure (skin, orbit, lacrimal gland, and muscles) as well as anterior and posterior segments. Optic nerve involvement is less common. Uveitis associated with sarcoidosis is discussed in greater detail in BCSC Section 9, *Uveitis and Ocular Inflammation*.

Diagnosis

Histologic examination is valuable in confirming the diagnosis. Common biopsy sites include lung, lymph node, skin, liver, and bone marrow. Conjunctival biopsy of nodules suggestive

of sarcoidosis may reveal confirmatory histologic findings. Pathology reveals granulomatous inflammation (usually noncaseating). In 3 situations, however, a diagnosis can be reasonably established without biopsy:

- Löfgren syndrome (erythema nodosum, hilar adenopathy, migratory polyarthralgia, and fever)
- Heerfordt-Waldenström syndrome (parotid gland swelling, facial nerve palsy, uveitis, and fever)
- asymptomatic bilateral hilar adenopathy

Biopsy of erythema nodosum skin lesions is not helpful, because granulomas are not associated with the eruption.

No serologic test is pathognomonic for sarcoidosis. Although serum angiotensin-converting enzyme (ACE) level is elevated in 75% of patients with sarcoidosis, poor sensitivity and reduced specificity limit its usefulness. Pulmonary imaging is helpful and may include radiography, computed tomography, or positron emission tomography scans.

Treatment

Patients with asymptomatic disease often do not require treatment. Spontaneous remission is common for mild disease. For patients with more extensive manifestations, treatment is tailored to the affected systems. Glucocorticoids are typically the first line of treatment, and maintenance doses are sometimes required for years. For refractory cases, DMARDs are sometimes used. See also BCSC Section 9, *Uveitis and Ocular Inflammation.*

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder that predisposes patients to arterial or venous thrombosis. It occurs as a primary condition or in association with other autoimmune diseases, especially SLE.

Clinical Findings

Deep venous thrombosis is the most common type of thrombosis, occurring in approximately one-third of patients with APS. Episodes of thrombosis can recur, particularly in patients with high antiphospholipid antibody titers. Patients may also have pulmonary embolism and superficial thrombophlebitis. CNS disease can include strokes, transient cerebral ischemia (formerly called transient ischemic attack), dementia, and even psychosis. APS should be considered when thrombosis or cerebrovascular disease occurs in a young patient without other risk factors for stroke.

This syndrome can cause complications during pregnancy. Patients may have multiple first-trimester spontaneous abortions and premature births due to preeclampsia or placental insufficiency; late-term fetal death may also occur.

Other manifestations of APS include thrombocytopenia, hemolytic anemia, nephropathy, and livedo reticularis. Cardiac manifestations include valvular thickening and nodules *(Libman-Sacks endocarditis).* In rare instances, a severe form of APS can occur with multiple

vessel occlusions and multiorgan failure. This form of the disease is called *catastrophic antiphospholipid syndrome* and has a mortality rate of 48%.

Diagnosis

In patients suspected of having APS, immunoassays are performed to detect the presence of anticardiolipin antibodies (immunoglobulin [Ig] G and IgM), anti–β_2-glycoprotein antibodies (IgG and IgM), and lupus anticoagulants. Additional testing for underlying autoimmune disease in patients newly diagnosed with APS should be considered because SLE, in particular, is present in up to 36% of cases.

Ophthalmic considerations Ocular manifestations of APS include transient monocular blindness, ischemic optic neuropathy, and retinal vascular occlusion. Visual field loss, diplopia, and even proliferative retinopathy have also been reported. Clinicians should consider APS when atypical ocular vaso-occlusive disease occurs in patients who are younger than 50 years or who have bilateral findings. Coordination with the patient's primary care physician or rheumatologist is important in the workup.

Treatment

Therapy for thrombosis usually consists of heparin, followed by warfarin. The optimal duration of treatment is not known: some experts believe that anticoagulation can be discontinued if the antiphospholipid antibody titers decrease, but lifelong treatment is recommended for patients with recurrent disease. Associated autoimmune disorders are often treated with drugs such as hydroxychloroquine to help reduce the risk of APS complications. Treatment of patients who are pregnant remains controversial; it may include some combination of heparin or low-molecular-weight heparin and aspirin because warfarin is teratogenic. Patients with antiphospholipid antibodies without a history of thrombosis may benefit from prophylactic aspirin. The use of autologous stem cell transplantation or rituximab has been investigated, but the benefits remain questionable.

Erkan D, Ortel TL. Management of antiphospholipid syndrome. UpToDate.com. Updated November 8, 2022. Accessed October 6, 2023. https://www.uptodate.com/contents/management-of-antiphospholipid-syndrome

Systemic Sclerosis

Systemic sclerosis (SSc), formerly known as *scleroderma,* is a relatively uncommon connective tissue disorder characterized by fibrous and degenerative changes in the skin and other organ systems. The term *scleroderma* is often used for sclerosis affecting only the skin. SSc is further classified into *limited* and *diffuse* subtypes, depending mainly on the extent of skin involvement. The etiology of this disease is poorly understood but involves activation of fibroblasts that cause excessive collagen deposition, inflammation, and fibrosis. SSc is 4 times more common in women than in men, with age at onset typically in the third or fourth

decade of life. African American individuals have higher rates of the diffuse form than other racial groups. The limited form of SSc rarely involves internal organs, and affected patients have a better prognosis, often with a normal life span. It is frequently associated with *CREST syndrome* (*c*alcinosis, *R*aynaud phenomenon, *e*sophageal involvement, *s*clerodactyly, and *t*elangiectasia).

Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. *Expert Rev Clin Immunol.* 2019;15(7):753–764.

Clinical Findings

The hallmarks of SSc are changes to the skin, namely thickening, tightening, and induration, with subsequent loss of mobility and contracture (Fig 10-6). The disease usually begins peripherally, in the fingers and hands, and subsequently spreads centripetally up the arms to involve the face and body. Telangiectasia and calcinosis are common. Vascular effects also occur; more than 95% of SSc patients experience Raynaud phenomenon (see Fig 10-5). Less frequently, permanent damage to blood vessels can result in digital ulcers and ischemia.

Organ involvement is present in more than 90% of patients; the most common is esophageal dysmotility with gastroesophageal reflux secondary to stricture formation and submucosal fibrosis. The small and large intestines may also be affected, with decreased motility, malabsorption, and diverticulosis. Cardiopulmonary disease is manifested primarily by pulmonary vascular fibrosis leading to restrictive lung disease and decreased diffusing capacity, pulmonary hypertension, and right-sided heart failure. These complications, along with arrhythmias arising from cardiac fibrosis, account for a cumulative 5-year survival rate of approximately 75% from the time of diagnosis. Musculoskeletal characteristics include polyarthralgias, tendon friction rubs, and occasionally myositis. Renal disease is seen in approximately 50% of patients.

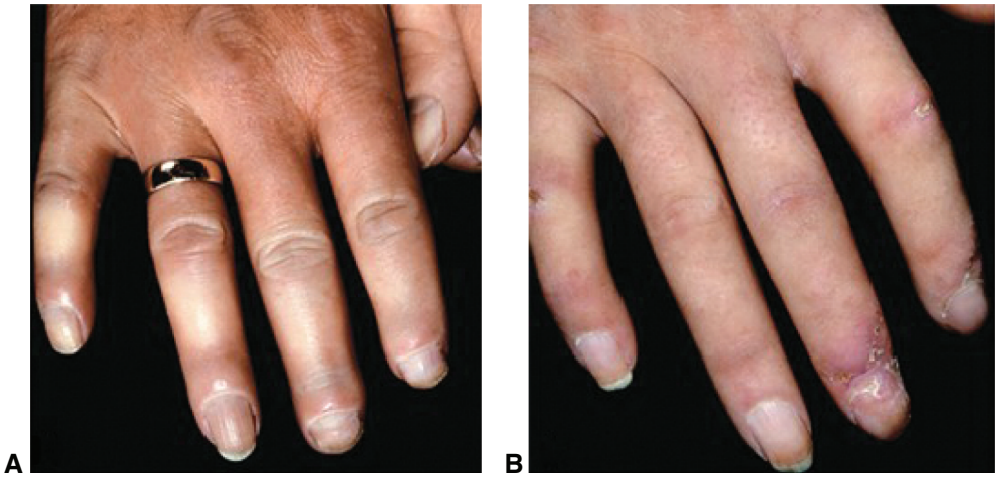

Figure 10-6 Typical skin changes in systemic sclerosis. **A,** Thickening and tightening of the fingers. **B,** Associated ischemic changes in the peripheral digits. *(From Wolff K, Johnson RA, Saavedra AP.* Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. *7th ed. Copyright © 2013. Courtesy of Klaus Wolff, MD.)*

Ophthalmic considerations Ocular involvement occurs in approximately 50% of patients with SSc; the most common manifestations are periocular skin fibrosis and tightening, along with keratoconjunctivitis sicca. The skin changes may lead to blepharophimosis or lagophthalmos. Patchy choroidal nonperfusion related to diffuse microvascular damage may appear on fluorescein angiography. Occasionally, as a result of renal involvement, a patient can develop retinopathy from malignant hypertension, with cotton-wool spots, intraretinal hemorrhages, and optic nerve head edema.

Diagnosis

The great majority of patients with SSc test positive for ANA. Other useful serologic tests include anti–DNA topoisomerase I and anti–RNA polymerase III, which are highly specific for the disease. Anticentromere antibody is often present in the limited subtype of SSc. These specific serologies help classify the disease and various syndromes that overlap with SSc.

Treatment

Treatment is aimed at controlling problems in the specific organ systems involved. Several agents in the antihypertensive class of endothelin-1 receptor antagonists are sometimes beneficial in patients with pulmonary hypertension. ACE inhibitors are typically used for the treatment of hypertension due to renal disease. Patients with Raynaud phenomenon are treated with calcium channel blockers. Immunosuppressive agents, including methotrexate and cyclophosphamide, have proved effective in the treatment of diffuse SSc cutaneous manifestations and may slow the progression of disease. Management of inflammatory joint disease is similar to that of RA.

Sjögren Syndrome

Sjögren syndrome is a chronic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. It can occur alone (primary form) or in conjunction with other autoimmune disorders (secondary form), especially RA, SLE, or SSc. The syndrome can present at any age and in either sex, although women in the fifth and sixth decades of life are the most commonly affected. Typical symptoms include dry eyes, dry mouth with difficulty swallowing, and dry skin (xerosis). Parotid and lacrimal gland enlargement *(Mikulicz syndrome)* can occur in more severely affected individuals. Because of the ocular symptoms, the ophthalmologist may be the first physician to see these patients and may either lead the diagnostic workup or collaborate with a rheumatologist.

Patients with primary Sjögren syndrome may have a number of systemic manifestations, including upper-airway dryness, mucous plug development, purpuric vasculitis, and hyperglobulinemia. Although approximately 50% of patients report symptoms of arthralgia, arthritis is less common; and some patients may have subclinical inflammatory myopathy. Mild anemia across all cell lines is found in approximately 20% of patients, and

the overall risk of non-Hodgkin lymphoma is increased. Central and peripheral neurologic involvement may be present and mimic multiple sclerosis or psychiatric disorders.

The ACR and EULAR recently updated their classification criteria for primary Sjögren syndrome based on 5 objective measures. These include specific findings on labial salivary gland biopsy, presence of anti-Ro antibodies, abnormal ocular surface staining, abnormal Schirmer test result, and reduced unstimulated salivary flow. The classification is primarily used in research and has limited clinical usefulness.

Serologic workup often includes ANA, RF, and the autoantibodies anti-SS-A/Ro and anti-SS-B/La, of which up to 80% of patients have 1 or both present. Labial salivary gland biopsy can be helpful to confirm the disease in patients lacking evidence of autoimmunity (absent or low titers of autoantibodies or the absence of an associated autoimmune disorder). Research is directed at finding key biomarkers for Sjögren syndrome to provide more sensitive and specific testing.

Treatment is aimed at relief of symptoms and substitution or supplementation for reduced or absent secretions. Immunosuppression may be necessary in patients with systemic manifestations. See also BCSC Section 8, *External Disease and Cornea.*

Shiboski CH, Shiboski SC, Seror R, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis.* 2017;76(1):9–16.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are idiopathic inflammatory diseases of skeletal muscle characterized by progressive weakness affecting proximal muscle groups, particularly those of the shoulders and hips. Pathogenetically, dermatomyositis is associated with immune complex deposition in the vessels, whereas polymyositis appears to reflect T-cell–mediated muscle injury. Women are affected more frequently than men (2:1), with a peak incidence between 40 and 50 years. Both disorders are associated with polyarthritis, dysphagia, and interstitial pulmonary disease. Ocular involvement is relatively uncommon. In rare cases, the extraocular muscles may be involved, resulting in ophthalmoplegia.

Dermatomyositis is distinguished from polymyositis by the presence of cutaneous lesions. These skin lesions appear as an erythematous to violaceous rash that can affect the eyelids (*heliotrope rash;* Fig 10-7), cheeks, nose, chest *(V-neck sign),* and extensor surfaces *(Gottron sign).* The heliotrope rash is very specific for the disease.

Laboratory findings in both disorders include elevated levels of serum muscle enzymes and serum and urine myoglobin, as well as abnormal electromyography results. A wide range of autoantibodies is found in most patients, including several myositis-specific autoantibodies. Muscle biopsy may confirm the muscle damage from inflammation.

Glucocorticoids are typically initiated at the time of diagnosis and are usually tapered over a period of 9–12 months. Immunosuppressive agents, such as azathioprine or methotrexate, are sometimes used in patients unresponsive to steroid treatment or in those who develop adverse effects.

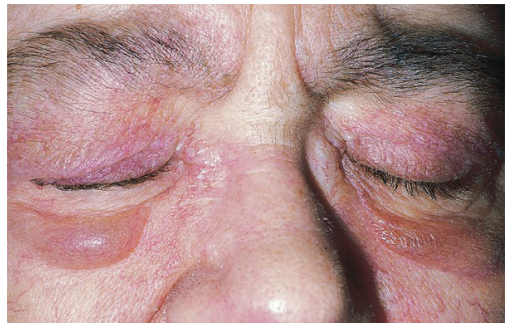

Figure 10-7 Heliotrope rash in dermatomyositis, with typical reddish-purple appearance and associated eyelid swelling. *(From Wolff K, Johnson RA, Saavedra AP.* Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. *7th ed. Copyright © 2013. Courtesy of Klaus Wolff, MD.)*

Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is a relatively common chronic inflammatory condition affecting older adults that is characterized by proximal myalgia and morning stiffness of the neck, shoulders, and hip girdle. The lifetime risk of this disease is second only to RA among rheumatic conditions in adults. PMR is notable for its association with giant cell arteritis (GCA), which approximately 10% of patients with PMR will develop. Similarly, up to 50% of patients diagnosed with GCA have manifestations of PMR. Although the etiology of both is unclear, many believe that the 2 entities share a common pathophysiology. People of European descent are at greatest risk, whereas Asian, Latino, and African American individuals are the least susceptible.

The onset of symptoms can be abrupt. They are most noticeable when arising from bed in the morning; in fact, the absence of morning stiffness helps to exclude the diagnosis. Associated synovitis can limit the range of motion of affected joints: the classic finding in a patient with PMR is the inability to raise the arms above 90°. Patients with PMR should be asked about symptoms characteristic of GCA (eg, scalp tenderness, jaw claudication). The ESR and CRP level are often elevated. Temporal artery biopsy is not indicated in patients without signs and symptoms of GCA because it rarely yields positive results. For more information on GCA, see BCSC Section 5, *Neuro-Ophthalmology.*

Prednisone typically brings dramatic relief in 2–3 days, with complete recovery often occurring within 3 weeks. In patients without relapses, prednisone can usually be tapered off in 1 year. If patients need longer-term treatment, methotrexate may be helpful in reducing the corticosteroid requirement. Biologics have not shown consistent results.

Relapsing Polychondritis

Relapsing polychondritis is a rare, episodic autoimmune disorder characterized by widespread, potentially destructive inflammation of cartilage throughout the body, including ears (most commonly involved), nose, cardiac and respiratory structures, joints, and eyes. Males and females of all ages and races can be affected, although White individuals seem more susceptible. In up to one-third of patients, relapsing polychondritis can be

associated with other connective tissue diseases (eg, SLE or RA), systemic vasculitis, or malignancy.

The disease is variable in duration and severity. Nasal bridge involvement can progress to cause saddle nose deformity from cartilage collapse. Laryngotracheobronchial disease may be insidious but can lead to the fatal complication of laryngeal collapse. Ocular manifestations, which occur in up to 60% of patients, include episcleritis, scleritis, uveitis, and, rarely, retinal vasculitis. Involvement of the inner ear, cardiovascular system, and skin is less common. Cardiovascular problems include aortic insufficiency (due to progressive dilation of the aortic root) and vasculitis. Skin lesions are most often caused by cutaneous vasculitis.

Treatment focuses on reducing symptoms and preserving the integrity of cartilaginous structures. Pharmacotherapy includes systemic corticosteroids, dapsone, methotrexate, and cyclophosphamide. Patients may require surgical interventions such as tracheostomy, aortic aneurysm repair, and cardiac valve replacement.

Vasculitis

The systemic vasculitides are a group of diseases whose principal pathology involves autoimmune damage to blood vessels, which can result in ischemia and necrosis of supplied tissues. These diseases are grouped according to the size and location of affected vessels. Vasculitis can occur as a primary disease state or as a secondary condition associated with other immune disorders or with exogenous factors such as infection, neoplasia, or medication. Table 10-3 outlines the most recent Chapel Hill Consensus Conference names for some of the more common vasculitides. The following subsections emphasize the primary vasculitides that are more likely to have ophthalmic involvement.

Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum.* 2013;65(1):1–11.

Large-Vessel Vasculitis

Giant cell arteritis

Giant cell (temporal) arteritis (GCA) is a potentially blinding granulomatous inflammatory disease involving the aorta and its branches. The disease almost exclusively affects individuals older than 50 years and is of particular concern to ophthalmologists. See BCSC Section 5, *Neuro-Ophthalmology,* for further discussion.

Takayasu arteritis

Like GCA, Takayasu arteritis affects large arteries, particularly branches of the aorta. Unlike GCA, it occurs primarily in children and young women. The disease is rare in Western countries but is more common in Asia, particularly Japan.

Takayasu arteritis (also called *aortic arch arteritis, aortitis syndrome,* and *pulseless disease*) may involve the entire aorta, or it may be localized to any segment of the aorta or its primary branches. The inflammatory process is characterized by panarteritis with granulomatous inflammation. The involved vessels may ultimately become narrowed or obliterated, resulting in ischemia of the supplied tissues. Areas of weakened vascular walls may develop dissections or aneurysms.

Table 10-3 Names of Vasculitides Adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides[a]

Large-vessel vasculitis
Giant cell (temporal) arteritis
Takayasu arteritis
Medium-sized–vessel vasculitis
Polyarteritis nodosa[b]
Kawasaki disease
Small-vessel vasculitis
ANCA-associated small-vessel vasculitis
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
Microscopic polyangiitis
Immune complex vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
Anti-GBM disease
Variable-vessel vasculitis
Behçet disease
Cogan syndrome

ANCA = antineutrophil cytoplasmic antibody; GBM = glomerular basement membrane; IgA = immunoglobulin A.

[a] *Large vessel* refers to the aorta and the largest branches directed toward major body regions (eg, to the extremities and the head and neck); *medium-sized vessel* refers to the main visceral arteries (eg, renal, hepatic, coronary, and mesenteric arteries); and *small vessel* refers to venules, capillaries, arterioles, and the intraparenchymal distal radial arteries that connect the arterioles.

[b] Strongly associated with ANCA.

Adapted with permission from Jeanette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1–11. Copyright © 2013 American College of Rheumatology.

Systemic features such as fatigue, headache, weight loss, and low-grade fever are common. Evidence of vascular insufficiency due to large-artery narrowing leads to the characteristic pulseless phase. Angiography, including magnetic resonance angiography, is essential in confirming the diagnosis. Treatment is generally with systemic corticosteroids, which may successfully suppress the disease. Cyclophosphamide or methotrexate is added in refractory cases. Surgical reconstruction of stenotic vessels may be necessary.

Ophthalmic considerations Patients with Takayasu arteritis may report transient visual disturbances and blindness due to decreased perfusion. The most characteristic ocular findings are retinal arteriovenous anastomoses, best demonstrated by fluorescein angiography. Milder changes found earlier in the disease course include small-vessel dilatation and microaneurysm formation. More severe ischemia may result in peripheral retinal nonperfusion, iris and retinal neovascularization, and vitreous hemorrhage.

Medium-Sized–Vessel Vasculitis

Polyarteritis nodosa

Classic polyarteritis nodosa (PAN) is characterized by necrotizing vasculitis of medium-sized and small muscular arteries. The lesions are segmental, and aneurysms may develop, which are detectable by angiography. *Mononeuritis multiplex,* a painful vasculitic neuropathy involving peripheral motor or sensory nerves, may be a presenting feature. CNS lesions can also occur. Renal involvement is common and is often associated with hypertension due to glomerular ischemia. GI disease with infarction of the viscera is also common. PAN may be limited to a single organ, such as the appendix, uterus, or testes. Although most cases of PAN are idiopathic, hepatitis B and C virus infections as well as hairy cell leukemia have been linked to its onset. Biopsy of involved tissues or organs is helpful for confirming the diagnosis.

PAN primarily affects persons in the fifth and sixth decades of life, with men affected more often than women. Survival in patients with untreated PAN is poor. However, most patients can be treated with a combination of corticosteroids and an immunosuppressive drug such as cyclophosphamide. Therapy appears to improve disease control and long-term outcomes. Systemic antivirals may be helpful for treating PAN related to hepatitis B or C. See also BCSC Section 9, *Uveitis and Ocular Inflammation*.

Ophthalmic considerations Ocular manifestations occur in up to 20% of patients with PAN and may include hypertensive retinopathy, retinal vasculitis, and visual field loss from CNS lesions. Cranial nerve palsies can occur, as well as scleritis and marginal corneal ulceration. Choroidal vasculitis is often overlooked in PAN and may cause transient visual symptoms, exudative retinal detachments, and pigmentary changes *(Elschnig spots)*. Fluorescein angiography may be necessary to identify choroidal involvement.

Kawasaki disease

Kawasaki disease, also known as *mucocutaneous lymph node syndrome,* is a condition associated with inflammation in the walls of medium-sized vessels throughout the body. The disease typically affects infants and young children. Patients often develop a persistent high fever, swollen lymph nodes, bilateral conjunctivitis, and truncal rash. A characteristic feature of Kawasaki disease is *strawberry tongue*—an extremely red, swollen tongue.

Although the disease is typically self-limited, cardiovascular complications, including coronary artery aneurysms, myocarditis, and dysrhythmias, may develop. Prompt treatment, which includes intravenous immunoglobulin and aspirin, reduces the potential for long-term complications.

Small-Vessel Vasculitis

Inflammation in small-vessel disease predominantly affects the arterioles, venules, and capillaries. This group of vasculitic disorders is further categorized based on the presence or relative absence of vessel-wall deposition of immunoglobulin and/or complement components. Subtypes include antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis and immune complex small-vessel vasculitis.

ANCA-associated vasculitis

Granulomatosis with polyangiitis Granulomatosis with polyangiitis (GPA; formerly known as *Wegener granulomatosis*) is an immune-mediated necrotizing granulomatous vasculitis. The disease, which affects small vessels, occurs in older adults, with both sexes affected equally. GPA can occur in all racial groups, but White individuals are predominantly affected.

The clinical features of GPA include granulomatous inflammation of the paranasal sinuses or nasopharyngeal tissues, which is present in most cases. Glomerulonephritis occurs in up to 85% of affected patients and can be asymptomatic until later stages of the disease. Other findings include cutaneous vasculitis and, less commonly, neurovasculitis. Limited forms of GPA may occur without substantial systemic involvement, making diagnosis difficult. Ocular disease, found in up to 50% of patients, may be the presenting feature of GPA. Ocular findings include scleritis with or without peripheral keratitis, idiopathic orbital inflammatory disease, and vasculitis-mediated retinal vascular or neuro-ophthalmic lesions. More than 85% of patients with GPA are seropositive for ANCA. Histologic examination remains the definitive way to confirm the diagnosis. (See also BCSC Section 7, *Oculofacial Plastic and Orbital Surgery,* and Section 9, *Uveitis and Ocular Inflammation.*)

Early and aggressive treatment of systemic GPA is critical, because the mortality rate of untreated severe disease approaches 90% within 2 years of onset. Glucocorticoids in combination with rituximab (preferred over cyclophosphamide) is highly effective in inducing and maintaining remission of disease. Trimethoprim-sulfamethoxazole prophylaxis is sometimes used to help prevent opportunistic infections during treatment.

Eosinophilic granulomatosis with polyangiitis Formerly known as *Churg-Strauss syndrome,* eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis of small- to medium-sized arteries characterized by chronic rhinosinusitis, asthma, and eosinophilia. The cause is unknown. The average age at onset is between 50 and 60 years, with no sex predominance.

Any organ can be affected, but the lungs and skin (tender subcutaneous nodules) are most commonly involved. Cardiovascular involvement is responsible for half of the deaths among affected patients. Peripheral mononeuropathy or polyneuropathy is common. Renal and GI involvement is sometimes evident. Ocular manifestations include conjunctival granulomas, retinal vasculitis and occlusion, uveitis, and cranial nerve palsies.

Diagnosis of EGPA depends on the presence of several criteria, including asthma, eosinophilia, eosinophilic vasculitis, transient pulmonary infiltrates, and neuropathy. Biopsy of tissue from the lung or a skin nodule is helpful in establishing the diagnosis; pathologic examination often shows granulomas with eosinophilic tissue infiltration of smaller vessels. Positive results for ANCA occur in approximately 50% of patients with EGPA.

Many patients achieve remission with glucocorticoids alone, although combination with rituximab or cyclophosphamide may be necessary in more severe cases.

Microscopic polyangiitis Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis that is similar to GPA in targeting small vessels, and it is sometimes difficult to distinguish between the 2 entities. However, on histologic examination, MPA lacks the necrotizing granulomatous formation seen in GPA. Patients with MPA are also less likely to relapse. In both conditions, most patients are ANCA positive, but patients with GPA tend to have an

elevated level of ANCA directed against proteinase 3 (PR3), whereas patients with MPA tend to have a higher level of ANCA directed against myeloperoxidase (MPO). Treatment of MPA is similar to that of GPA.

Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Care Res (Hoboken).* 2021;73(8):1088–1105.

Variable-Vessel Vasculitis

In variable-vessel vasculitis, no specific type of vessel is predominantly affected. Two examples are Behçet disease and Cogan syndrome vasculitis.

Behçet disease

Behçet disease was initially described as a triad of oral ulcers, genital ulcers, and uveitis with hypopyon. It is now recognized as a multisystem vasculitis of unknown etiology that can affect arterial and venous vessels of any size. The disease is most common in the Middle East and Asia, affects men and women equally, and usually has its onset during the third or fourth decade of life.

Recurrent oral ulcers are the most common clinical feature, affecting more than 95% of patients. Recurrent genital ulcers and skin involvement each occur in approximately 75% of cases. Skin disease can include erythema nodosum (see Fig 10-3), superficial thrombophlebitis, pyoderma, and pathergy (pustular response to skin injury). Approximately half of patients have asymmetric, nondeforming arthritis that commonly affects the knees, wrists, and ankles.

Vascular disease can present as migratory superficial thrombophlebitis, major-vessel thrombosis, arterial aneurysms, or even peripheral gangrene. CNS disease is found in 20% of patients and includes brainstem syndrome, meningoencephalitis, and confusional states. The major causes of mortality are CNS involvement and large-vessel disease, including arterial aneurysm.

Behçet disease may be associated with a number of nonspecific laboratory abnormalities, including elevated ESR, CRP values, and circulating immune complexes. Patients may also have serologic evidence of a hypercoagulable state, and the prevalence of HLA-B51 is higher in patients with Behçet disease than in unaffected individuals. However, laboratory findings are not pathognomonic for this disease. The diagnosis is based on clinical criteria that include recurrent oral ulcers and any 2 of the following: uveitis, recurrent genital ulcers, skin involvement, and pathergy. Other criteria may be used, depending on regional differences in disease presentation.

Management varies according to disease severity and the organ systems involved. Patients with mild disease may benefit from colchicine for treatment of arthritis and ulcers. Oral and genital lesions may respond to topical corticosteroid solutions or require systemic therapy if severe. The use of corticosteroids alone may control acute exacerbations but does not seem to alter the disease outcome. As a result, 1 or more immunosuppressive agents are usually added as therapy. Interferon-alfa has also been effective, especially for mucocutaneous manifestations. Treatment of posterior uveitis may include azathioprine and corticosteroids.

Alkylating agents such as cyclophosphamide can be used in refractory cases, although these drugs may have considerable toxicity. TNF-α inhibitors may also be helpful.

Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Bechet's syndrome. *Ann Rheum Dis.* 2018;77(6):808–818.

Ophthalmic considerations Ocular disease is a significant cause of morbidity in Behçet disease, affecting up to 70% of patients, often bilaterally. The most common ocular manifestations are uveitis, with or without hypopyon, and retinal vasculitis. Posterior uveitis and retinal vasculitis are often associated with ischemia, macular edema, and exudates, leading to significant vision loss. See BCSC Section 9, *Uveitis and Ocular Inflammation,* for additional discussion.

Cogan syndrome

Cogan syndrome is an immune-mediated disorder that affects young adults and is characterized by inflammatory lesions of the eye and inner ear. Patients may present with nonspecific symptoms such as fatigue, fever, and weight loss. Medium- or large-vessel vasculitis, including aortitis, occurs in 10% of cases. Ophthalmic findings may include interstitial keratitis, uveitis, and scleritis. Dizziness and hearing problems may reflect inner ear disease such as vestibular dysfunction and sensorineural hearing loss, respectively. Untreated recurrent inflammation may lead to blindness and deafness. Patients are commonly treated with oral corticosteroids and other immunosuppressive medications, including methotrexate, azathioprine, and mycophenolate. See BCSC Section 8, *External Disease and Cornea,* for further discussion.

COVID-19 and Rheumatic Disease

As more is known about the risks involved with SARS-CoV-2 infection and COVID-19 in patients with rheumatic disorders, new recommendations will continue to be developed. Current evidence is unclear whether patients with rheumatic disorders are at increased risk of a poor outcome compared with the general population. Patients receiving immunomodulatory therapy may have an impaired immune response after COVID-19 vaccination, which prompted the American College of Rheumatology COVID-19 Vaccine Clinical Guidance Task Force to advise boosters of the COVID-19 vaccine (August 2022), as well as to provide guidance on the timing of vaccination in relation to specific treatments being used.

Although COVID-19 infection in children is usually mild, rare cases of a severe manifestation known as *multisystem inflammatory syndrome in children (MIS-C)* have occurred with similarities to Kawasaki disease or toxic shock syndrome. Intensive hospitalized care is often required, and patients are at risk for thrombotic complications. Despite its severity, MIS-C has a mortality rate of <1%.

Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. *Nat Rev Rheumatol.* 2022;18(4):191–204.

Medical Therapy for Rheumatic Disorders

Medications are used in patients with rheumatic disorders for several purposes, including analgesia, control of inflammation, and immunosuppression. The use of these drugs in treating ocular inflammatory diseases is discussed in BCSC Section 9, *Uveitis and Ocular Inflammation*.

Corticosteroids

Glucocorticoids decrease inflammation by inhibiting the breakdown of phospholipid to arachidonic acid and blocking the production of inflammatory mediators, including prostaglandins and leukotrienes. Glucocorticoids have a variety of other systemic effects apart from their anti-inflammatory activity. They promote gluconeogenesis, with a concomitant negative nitrogen balance and reduction in protein production. Fat oxidation, synthesis, storage, and mobilization are also affected. After glucocorticoid administration, the number of circulating neutrophils increases because mature neutrophils are released from bone marrow, and their movement from the blood into other tissues is reduced, while the number of other circulating leukocytes decreases. Associated mineralocorticoid activity increases sodium retention and potassium excretion.

Table 10-4 lists the relative potency of commonly used glucocorticoid preparations. The molecular structure of the corticosteroid nucleus can be modified to dissociate glucocorticoid from mineralocorticoid activity. Unfortunately, isolating the beneficial anti-inflammatory effects from the less desirable glucocorticoid effects has not been fully achieved. The ophthalmologist must be aware of the ocular and systemic toxicities associated with systemic corticosteroids.

Adverse effects

Ocular adverse effects of systemic corticosteroids include posterior subcapsular cataracts, glaucoma, mydriasis, ptosis, papilledema associated with idiopathic intracranial hypertension, worsening of ocular infection, and delay in wound healing. Systemic complications may include peptic ulceration, osteoporosis, and aseptic necrosis of the femoral head, as well as muscle and skin atrophy. Corticosteroids can also cause hyperglycemia, hypertension, edema, weight gain, and changes in body fat distribution, resulting in a cushingoid habitus. Other adverse effects include hyperosmolar nonketotic states, hypokalemia, and

Table 10-4 Potency of Commonly Used Glucocorticoids

Glucocorticoid	Approximate Equivalent Dose, mg	Relative Anti-inflammatory Potency
Cortisone	25	0.8
Hydrocortisone	20	1.0
Prednisone	5	4.0
Prednisolone	5	4.0
Methylprednisolone	4	5.0
Triamcinolone	4	5.0
Dexamethasone	0.75	25.0

growth delay in children. Mental changes are a common problem, ranging from mild mood alterations to severe psychological reactions, including psychological dependence.

Osteoporosis is a significant problem that can increase the risk of fractures as early as a few months after beginning corticosteroid therapy. Bone mineral density testing is used to assess the degree of osteoporosis. In addition to calcium and vitamin D supplementation, hormone replacement therapy and bisphosphonates are sometimes employed.

Cessation of therapy

Rapid withdrawal of systemic corticosteroid therapy can cause complications. The rate of corticosteroid withdrawal is determined by 2 criteria: (1) the degree of hypothalamic-pituitary-adrenal (HPA) suppression, which in turn is related to corticosteroid potency, dose, and duration of therapy; and (2) the response of the underlying disease to the corticosteroid withdrawal. HPA suppression is likely present in patients who have a cushingoid appearance or who have received a glucocorticoid equivalent daily dose ≥10 mg of prednisone (alternatively, a continuous evening or bedtime dose of ≥5 mg) for more than 3 weeks. Below these parameters, HPA suppression is reduced. When tapering becomes necessary, a practical approach is to reduce the corticosteroid requirement by 5%–10% every 2 to 4 weeks while response is carefully monitored. Otherwise, sudden cessation of corticosteroid therapy could result in adrenal insufficiency, with symptoms such as fatigue, weakness, arthralgias, nausea, orthostatic hypotension, and hypoglycemia. In severe cases, adrenal suppression may be fatal.

After corticosteroid therapy has been discontinued, adrenal function may not return to normal for a year or more, and coverage with supplementary corticosteroids may be required if the patient has a serious illness or undergoes surgery during this recovery period.

Other considerations

Ophthalmologists who initiate systemic corticosteroid therapy for ophthalmic diseases should consider requesting assistance from the patient's primary care provider to monitor for adverse effects. For patients who require high-dose or extended corticosteroid treatment, clinicians should strongly consider the early use of other immunosuppressive medications, which can decrease patient dependency on, and long-term complications of, corticosteroid use.

Nonsteroidal Anti-inflammatory Drugs

Clinicians use a wide variety of NSAIDs to treat RA and other rheumatic diseases. These agents decrease synthesis of inflammatory mediators such as prostaglandins by inhibiting the enzyme *cyclooxygenase (COX),* and all are analgesic, antipyretic, and anti-inflammatory. The COX enzyme has 2 isoforms. *COX-1* is present in most cells and appears to be involved in various aspects of cellular metabolism, such as gastric cytoprotection, platelet aggregation, and renal function. *COX-2* is present in some tissues, including brain and bone, but is also expressed at other sites in response to inflammation. *Traditional NSAIDs* (eg, ibuprofen, naproxen) inhibit both isoforms of COX.

Complications from the use of oral NSAIDs account for approximately 12% of hospital admissions and a significant number of deaths each year in the United States. Their

most significant adverse effects include GI bleeding, renal failure, hypertension, and heart failure, as well as induction of asthma in aspirin-sensitive individuals. Oral NSAIDs can also interfere with platelet function and can cause bone marrow suppression; hepatic toxicity; and CNS symptoms, including headache, dizziness, and confusion. In rare cases, NSAIDs have been associated with ocular adverse effects such as nonspecific blurred vision and diplopia. There have also been reports of possible optic neuropathy and macular edema, especially with use of ibuprofen.

Selective COX-2 inhibitors, a newer class of NSAIDs, were developed to reduce the risk of GI damage caused by nonselective NSAIDs. They also have less effect on platelet function than traditional NSAIDs. Celecoxib, the only COX-2 inhibitor available in the United States, carries additional warnings related to risk of cardiovascular thrombotic events when it is used at higher dosages. Parecoxib and etoricoxib are available in some European countries. Ophthalmologists should be aware that conjunctivitis, transient visual loss, and blurred vision have been reported with the use of COX-2 inhibitors.

Systemic NSAIDs may be useful in helping to control uveitis or scleritis in some patients, but they are not as effective as corticosteroids. Several topical NSAIDs have been approved by the FDA for ocular use; they are discussed in BCSC Section 8, *External Disease and Cornea,* and Section 9, *Uveitis and Ocular Inflammation.*

Disease-Modifying Antirheumatic Drugs

As mentioned previously, there are 2 major categories of DMARDs: nonbiologic and biologic agents. See Table 10-5 for the classification, mechanism of action, and adverse effects of these agents.

Nonbiologic drugs

Methotrexate A structural analogue of folic acid, methotrexate interferes both with folate-dependent metabolic pathways, such as purine, and with pyrimidine metabolism. Its disease-modifying effect may be mediated partly through increased extracellular adenosine, which has intrinsic anti-inflammatory activity. Methotrexate is given weekly, usually beginning at a dose of 7.5–10 mg and gradually increasing to a maximum dose of 25 mg, depending on disease response. Supplementation with folic acid is used to decrease adverse effects associated with methotrexate use. Major adverse effects include hepatic fibrosis, interstitial lung disease, bone marrow toxicity, teratogenicity, sterility, and in higher dosages, renal toxicity. Baseline and periodic monitoring should include complete blood cell count with differential, liver enzymes, albumin levels, and creatinine levels.

Leflunomide The immunosuppressive agent leflunomide targets rapidly dividing cell populations such as activated lymphocytes. It is most commonly used to treat RA, although it has also been effective in managing other conditions, including psoriatic arthritis, juvenile polyarthritis, refractory dermatomyositis, and SLE. This drug is similar in efficacy to methotrexate, and the 2 drugs are sometimes used in combination when methotrexate alone is ineffective. Adverse reactions of leflunomide include GI symptoms, hepatotoxicity, and hypertension (especially if the drug is taken with NSAIDs). Close monitoring of patients is advised.

Table 10-5 Disease-Modifying Antirheumatic Drugs

Drugs	Mechanism of Action	Adverse Effects
	Nonbiologic Agents	
Methotrexate	Inhibits folate metabolism/DNA synthesis	GI symptoms, liver, pneumonitis, cytopenia, sterility, teratogenicity
Leflunomide	Inhibits DNA/RNA synthesis	GI symptoms, hepatotoxicity, hypertension, pneumonitis (rare)
Hydroxychloroquine	Inhibits lysosomal enzymes	GI symptoms, retinal toxicity, hemolytic anemia in G6PD deficiency
Sulfasalazine	Exact mechanism unknown	GI symptoms, allergic reaction, hemolytic anemia in G6PD deficiency
Azathioprine	Inhibits purine synthesis, interferes with DNA replication and RNA transcription	GI symptoms, infection, cytopenia, lymphoma
Cyclophosphamide, chlorambucil	Cytotoxic effect/DNA cross-linking	Cytopenia, infection, infertility, malignancy
Cyclosporine, tacrolimus	Inhibit T-cell activation	Hypertension, renal toxicity
Mycophenolate mofetil	Inhibits T-cell/B-cell proliferation	GI symptoms, cytopenia, infection
	Biologic Agents	
TNF-α inhibitors		
Adalimumab, certolizumab pegol, etanercept, infliximab	Inhibits cytokines	Allergic reaction, rash, infection, lymphoma Potential optic neuritis, uveitis
Interleukin inhibitors		
Anakinra, canakinumab, ixekizumab, rilonacept, sarilumab, secukinumab, tocilizumab, ustekinumab	Inhibits interleukin cytokines	Cytopenia, infection
Other biologic agents		
Abatacept	Inhibits T-cell activation	Infusion reaction, infection
Alemtuzumab	Lymphocyte depletion	GI symptoms, infection, cytopenia
Belimumab	Inhibits B-cell activation	GI symptoms, allergic reaction, leukopenia
Rituximab	B-cell lysis/suppression	Infusion reaction, which may be severe; progressive multifocal leukoencephalopathy
Kinase inhibitors		
Baricitinib, filgotinib, tofacitinib, upadacitinib	Inhibits Janus kinase/cytokine	GI symptoms, infection, anemia

G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; IL = interleukin; TNF = tumor necrosis factor.

Hydroxychloroquine An antimalarial compound, hydroxychloroquine is also commonly used to treat rheumatic diseases. In addition to its anti-inflammatory activity, the drug raises the pH of various cellular compartments, which decreases both cytokine production and lymphocyte proliferation. Response to treatment may take weeks to months, in part because of the drug's long half-life (1–2 months) and the time required to achieve steady-state levels.

Hydroxychloroquine is one of the safest immunosuppressive drugs used in the management of rheumatic disease. Retinopathy (bull's-eye maculopathy) due to hydroxychloroquine use is a relatively unusual complication, but it can cause irreversible vision loss if not detected early (see "Ophthalmic considerations").

Ophthalmic considerations Updated recommendations suggest that *actual* body weight is more predictive than *ideal* body weight in assessing risk of retinopathy from hydroxychloroquine (at a maximum daily dose of 5 mg/kg). A baseline fundus examination is advised within the first year of therapy. Annual follow-up examinations can be delayed until 5 years after initiation; for higher-risk patients, annual screening should be performed sooner. Duration of treatment is one of the risk factors; approximately 20% of patients have a toxic reaction after 20 years of medication usage. Other risk factors include preexisting retinal disease, presence of renal disease, and concurrent tamoxifen use.

In addition to comprehensive dilated examinations, spectral-domain optical coherence tomography (SD-OCT) and 10-2 visual field (VF) testing should be performed regularly. Because Asian patients appear to have a different clinical presentation, with more peripheral retinal findings, a 24-2 or 30-2 VF assessment should be considered instead for these patients. Amsler grid, color vision testing, and electro-oculogram are not recommended for screening. The American Academy of Ophthalmology's screening guidelines are available at www.aao.org/clinical-statement/revised-recommendations-on-screening-chloroquine-h. The recommended screening frequency is summarized in Table 10-6. Retinopathy is discussed more fully in BCSC Section 12, *Retina and Vitreous*.

Table 10-6 American Academy of Ophthalmology Recommended Screening Frequency for Hydroxychloroquine Retinopathy

Baseline screening
Fundus examination within first year of use
Add visual fields and SD-OCT if maculopathy is present
Annual screening
Begin after 5 years of use
Sooner in the presence of major risk factors

SD-OCT = spectral-domain optical coherence tomography.

Modified with permission from Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386–1394.

Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386–1394.

Sulfasalazine Although its exact mechanism of action is unclear, sulfasalazine is effective in treating RA. It is often used in combination with other drugs, such as hydroxychloroquine and methotrexate.

Azathioprine An antimetabolite, azathioprine interferes with purine metabolism. Use of azathioprine, especially in patients with inflammatory bowel disease, is limited because of its toxicity. The most common adverse effects are GI symptoms, risk of infection, and bone marrow suppression. Patients treated with this drug have up to a fourfold increased risk of lymphoma.

Alkylating agents *Cyclophosphamide* and *chlorambucil* are alkylating agents that are very potent immunosuppressive drugs. Their primary mechanism of action involves cross-linking of DNA molecules, which blocks DNA replication. They have potentially severe adverse effects, including infertility, bone marrow suppression, increased risk of infection, and increased risk of malignancy. Consequently, these drugs are reserved for very resistant or life-threatening diseases such as GPA, for which the benefits outweigh the risks. Cyclophosphamide is available as an oral or intravenous agent. The oral form is associated with increased rates of bladder cancer.

Calcineurin inhibitors *Cyclosporine* and *tacrolimus* block calcineurin, thereby inhibiting the transcription of IL-2 and other cytokines, primarily in helper T cells. These drugs are chiefly used to prevent rejection in patients who have undergone transplants, but clinicians are increasingly recognizing their benefit in treating autoimmune diseases. The main adverse effects of both drugs are nephrotoxicity and hypertension. Other potential problems include infections and nonmelanoma skin cancers. Because of such risks, these agents are reserved for recalcitrant cases that do not respond to standard therapies.

Mycophenolate Initially used as an antirejection drug in the United States, *mycophenolate mofetil* is increasingly being used in patients with immunologic diseases. It inhibits the production of guanosine in lymphocytes, thereby decreasing cellular proliferation and antibody production. Primary adverse effects include GI symptoms, bone marrow suppression, and increased risk of infection. An enteric-coated formulation of *mycophenolate sodium* typically reduces the incidence of GI adverse effects. Overall, the drug seems to be well tolerated by patients and may serve as an adjunct to other medications.

Biologic and other anticytokine agents

TNF-α inhibitors Research that facilitated improved understanding of the immune response has led to the development of drugs targeting specific mediators. Cytokines, cell-signaling proteins generated by activated immune cells, can enhance or inhibit the immune response. *TNF-α* is a major proinflammatory cytokine involved in the pathogenesis of inflammatory diseases. The FDA and the European Medicines Agency have approved 5 TNF-α antagonists: *adalimumab, certolizumab pegol, etanercept, golimumab,* and *infliximab.* Certolizumab pegol

is unique in this group as being an FDA category B drug and, therefore, is a treatment option for patients who are pregnant or nursing.

The drugs are usually well tolerated, but there is potential for severe adverse effects (see Table 10-5). Although not established, there may be a link between TNF-α inhibition and demyelinating disease, including optic neuritis. Anterior uveitis and posterior uveitis have also been reported, especially with etanercept use. All patients receiving immunosuppressive therapy require close monitoring for the development of serious adverse effects.

Susanna FN, Pavesio C. A review of ocular adverse events of biological anti-TNF drugs. *J Ophthalmic Inflamm Infect*. 2020;10(1):11.

Interleukin inhibitors Biologic agents have been developed to block specific interleukins. Although these agents are not as potent as the TNF-α inhibitors, IL-1 drugs, including *anakinra, canakinumab,* and *rilonacept,* are used in many autoimmune disorders. The IL-6 inhibitor *tocilizumab* is used primarily for RA and JIA but may also be effective in treating GCA and PMR. The drugs *secukinumab* and *ixekizumab* block the IL-17 pathway and are mainly used in psoriatic arthritis, as is the IL-12/23 inhibitor, *ustekinumab*.

Other biologic agents *Abatacept* is used in the treatment of RA and JIA. This drug blocks the CD28 receptor, which is involved in T-cell activation. It can be very effective in treating refractory disease.

Rituximab is a B-cell–depleting monoclonal antibody used primarily in chemotherapy but also in cases of RA unresponsive to other agents.

Belimumab is a human monoclonal antibody that inhibits B-cell activation. Approved by both the FDA and the European Medicines Agency for the treatment of SLE, it may also be helpful for other immune disorders.

Alemtuzumab is a monoclonal antibody that binds to CD52, a protein on mature lymphocytes. The drug is used to treat chronic lymphocytic leukemia and has shown promise in the treatment of autoimmune diseases.

JAK inhibitors Kinase inhibitors are another group of immunosuppressive agents that have shown benefit in treating rheumatic disease. Janus kinase (JAK) is 1 enzyme targeted by these drugs. *Tofacitinib* and *baricitinib* are small-molecule oral agents. The former inhibits JAK-1 and JAK-3; the latter, JAK-1 and JAK-2. *Upadacitinib* and *filgotinib* are selective JAK-1 inhibitors. The role of these 4 drugs may be in cases that are refractory to other classes of agents, including nonbiologic agents and TNF-α inhibitors. Tofacitinib also has the distinction of being the first JAK inhibitor approved by the FDA to treat JIA.

Biosimilar agents The expiration of patent protection on some biologic agents has led to the development of *biosimilar agents.* A biosimilar has amino acid sequencing that is analogous (not identical) to that of the original compound *(reference product)* on which it is based. The FDA requires a biosimilar to be "highly similar to," and to have "no clinically meaningful differences" from, the reference product for approval. Currently, more than a dozen biosimilar agents have been approved by the FDA to treat rheumatic diseases, and more are expected.

Mysler E, Caubet M, Lizarraga A. Current and emerging DMARDs for the treatment of rheumatoid arthritis. *Open Access Rheumatol.* 2021;13:139–152.

Wiseman AC. Immunosuppressive medications. *Clin J Am Soc Nephrol.* 2016;11(2):332–343.

CHAPTER 11

Geriatrics

Highlights

- The median age of the world's population is increasing almost exponentially, and the expanding older population presents a growing challenge to health care.
- The subspecialty of geriatrics emphasizes functional assessment and a more holistic approach to patient care. For example, given the range of perioperative considerations in the management of older patients, loss of vision alone may not be an indication for surgical intervention.
- Cataract, age-related macular degeneration, ischemic optic neuropathy, giant cell arteritis, diabetic retinopathy, glaucoma, and certain ocular malignancies are diseases that disproportionately affect older persons.
- The ophthalmologist is uniquely qualified to assess the visual limitations and visual needs of an older patient and to communicate these findings to the geriatrician or primary care physician.
- Referral for vision rehabilitation is appropriate for patients with visual acuity <20/40, central scotomas, visual field loss, or contrast sensitivity loss.

Introduction

The median age of the world's population is increasing almost exponentially. In the United States, the population aged 65 years and older is projected to nearly double, from 54 million in 2019 to >98 million by 2060, representing 14.9% and nearly 25% of the total population, respectively. Worldwide, over the same period, the population aged 65 years and older is projected to increase by approximately 617 million, up to 1.6 billion, from 8.5% to 16.7% of the population, respectively. In the next 15 years, the number of older persons is expected to grow fastest in Latin America and the Caribbean, with a projected 71% increase, followed by Asia at 66%, Africa at 64%, Oceania at 47%, and Europe at 23%.

This expanding older population presents a growing challenge to primary care physicians and medical subspecialists in the United States and Western Europe. The subspecialty of geriatrics emphasizes a different medical paradigm of functional assessment and a more holistic approach to patient care compared with the traditional medical paradigm.

United Nations Statistics Division Demographics and Social Statistics. Population censuses' datasets (1995–present). Accessed August 8, 2022. https://unstats.un.org/unsd/demographic-social/products/dyb/dybcensusdata.cshtml

United States Census Bureau. Accessed October 26, 2022. www.census.gov

The Aging Eye: Physiologic Changes and Pathologic Findings

Age-related changes in sensation and perception can isolate individuals from their environments and trigger complex psychological reactions. These changes can include diminished hearing and vision, slower intellectual and physical response times, and increased difficulty with memory. However, many physical and intellectual abilities are retained throughout an individual's life span, and their loss should not be assumed to be part of the normal aging process. These include the senses of taste and smell, intelligence, the ability to learn, and sexuality. Any change in physical, intellectual, or emotional capabilities may reflect underlying organic or psychological disease.

Age-related changes in the eye affect individuals differently. The periorbital and eyelid skin and soft tissues atrophy with age. Dermatochalasis and levator dehiscence may produce secondary ptosis. Eyelid laxity may cause entropion, ectropion, and trichiasis. Lacrimal gland dysfunction, decreased tear production, meibomian gland dysfunction, and goblet cell dysfunction may cause dry eye symptoms. The conjunctiva undergoes atrophic changes, and corneal sensitivity is reduced. The pupils become progressively miotic and less reactive to light. There is an increasing incidence of presbyopia, cataract, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy. Contrast sensitivity and visual field sensitivity are reduced. In addition, refractive error of some type is present in more than 90% of older patients and remains a significant cause of visual disability among nursing home patients.

Worldwide, the 4 leading causes of vision loss in the older population are AMD, glaucoma, cataract, and diabetic retinopathy. It is estimated that by 2030, 3.7 million persons in the United States will have AMD, 4.3 million will have glaucoma, and 38.7 million will have cataracts. Diabetic retinopathy is a leading cause of new cases of legal blindness among working-aged Americans. The prevalence of retinopathy in individuals with diabetes aged 40 years and older in the United States is 28.5% (4.2 million persons), and the prevalence of vision-threatening retinopathy is 4.4% (0.7 million persons). Assuming a similar prevalence for diabetes, the projected numbers in 2050 would be 16.0 million persons with diabetic retinopathy and 3.4 million persons with vision-threatening diabetic retinopathy.

National Eye Institute. Accessed August 8, 2022. www.nei.nih.gov

Saaddine JB, Honeycutt AA, Narayan KM, Zhang X, Klein R, Boyle JP. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005–2050. *Arch Ophthalmol.* 2008;126(12):1740–1747.

Ophthalmic considerations Ophthalmology is largely an outpatient specialty. For older patients, access to the ophthalmologist's office can be a major physical barrier to eye care. The ideal outpatient office is designed to accommodate older patients with various disabilities. The following features are particularly helpful:

- a safe, well-lit office that is close to drop-off areas and parking
- automatic or assisted doors (doors with pull levers or handles, not doorknobs)

- large-print, legible, well-placed signage
- wheelchair-accessible entryways and waiting rooms
- chairs with armrests
- obstacle-free (free of rugs, electrical cords, and tripping hazards such as toys) and well-lit, high-contrast walkways, hallways, and waiting areas
- accessible bathrooms with elevated toilet seats, grab bars, and a wheelchair-accessible sink
- trained staff to assist patients with disabilities to and from the examination room
- sound-amplifying headphones for patients with hearing loss
- a private area where patients with decreased hearing and vision can receive assistance from office staff to complete forms
- patient instructions provided in large-print format and lay language without jargon
- simplified medication dosing regimen and caregiver support

The American Academy of Ophthalmology's Initiative in Vision Rehabilitation page on the ONE Network (www.aao.org/low-vision-and-vision-rehab) provides resources for low vision management, including patient handouts and information about vision rehabilitation opportunities beyond those provided by the ophthalmologist.

Fontenot JL, Bona MD, Kaleem MA; American Academy of Ophthalmology Preferred Practice Pattern Vision Rehabilitation Committee. Vision Rehabilitation Preferred Practice Pattern. *Ophthalmology.* 2018;125(1):P228–P278. doi:10.1016/j.ophtha.2017.09.030

Psychology of Aging

The psychology of aging is influenced by a wide range of factors, including physical changes, adaptive mechanisms, and psychopathology. Each older patient has a unique psychological profile and social life history. Deleterious changes are not universal; in fact, in the absence of disease, growth of character and the ability to learn continue throughout life.

With age, the issue of loss becomes more prevalent. Losses—of status, physical abilities, loved ones, and income—become more frequent. A fear of loss of social and individual power, and the attendant loss of independence, is common. In addition, the reality of death has increasing influence on a person's psychological status. All of these losses increase the incidence of depression.

Depression

Depression is the most frequent psychiatric problem in the older population. Approximately one-quarter of older patients seen in primary care settings are clinically depressed. The prevalence of depression in patients with macular degeneration is even higher, at 30%–40%. The suicide rate in White American men older than 65 years is 5 times greater

than that of the general population; loneliness is the main reason cited, along with financial problems and poor health. Successful suicide is much less common in older American women, but older women attempt suicide more often than do older men. Fortunately, the suicide rates in older adults have decreased in the United States and almost all European Union countries; factors contributing to the decline include improved access to mental health care, suicide prevention training, reduction of access to lethal means (firearms and pharmaceuticals), responsible media reporting, increased awareness, and education to reduce the stigma of mental health issues.

The criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; *DSM-5*) make a clear distinction between late-life depression and depressive symptoms that result from a general medical condition (and the medication used to treat it). *Mood disorder* is the preferred diagnostic term for the latter.

Major depressive disorder is characterized by episodes of at least 2 weeks of depressed mood or loss of interest or pleasure in activities, along with 4 or more of the following symptoms:

- changes in appetite with associated weight loss or gain
- significant weight loss or gain
- sleep disturbance
- agitation
- diminished libido
- retardation (slowing down)
- loss of energy
- feelings of worthlessness or guilt
- difficulties in concentration and decision-making
- recurrent thoughts of suicide or death

Although the signs and symptoms of depression in older individuals are similar to those seen in younger age groups, older depressed patients are *more likely* than younger patients to have somatic or hypochondriacal concerns, to minimize symptoms of depression (masked depression), and to have psychotic delusional disease. However, they are *less likely* to report symptoms of guilt. The most frequent presentations of subclinical depression include new medical concerns, fatigue, poor concentration, exacerbation of existing symptoms and medical problems, preoccupation with health, and diminished interest in pleasurable activities.

The ophthalmologist's role is to recognize and refer the patient with depression or to be aware of precipitating factors. For instance, loss of function, such as moderate or severe vision loss, which can be sudden as in neovascular AMD, can precipitate depression, as can the recent death of a spouse. Charles Bonnet syndrome associated with vision loss can cause depression because people may fear that they are developing a serious mental health problem or dementia. Ophthalmic medications such as β-blockers and α-agonists can cause fatigue, depression, and diminished cognition. Red flags may include frequent visits to the ophthalmology office and unexplained vision loss. Although testing patients for depression is not common in the ophthalmology setting, it could be enormously helpful in obtaining care for patients with this disorder; an appropriate referral for such testing may be necessary.

Many targeted screening tests, also called *case-finding instruments,* ask about depressed mood and *anhedonia,* a psychological condition characterized by inability to experience pleasure in acts that normally produce it. One of these screening devices is the brief Patient Health Questionnaire-2 (PHQ-2). It is sensitive but not specific; it does not suggest or establish a final diagnosis or monitor depression severity but can act as a first step in screening for depression. The self-reported questionnaire consists of the following 2 questions using a 0 to 3 scale:

1. During the past month, have you been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?

If the first question is answered in the affirmative, it is highly likely that the patient has depression, while the second question adds greater sensitivity and specificity. A score of 2 or 3 on either question is considered a positive response and is in line with *DSM* criteria for depression; these findings should be discussed with the patient's primary care physician. Further information on the PHQ-2 is available on the website of the American Psychological Association (www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/patient-health).

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care.* 2003;41(11):1284–1292.

Miguel A, Henriques F, Azevedo LF, Pereira AC. Ophthalmic adverse drug reactions to systemic drugs: a systematic review. *Pharmacoepidemiol Drug Saf.* 2014;23(3):221–233.

OECD/European Union. Adult mental health. In: *Health at a Glance: Europe 2020: State of Health in the EU Cycle*. OECD Publishing; 2020. doi:10.1787/89109c81-en

Alzheimer Disease and Dementia

Alzheimer disease and dementia are discussed in Chapter 12 of this volume.

Special Topics

Elder Abuse

Elder abuse is an important public health problem. It is a violation of human rights and is a significant cause of illness, injury, loss of productivity, isolation, and despair, according to the World Health Organization. The National Elder Abuse Incidence Study (1998) found that in 1996, nearly half a million persons aged 60 years or older had been physically abused, neglected, or in some way mistreated. This study, which was based on Adult Protective Service records and sentinel reports (eg, reports from community professionals), is likely to have underestimated the true scope of the problem because most elder abuse cases are not reported.

A 2017 systematic review and meta-analysis that pooled data from 52 studies in 28 countries estimated that in the prior year, 15.7% of people 60 years and older were subjected to some form of abuse. In the United States, the prevalence of elder maltreatment

was reported as 7.6%–10% of study participants and is estimated to affect 11.4% of adults aged 60 years and older. Worldwide, it is estimated that only 1 in 24 cases of elder abuse is reported, in part because older adults are often afraid to report the abuse to family, friends, or the authorities.

Major risk factors for elder abuse include external stresses due to marital, financial, and legal difficulties; dependent relationships (eg, the abuser may be dependent on the older patient for finances or housing, or vice versa); mental illness and substance use; social isolation; and misinformation about normal aging or about the patient's medical or nutritional needs. Maltreatment can occur at home, in assisted living facilities, or in nursing homes and may include the following:

- *Physical abuse:* physical pain, injury, or sexual abuse
- *Psychological abuse:* verbal assaults, threats, harassment, intimidation
- *Material misappropriation:* theft of money or property, misuse of credit/debit cards, forging of signature, pressure to change a will or insurance beneficiary
- *Neglect or abandonment:* failure to provide necessities such as food, medicine, shelter
- *Deprivation of basic rights:* denial of decision-making authority regarding care and privacy

The ophthalmologist may be the first physician to see an older patient who is being abused or neglected. The signs may be subtle, and early recognition is key. Circumstances that can alert the clinician to possible abuse include the following:

- broken eyeglasses, with a report by the patient of being slapped or abused
- evidence of physical abuse (eg, bruises; black eyes; fractures; lacerations; wounds in various stages of healing; burns; welts; patches of hair loss; or unexplained subconjunctival, retinal, or vitreous hemorrhage)
- repeated visits to the emergency department or office
- conflicting or noncredible history from caregiver or patient
- unexplained delay in seeking treatment
- unexplained, inconsistent, vague, or poorly explained injuries
- history of being "accident prone"
- expressions of ambivalence, anger, hostility, or fear by the patient toward the caregiver
- poor adherence to follow-up or care instructions

Sometimes it is necessary to obtain the patient history with the caregiver out of the room. Directed questions for the patient include the following:

- Has anyone at home tried to harm you?
- Has anyone tried to make you do things that you don't wish to do?
- Has anyone taken anything from you without your consent?

Any suspected case of elder neglect or abuse should prompt a complete written report. Documentation of any suspicious injuries is mandatory, including type, size, location, and characteristics of injury and stage of healing. Requirements for reporting elder

abuse vary from state to state, and many areas have abuse hotlines for reporting maltreatment. The physician should be aware of local services for adult protection, community social services, and law enforcement agencies.

Acierno R, Hernandez MA, Amstadter AB, et al. Prevalence and correlates of emotional, physical, sexual, and financial abuse and potential neglect in the United States: the National Elder Mistreatment Study. *Am J Public Health.* 2010;100(2):292–297.

National Council on Aging. Get the facts on elder abuse. Accessed August 8, 2022. www.ncoa.org/article/get-the-facts-on-elder-abuse

Yon Y, Mikton CR, Gassoumis ZD, Wilber KH. Elder abuse prevalence in community settings: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(2):e147–e156.

Osteoporosis

Osteoporosis is defined by the World Health Organization as a disease "characterized by low bone mass and structural deterioration of bone tissue, leading to an increased susceptibility to fractures, especially of the hip, spine, and wrist." Osteoporosis is a significant, worldwide public health problem that is becoming increasingly common. Although it occurs in all races and ethnicities, non-Hispanic White women and Asian women are at an increased risk compared with other groups. It is estimated that, globally, 1 of every 2 women and 1 of every 4 men older than 50 years will have an osteoporosis-related fracture in their lifetime. In the United States, 1.5 million fractures related to osteoporosis occur annually. In older patients, a broken hip can increase mortality 4-fold, with 30% dying within 12 months. Those with hip fractures have a 20% risk of entering a nursing home within a year of their fracture, and it is estimated that almost 50% of women with hip fractures do not fully regain previous function. Many patients with hip fractures experience a decline in function, along with increased feelings of isolation, depression, and fear of falling. In the European Union, fractures accounted for 2 million disability-adjusted life-years (DALYs) annually, more than hypertensive heart disease or rheumatoid arthritis.

Papadimitriou N, Tsilidis KK, Orfanos P, et al. Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium. *Lancet Public Health*. 2017;2(5):e239–e246.

Ophthalmic considerations It is important to note what medications the patient with osteoporosis is taking. The class of drugs known as bisphosphonates, commonly prescribed for postmenopausal women to inhibit bone resorption, can affect eye health. Some studies have reported an association between bisphosphonates and inflammatory disease of the eye, including conjunctivitis, uveitis, and episcleritis, as well as scleritis, which can be vision threatening. On the other hand, a study of veterans determined that the rates of uveitis and/or scleritis following dispensing of a bisphosphonate drug were low and did not differ significantly from those of the control group.

French DD, Margo CE. Postmarketing surveillance rates of uveitis and scleritis with bisphosphonates among a national veteran cohort. *Retina.* 2008;28(6):889–893.

Falls

Falls are a leading cause of injury and death in older Americans. The incidence and severity of falls rise with increasing age. Approximately one-third of US adults older than 65 years fall each year, yet less than half talk to their physicians about it. In 2019, 3 million older Americans were treated in emergency departments for falls, and 34,000 older adults died as a result of unintentional fall injuries. Falls are responsible for >60% of all traumatic brain injuries (TBIs) in people older than 65 years. In the United States, fall-related TBIs are responsible for 17,408 deaths per year. In 2015, the total medical cost for falls was more than $50 billion, with Medicare and Medicaid shouldering 75% of these costs. Men are more likely to die from a fall. Older White individuals are 2.4 times more likely to die from falls than are older Black individuals. Fatal fall rates differ among ethnic groups: older non-Hispanic persons have higher fatal fall rates than do older Hispanic persons. Fear of falling may cause older adults to limit activities, leading to reduced physical fitness, which, in turn, increases the actual risk of falling.

Prevention of falls is key. Older adults may reduce their chances of falling by exercising regularly, increasing leg strength and balance, asking their physician or pharmacist to review any of their medications that might cause dizziness or drowsiness, and having their eyes checked annually to update glasses or evaluate for eye diseases that limit vision. In the home, older adults can make their living areas safer by removing tripping hazards, installing grab bars in the bathroom and railings on the side of stairways (such as the entry to the home), and improving lighting.

Visual disorders are a frequent cause of falls. Recent studies in the United States and the United Kingdom suggest that older individuals are almost twice as likely to fall when they are visually impaired. An ophthalmologist may help patients reduce the risk of falls by

- asking patients appropriate questions about the activities listed previously that might reduce fall risk
- recognizing and treating visual disorders, including refractive errors, to minimize ocular reasons for falls
- referring patients to vision rehabilitation for a comprehensive evaluation as well as training to optimize use of residual vision

Patients with reduced vision from any eye disease, especially those with reduced visual field and contrast sensitivity loss, are at the highest risk of falling. Patients with low vision and at least 1 other chronic condition report more difficulty completing their activities of daily living compared with those who have only visual impairment or those who have only a chronic condition. Once a history of falls is obtained, it is incumbent upon the ophthalmologist to notify the patient's primary care physician about this finding or refer the patient to a multidisciplinary medical facility with resources for managing falls in older adults.

Centers for Disease Control and Prevention. Stopping elderly accidents, deaths & injuries (STEADI): older adult fall prevention. Accessed August 8, 2022. www.cdc.gov/steadi

Crews, JE, Jones GC, Kim JH. Double jeopardy: the effects of comorbid conditions among older people with vision loss. *J Visual Impairment Blindness*. 2019;100(suppl):824–848. doi:10.1177/0145482X0610001S07

Ophthalmic considerations Many activities of daily living require adequate functioning of different visual components such as near, intermediate, and distance vision, as well as peripheral vision, binocular vision, depth perception, contrast sensitivity, and color vision. Cataract surgery improves functional vision status, resulting in overall improved health-related quality of life, mental health, and emotional well-being. Visual function plays an important role in physical performance, especially in terms of mobility. The rate of falls in older adults is diminished after cataract removal, with a lower incidence of hip fracture 1 year after the procedure when compared with patients with cataract who did not have cataract surgery. After surgery for the second eye is performed, the risk of falls is further decreased because of improvement in stereopsis.

Flaxel CJ, Adelman RA, Bailey ST, et al; American Academy of Ophthalmology Retina/Vitreous Preferred Practice Pattern Panel. Age-Related Macular Degeneration Preferred Practice Pattern. *Ophthalmology.* 2020;127(1):P1–P65. doi:10.1016/j.ophtha.2019.09.024

Olson RJ, Braga-Mele R, Chen SH, et al; American Academy of Ophthalmology Preferred Practice Pattern Cataract and Anterior Segment Panel. Cataract in the Adult Eye Preferred Practice Pattern. *Ophthalmology.* 2017;124(2):P1–P119. doi:10.1016/j.ophtha.2016.09.027

Perioperative Considerations in the Management of Older Adult Patients

There are several considerations that the ophthalmologist should take into account in the preoperative evaluation and perioperative management of older adult patients; loss of vision alone may not be an appropriate sole indication for surgical intervention (eg, cataract surgery). Other factors to consider include coexisting neurologic and psychiatric conditions, ability to adhere to the postoperative medication regimen, and the availability of caregivers.

Frailty, defined as an aging-related syndrome of physiologic decline characterized by marked vulnerability to adverse health outcomes, will render some older adults less able to tolerate and adapt to stressors such as acute illness or medical and surgical interventions such as ocular surgery. Tools to assess frailty such as the FRAIL scale (https://frailtyscience.org/frailty-assessment-instruments) may be helpful for risk stratification prior to ophthalmologic procedures. The scale measures:

- *F*atigue: How much of the time do you feel tired? Most/all of the time = 1; some, a little, or none of the time = 0
- *R*esistance: Do you have difficulty walking up 1 flight of stairs? Yes = 1, No = 0
- *A*erobic/Ambulation: Do you have difficulty walking 1 block or several hundred yards? Yes = 1, No = 0
- *I*llness: Do you have more than 5 illnesses? Yes = 1, No = 0
- *L*oss of Weight: Have you lost more than 5% of your weight in the past 6 months? Yes = 1, No = 0

Scores range from 0 to 5 (0 = best, 5 = worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status.

Functional assessment to determine the effect of vision loss on tasks such as reading, driving, taking medications properly, and using the telephone independently should be documented preoperatively. All prescription medications should be documented to ensure that they do not interact with perioperative medications. Some of these medications may also have ocular side effects. See Chapter 16 for further discussion of perioperative management, and Chapter 12 for special considerations regarding informed consent for patients with mild dementia and for those who have legal guardians or caregivers who will need to participate in the process.

Older adult patients undergoing surgery may be liable to confusion or delirium perioperatively. Delirium is estimated to occur in approximately 4%–5% of patients after cataract surgery. Confusion may be eased or prevented by the following:

- minimizing preoperative sedation or psychotropic medications
- providing appropriate patient and family education and orientation by nursing or ancillary staff
- maintaining careful supervision and reassurance in the postoperative period (familiar faces may be helpful in calming the patient)
- minimizing the use of restraints
- having a family member in the recovery room as soon as possible
- removing the patch as soon as possible and providing appropriate eye protection

Topical anesthetic alone may not be indicated because of comorbidities such as cognitive impairment and other conditions that make it difficult for the patient to cooperate during surgery. In addition, patients with decreased vision after intraocular surgery may experience limited mobility or be at increased risk for falls. However, prolonged immobilization carries the risk of weakness, development of pressure ulcers, and other problems. For these patients, active rehabilitation should be encouraged as soon as possible.

Although surgical or anesthesia complications are rare in outpatient ophthalmic surgery, they could potentially result in life-threatening conditions. The surgeon must be attentive to preexisting directives (eg, a do-not-resuscitate order or living will) prior to any surgical intervention (including laser treatment and periocular injections or anesthetics) and discuss possible treatment decisions with the patient and family members before any serious issues arise. Some potential issues for discussion include limits of treatment, antibiotics, and changes in the patient's living situation. Candid and open discussion of these important issues with the patient and the family (especially in cases of dementia) before the procedure allows them to consider these matters in the context of their belief systems and without the disorientation and confusion created by an emergency. The content, context, time, and date of such discussions should be well documented in the medical record and shared with the patient, the family, and the primary care physician or geriatrician.

Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601–608.

CHAPTER 12

Behavioral and Neurologic Disorders

Highlights

- Each year, 1 in 5 adults is affected with a mental health disorder, of which only half are ever diagnosed by a physician.
- Visual impairment nearly doubles the risk of acquired depression.
- Second-generation antipsychotics (SGAs) may be associated with the onset or worsening of diabetes and its associated ocular findings; the diabetes may develop as a result of weight gain, which is an adverse effect of SGAs.
- The antiepileptic medication vigabatrin is associated with irreversible and often asymptomatic concentric visual field loss in up to 50% of patients taking it.

Introduction

Since the 1980s, the World Health Organization (WHO) has focused its efforts on common behavioral and neurologic disorders that cause substantial disability and challenges to individuals, families, and societies. The global impact of mental illness, substance use disorders, suicide, and neurologic disease is significant, accounting for more than one-third of the global burden of disability and 14% of deaths. Furthermore, less than 1% of affected individuals receive minimum adequate care in low-income countries compared with 50% in most high-income countries. It is estimated that the median global spending by governments on mental health alone is less than 2% of their health budgets. The increasing impact of these disorders has dramatically outpaced any measures to ameliorate this global burden, even in high-income countries.

Vigo DV, Patel V, Becker A, et al. A partnership for transforming mental health globally. *Lancet Psychiatry.* 2019;6(4):350–356.

World Health Organization. *World Mental Health Report: Transforming Mental Health for All.* World Health Organization; 2022.

Behavioral Disorders

Behavioral disorders encompass a wide range of conditions in which the common factor is disordered functioning of thought, behavior, and/or interpersonal relationships. In the absence of screening, it is estimated that only about 50% of persons with depression and other mental health conditions are diagnosed. Recent reports indicate that less than 5% of adults in primary care settings are formally screened for depression. Because electronic health records are starting to include standardized screening tools, including questions targeting depression, this percentage may improve. In the United States, the prevalence of behavioral disorders is staggering: each year, 1 in 5 adults will experience a mental health condition, and 75% of these conditions develop by age 24 years. The goal of the WHO's Mental Health Gap Action Program is to raise awareness of the challenges related to mental health disorders and to facilitate solutions for the many people who need these services, particularly in resource-poor regions.

Mood Disorders Associated With Medical Conditions

Because mood disorders are sometimes associated with other conditions, it can be challenging for clinicians to understand the cause and determine the best course of treatment. In some cases, the disorder is caused by the medical condition itself, and in others, the etiology is multifactorial. Potential causes include adverse effects from medication or stressors related to dealing with the medical condition, such as the associated financial burden, limited access to appropriate care, or the lack of an adequate support network.

Almost any disease can cause mood changes, so clinicians must look for indicators of underlying causal factors. For example, mental disorders that develop later in life are more likely to be related to an underlying medical condition. In addition, mood alterations may occur acutely as a result of a physiologic change such as a cerebrovascular event, infection, environmental exposure, electrolyte imbalance, or hormonal change. Finally, mood abnormalities associated with motor system disorders, such as gait and balance problems, speech irregularities, or unusual tics, suggest possible neuropathology, warranting further investigation. Neurologic disease states that can cause mood changes include head trauma and postconcussion syndrome, stroke, multiple sclerosis, and brain tumors, especially tumors involving the frontal lobe. Visual impairment almost doubles the risk of depression. In a recent study, the prevalence of depression in patients with macular degeneration was as high as 39%. The American Academy of Ophthalmology's Preferred Practice Pattern guidelines recommend screening all macular degeneration patients and providing appropriate referrals for those suspected of having depression.

Chronic disease states, such as disabling rheumatoid arthritis, chronic pulmonary illness, or cardiovascular disease, are associated with higher rates of depression in adults. Other illnesses associated with mood changes include untreated thyroid disorders, Lyme disease, hemochromatosis, and hepatolenticular disease (Wilson disease). Some diseases may present with only minor mood changes, whereas others present with major depression, hallucinations, and delusions. As noted, mood changes may be induced by medications, including carbonic anhydrase inhibitors, steroids, and chemotherapeutic agents.

Mood (Affective) Disorders

Mood disorders, also called *affective disorders,* represent a spectrum of mental illness in which prolonged periods of sadness *(depression)* are on one end and signs of excessive elation *(mania)* are on the other end. Manifestations of both ends of the spectrum at different times are termed *bipolar disorder.*

Major depression manifests as significant depressive episodes without any manic symptoms, often referred to as *unipolar depression;* it is far more common than mania alone and is the fourth-leading cause of disability worldwide. The lifetime risk of a major depressive disorder is 9% for men and approximately 17% for women. In high-income countries, the prevalence of this disorder is approximately 18%, whereas in other nations it is approximately 9%. Major depression may occur at any age, but it most commonly affects middle-aged persons. Older adults (individuals 65 years and older) who live in health care facilities and those affected by a wide range of acute and chronic diseases also appear to be at higher risk. Various screening tools are available to help clinicians diagnose depression and monitor treatment effectiveness. One such tool, the Patient Health Questionnaire-9 (PHQ-9), is commonly used and has a sensitivity and specificity of 88% and 85%, respectively.

Major depression is a disabling condition that causes impairment of basic physical functions, as manifested by sleep disturbances, changes in appetite with associated weight loss or gain, diminished libido, and *anhedonia,* a psychological condition characterized by inability to experience pleasure in acts that would normally produce it. Social withdrawal and psychomotor retardation are common, although agitation can also occur. Patients commonly report somatic symptoms such as fatigue and headache, as well as various nonspecific symptoms. The risk of suicide among individuals with depression is more than 25 times that of the general population. Factors associated with suicide risk include the degree or longevity of the disorder, male sex, family history of psychiatric disorder, and presence of comorbidity. Patients with *dysthymic disorder* have chronic, less severe depressive symptoms that do not meet the criteria for major depression.

Mania is a period of abnormally and persistently elevated or irritable mood that is sufficiently severe to impair social or occupational functioning. Typical symptoms include euphoria or irritability, grandiosity, decreased need for sleep, increased speed of thought and speech *(flight of ideas),* and increased goal-directed activity. Formerly called manic depression, *bipolar disorder* is found in approximately 3% of people 18 years and older. It manifests in 2 forms. *Bipolar I disorder* describes any illness in which mania is present, whether or not depression occurs. *Bipolar II disorder* refers to patients with major depressive episodes and at least 1 mild manic episode *(hypomania). Cyclothymic disorder* describes cyclical episodes of mania and mild depression.

For the nonpsychiatric clinician, a patient's depression creates several challenges. In some patients, mood change may not be apparent, and the illness may manifest in somatic symptoms, leading to time-consuming, expensive workups. Conversely, in patients with known depression, an organic disease may be overlooked as psychosomatic. Recommendations for psychotherapeutic intervention may be met with resistance, anger, or denial, disrupting the patient-physician relationship. Patients may have difficulty adhering to diagnostic and treatment regimens for medical disorders and surgical procedures.

A screening study of older patients attending an ophthalmology clinic showed that 1 in 5 patients had depression.

Demmin DL, Silverstein SM. Visual impairment and mental health: unmet needs and treatment options. *Clin Ophthalmol.* 2020;14:4229–4251.

Flaxel CJ, Adelman RA, Bailey ST, et al; American Academy of Ophthalmology Retina/Vitreous Preferred Practice Pattern Panel. Age-Related Macular Degeneration Preferred Practice Pattern. *Ophthalmology.* 2020;127(1):P1–P65. doi:10.1016/j.ophtha.2019.09.024

Somatization, Anxiety, and Stress-Related Disorders

Somatic symptom and related disorders

The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; *DSM-5*) has reclassified "somatoform disorders" as *somatic symptom and related disorders.* In 2022, the WHO replaced "somatoform disorder" with the term *bodily distress disorder* in the *International Classification of Diseases,* 11th Revision *(ICD-11)*. The term *somatization* is a more general description of the syndrome of symptoms that suggest physical illness or injury in the absence of objective findings or a known physiologic mechanism. These symptoms may result from anxiety, depression, or interpersonal conflicts.

The syndrome is not uncommon; the prevalence in the general population is approximately 6%. Risk factors associated with somatization include female sex, lower socioeconomic or educational level, and ethnic minority status. Somatization is a known problem among outpatient clinics, emergency department visits, and hospital admittances because each case requires investigation to rule out underlying disease. However, the disorder has significant ramifications for the affected individual because it can cause impaired functioning and disability. The most common presentation includes pain (eg, headache, back pain), gastrointestinal concerns, cardiopulmonary symptoms, and various neurologic symptoms. The manifestation can involve any system; ophthalmologists should be aware of this syndrome because patients may present with ophthalmic-related symptoms such as blurred or double vision.

Entities within the *DSM-5* designation of somatic symptom and related disorders include conversion disorder, illness anxiety disorder, and factitious disorder.

Conversion disorder This disorder is characterized by temporary and involuntary loss or alteration of physical functioning caused by psychosocial stress. Symptoms are typically neurologic and may include functional vision loss. In children who experience a traumatic, stressful event, including those subjected to bullying at school, symptoms can be more varied, for example, difficulty speaking or swallowing or tremors. Psychotherapy may be necessary if patient education is not effective. Diagnosis may be difficult because of the subjective nature of the symptoms.

Illness anxiety disorder Formerly called *hypochondriasis,* illness anxiety disorder is a preoccupation with the fear of having or developing a serious disease. Physical examination fails to support the patient's belief, and reassurance by the examining physician often fails to allay the fear. A subcategory of this entity relevant to ophthalmologists is *body dysmorphic disorder,* in which the patient believes that their body is deformed, even though

there is no physical defect, or the patient has an exaggerated concern about a mild physical anomaly. Ophthalmologists performing reconstructive and cosmetic surgery should be aware of this disorder because surgical repair of the "defect" is rarely successful in the patient's mind.

Factitious disorder and malingering *Factitious disorder* (previously known as *Munchausen syndrome*) is characterized by the willful production, feigning, or exaggeration of physical or psychological signs or symptoms in the absence of external causes. Treatment requires discovery of the true nature of the physical illness, a carefully planned confrontation, and psychotherapy. The prognosis for recovery is guarded. Typical ophthalmic presentations of this disorder are self-inflicted chronic conjunctivitis, keratitis, and scleritis.

Factitious disorder imposed on another, also known as *Munchausen syndrome by proxy,* is applied to cases in which a caregiver fabricates or causes an illness in or injury to a person under their care. Mild forms of this can be easily missed in the clinical setting.

Although related, *malingering* is not classified as a mental illness because it involves the fabrication of symptoms for secondary personal gain (eg, money, drugs). Malingering should be considered when symptoms and findings do not make sense. Ophthalmologists should become familiar with techniques for detecting patients who are malingering, as they are occasionally encountered in practice settings. See BCSC Section 5, *Neuro-Ophthalmology,* for a description of some of these techniques.

Generalized anxiety disorder

Anxiety disorders are another group of diseases that can significantly interfere with normal functioning. *Generalized anxiety disorder (GAD)* is common, with a lifetime prevalence of 5%. GAD affects women twice as frequently as men. The disorder is characterized by unrealistic or excessive anxiety and worry that is not focused on one particular life event. GAD is associated with depression in most cases and carries an increased risk of substance use disorder. Pharmacologic therapy and psychotherapy may be successful in treating patients with this disease.

Thibaut F. Anxiety disorders: a review of current literature. *Dialogues Clin Neurosci.* 2017; 19(2):87–88.

Panic disorder

The lifetime prevalence of *panic disorder* is close to 5%, with a median age of 24 years, and the disorder is more common in females. Individuals with this disorder have a higher risk of developing major depression. Patients with panic disorder report discrete periods of intense terror and sense of impending doom with associated physical symptoms (eg, trembling, difficulty breathing) that are almost intolerable. These episodes can occur abruptly, either in certain predictable situations or without any situational trigger. Mild cases may be treated with psychotherapy, but more significant disease may require treatment with antidepressant medication such as selective serotonin reuptake inhibitors.

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) occurs after an individual has been exposed to a traumatic event associated with intense fear. When exposed to reminders of the event,

the patient then persistently reexperiences the incident through intrusive recollections, nightmares, flashbacks, or distress. The lifetime prevalence of PTSD varies but has been reported at rates as high as 12% in the general population of North America and at significantly lower rates (approximately 1%) in other countries; this difference is poorly understood. Combat soldiers and survivors of assault are at particular risk. Treatment usually includes cognitive behavioral therapy, psychotherapy, and antidepressants.

Personality Disorders

Personality disorders, which affect approximately 6% of the global population, merit discussion here because they may be associated with substance use disorder and poor adherence to treatment. These disorders are diagnosed when personality traits become so inflexible and maladaptive that they create significant occupational and/or interpersonal dysfunction. Patients usually have little or no insight into their disorder. *DSM-5* categorizes these disorders into 3 types:

- *Cluster A personality disorders* include paranoid, schizotypal, and schizoid disorders.
- *Cluster B personality disorders* include antisocial, borderline, histrionic, and narcissistic personality disorders. Patients with these disorders may display dramatic or irrational behavior and may have a tendency for disruptive behavior in clinical settings.
- *Cluster C personality disorders* include avoidant, dependent, and obsessive-compulsive personality disorders.

Psychotherapy is generally the treatment of choice for all of these entities. No medications are indicated specifically for personality disorders, although psychotropic agents may help treat coexisting mental health disorders (eg, depression or substance use disorder).

Schizophrenia

With an estimated global prevalence of 1%, schizophrenia is ranked by the WHO among the top 10 disorders contributing to the global burden of disease. Schizophrenia usually begins when patients are young and continues to some extent throughout life.

The hallmarks of schizophrenia include hallucinations, delusions, disorganized thinking, and "negative" symptoms such as emotional and cognitive blunting. Motor disturbances range from uncontrolled, aimless activity to catatonic stupor, in which the patient may be immobile, mute, and unresponsive, yet fully conscious. Repetitive, purposeless mannerisms and an inability to complete goal-directed tasks are also common. Patients with schizophrenia may have other mental health conditions, such as major depression and anxiety disorders. Alternatively, manifestations of schizophrenia may be confused with symptoms of depression or anxiety. The lifetime occurrence of substance use disorder in individuals with schizophrenia is approximately 50%. Associated illnesses include *schizophreniform disorder,* in which schizophrenic manifestations occur for less than 6 months, and *brief psychotic disorder,* which lasts less than 1 month. Patients with *schizoaffective disorder* have a significant mood disorder, such as depression, in addition to psychotic manifestations.

Eating Disorders

Eating disorders, which include anorexia nervosa, bulimia nervosa, and binge-eating disorder, are increasing in frequency, especially among adolescents. The lifetime prevalence of these disorders in the United States is approximately 1 in 7 males and 1 in 5 females by age 40 years, with most cases occurring before age 25 years. The mortality rate is estimated to be 213 per 100,000 individuals. Further, a substantial number of people with these disorders may have other behavioral disorders, such as phobias, depression, PTSD, or substance use disorder.

Diagnosis can be challenging; to aid clinicians, several short screening questionnaires have been developed.

National Eating Disorders Association. Eating disorders screening tool. Accessed October 10, 2022. www.nationaleatingdisorders.org/screening-tool

Ophthalmic considerations Ocular findings in patients with eating disorders include lagophthalmos from orbital fat atrophy, nystagmus or ophthalmoplegia from vitamin B_1 deficiency, and nyctalopia from vitamin A deficiency. Patients with bulimia nervosa can also present with bilateral pinpoint conjunctival hemorrhages.

Substance Use Disorders

Drug dependence is the uncontrolled use of a drug to the point that one's physical health, psychological functioning, or ability to exist within the demands of society is threatened. Misuse of drugs and addiction are often considered strictly social problems. However, there is overwhelming evidence that substance use disorder has long-term effects on brain metabolism and activity in addition to the detrimental short-term effects. With habitual use, changes occur in the brain, turning drug use into an illness of addiction. Individuals who are addicted to drugs have compulsive drug cravings and are typically unable to quit by themselves; treatment is necessary to end the compulsive behavior.

Ophthalmic considerations Pupillary changes can occur as a result of drug use. For example, pupillary constriction commonly occurs with the use of opiates, and dilation occurs with the use of cocaine, amphetamines, or lysergic acid diethylamide (LSD). Pupillary dilation may also be observed in individuals undergoing opiate withdrawal.

Sustained horizontal gaze-evoked nystagmus may be a sign of sedative or ethanol use. *Toxic optic neuropathy* is noted in patients with alcohol use disorder (also called *alcoholism*) either as a direct effect of the disease or in association with the malnutrition that often accompanies alcoholism. *Wernicke encephalopathy,* which is most often associated with chronic alcoholism, is caused by thiamine deficiency; individuals with Wernicke encephalopathy present with ocular palsies, nystagmus, memory disturbance, and peripheral neuropathy. Children born to mothers with alcoholism may have *fetal alcohol*

syndrome (FAS). Ocular manifestations of FAS include epicanthal folds, ptosis, strabismus, optic nerve hypoplasia, microphthalmia, and retinal vascular anomalies. See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for further discussion of FAS.

Individuals who misuse intravenous drugs are at risk for retinovascular occlusion and endophthalmitis and are more likely than nonusers to have an HIV infection, which has associated ocular findings. Cocaine use can lead to optic neuropathy, intracranial microinfarcts causing internuclear ophthalmoplegia, and visual field defects. Cocaine use during pregnancy can cause intrauterine growth retardation, microcephaly, developmental delay, and learning disabilities; affected infants also have an increased risk of strabismus and neonatal retinal hemorrhages. In patients using methamphetamine, general anesthesia can cause hemodynamic instability and arrhythmias. In young patients who present with corneal ulcers or epithelial defects without an apparent cause, crack cocaine use in particular should be considered.

Dhingra D, Kaur S, Ram J. Illicit drugs: effects on eye. *Indian J Med Res*. 2019;150(3): 228–238.

Mandatory Reporting of Abuse and Neglect

Although state laws vary throughout the United States, clinicians are legally required to report suspected cases of neglect or abuse of children, persons with disability, and older adults. *Child abuse* affects 1 in 8 by age 18 years, and children who experienced abuse often have long-term consequences, including higher rates of depression through adulthood. *Intimate partner abuse* is found in nearly a third of women in their lifetime, although this can occur in men as well. In individuals 60 years and older, the prevalence of elder abuse is approximately 10%, and it is often unreported. (See the section Elder Abuse in Chapter 11.) Clinicians should not ignore patient encounters that might suggest abuse or neglect and should not hesitate to report concerns to local and state authorities. Most state laws require only a reasonable suspicion of abuse. Signs to look for include an observed violation, a disclosure from a person claiming abuse or a witness to that claim, or physical signs of harm. Clinicians making the report in good faith are protected from liability even when the allegations are unsubstantiated, and information is, by law, protected and confidential.

Thomas R, Reeves M. Mandatory reporting laws. *StatPearls* [Internet]. StatPearls Publishing; January 2022. Updated July 10, 2023. Accessed October 6, 2023. www.ncbi.nlm.nih.gov/books/NBK560690/

Pharmacologic Treatment of Psychiatric Disorders

Antipsychotic Drugs

Antipsychotic drugs have been used for more than 60 years and are broadly divided into 2 groups: *first-generation antipsychotics* (*FGAs;* also called *typical antipsychotics*) and

Table 12-1 Antipsychotic Medications

First-generation (typical) agents		Second-generation (atypical) agents	
Chlorpromazine	Perphenazine	Aripiprazole	Lurasidone
Droperidol	Pimozide	Asenapine	Olanzapine
Fluphenazine	Prochlorperazine	Brexpiprazole	Paliperidone
Haloperidol	Thioridazine	Cariprazine	Pimavanserin
Loxapine	Thiothixene	Clozapine	Quetiapine
Mesoridazine	Trifluoperazine	Iloperidone	Risperidone
Molindone		Lumateperone	Ziprasidone

second-generation antipsychotics (*SGAs;* also called *atypical antipsychotics*); see Table 12-1. The distinction between the 2 classes is based on differences in receptor activity, adverse effects, and overall efficacy, although there is overlap between the classes. FGAs are primarily dopamine receptor blockers, whereas SGAs inhibit both serotonin and dopamine. Antipsychotic medications are used in the treatment of schizophrenia as well as in the management of bipolar disorder and other psychiatric conditions. They effectively reduce many symptoms of acute and chronic psychoses, allowing more patients to function outside psychiatric institutions.

FGAs are more likely than SGAs to cause extrapyramidal Parkinson-like adverse effects (including rigidity and tremor) and tardive dyskinesia (involuntary movements of the face, tongue, trunk, and extremities). Other systemic adverse effects of antipsychotics include drowsiness, orthostatic hypotension, anticholinergic effects, and weight gain. Less common problems include cholestatic jaundice, blood dyscrasias, photosensitivity, and a rare idiosyncratic reaction known as *neuroleptic malignant syndrome (NMS).* NMS is characterized by "lead-pipe" muscle rigidity and hyperthermia and can lead to rhabdomyolysis and possible death if not recognized and promptly treated. SGAs may be less likely to cause these adverse effects, although at higher doses, they can still cause problems.

Ophthalmic considerations Second-generation antipsychotics such as clozapine, olanzapine, and quetiapine may be associated with a number of ocular manifestations, including those associated with diabetes. The onset or worsening of diabetes in patients using SGAs may be due in part to weight gain, which is an adverse effect of these medications. Anticholinergic effects, another systemic adverse effect, can lead to secondary dry eye and accommodative changes, as well as precipitating angle-closure glaucoma. A few studies have suggested an increase in cataract formation in patients taking antipsychotic drugs, particularly FGAs. Thus, drug manufacturers recommend that patients using antipsychotics have eye examinations every 2 years up to age 40 years and annually thereafter.

Other potential ocular findings, more commonly associated with FGAs than with SGAs, include periorbital and conjunctival pigmentation, corneal deposition, and vision loss from retinal pigmentary degeneration typically

associated with thioridazine. Blepharospasm and other ocular motility problems can be associated with extrapyramidal adverse effects.

Packer S. Ocular side effects of psychotropics: special considerations. *Psychiatr Times.* 2014;31(6). Accessed August 8, 2022. https://www.psychiatrictimes.com/view/ocular-side-effects-psychotropics-special-considerations

Antianxiety and Hypnotic Drugs

Benzodiazepines

The benzodiazepine class of medications is sometimes used to treat patients with GAD. They are also beneficial as an adjunct to anesthesia or for management of alcohol withdrawal, treatment of seizures, alleviation of muscle spasms, treatment of insomnia, and treatment of nocturnal myoclonus. Table 12-2 lists the antianxiety and hypnotic medications as well as the older class of barbiturates (the use of barbiturate drugs has declined because of their high potential for misuse and addiction). Although benzodiazepines are effective in treating these disorders, their use has also diminished because of concerns about dependency. First-line therapy has shifted to use of serotonin-norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs) because they tend to be safer.

The mechanism of action for benzodiazepines is centered around their effect on γ-aminobutyric acid (GABA) receptors in the central nervous system. Although these agents are similar in their effects, they vary in the time of onset, half-life, and process of metabolism. The potential to misuse benzodiazepines is mild compared with other drugs such

Table 12-2 Antianxiety and Hypnotic Medications

Benzodiazepines	
Alprazolam	Flurazepam
Chlordiazepoxide	Lorazepam
Clobazam	Midazolam
Clonazepam	Oxazepam
Clorazepate	Quazepam
Diazepam	Temazepam
Estazolam	Triazolam
Barbiturates	
Amobarbital	Phenobarbital
Pentobarbital	Secobarbital
Nonbenzodiazepine nonbarbiturates	
Antianxiety agents	*Hypnotic agents*
Buspirone	Eszopiclone
Hydroxyzine	Ramelteon[a]
Meprobamate	Suvorexant[b]
	Zaleplon
	Zolpidem

[a]Melatonin receptor agonist.
[b]Orexin receptor antagonist.

as hydromorphone and cocaine. Nevertheless, long-term use of these agents can cause physiologic dependence. Withdrawal symptoms, including anxiety, tremors, psychosis, and even seizures, are more likely when intake is abruptly stopped after long-term use. All benzodiazepine drugs have the potential to cause retrograde amnesia, and respiratory depression is possible, especially when these drugs are combined with alcohol.

Ophthalmic considerations Ocular adverse effects are sometimes associated with benzodiazepine use, including decreased accommodation, induced phorias, and nystagmus. These effects tend to be dose related and transient.

Antidepressants

A growing number of patients with major depression are being managed with medication alone, despite reports demonstrating the benefits of combining pharmacologic treatment with psychotherapy. Nevertheless, this group of drugs is effective in managing the symptoms associated with depression, improving the rate of recovery, reducing the risk of suicide, and aiding in social and occupational rehabilitation.

In general, antidepressants can take up to 6 weeks to show significant effect; treatment is generally continued for up to 12 weeks, although long-term management may be needed in selected cases. Antidepressants are associated with a 50%–60% response rate among patients with major depression in the primary care setting. These drugs can result in mood elevation, improved appetite, better sleep, and increased mental and physical activity.

Table 12-3 lists the various classes of antidepressants. The first-generation tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are not generally prescribed as first-line treatment owing to safety concerns (in particular, overdose) and adverse effects. Second-generation options include SSRIs, SNRIs, atypical antidepressants (such as bupropion, trazodone), and serotonin modulators. Of these, SSRIs are the most widely prescribed; they are very effective and tend to be better tolerated. Occasional adverse effects associated with SSRIs include sexual dysfunction, drowsiness, insomnia, weight gain, dizziness, headache, and blurred vision (likely related to dry eye and, to a lesser extent, mydriasis). Rare cases of angle-closure glaucoma have been reported.

Major depression is now thought to affect 5% of children and adolescents; consequently, the use of SSRIs has steadily increased in this population. There have been some reports of antidepressants leading to increased suicidal ideation in a small percentage of children and adolescents. Close monitoring for abnormal behavior, agitation, and suicidal thoughts is advised, especially within the first 4 weeks after the individual begins antidepressant therapy.

Mood stabilizers

Mood stabilizers are a heterogeneous group of medications that do not share a common mechanism of action. They are the drugs of choice for the treatment of bipolar disorder. *Lithium carbonate* was the first drug developed in this class and has been the most widely studied. Second-line agents include *valproic acid, quetiapine,* and *lamotrigine*.

Table 12-3 Antidepressant Medications

Tricyclic and tetracyclic antidepressants	
Amitriptyline	Imipramine
Amoxapine	Maprotiline
Clomipramine	Nortriptyline
Desipramine	Protriptyline
Doxepin	Trimipramine
Selective serotonin reuptake inhibitors	
Citalopram	Fluvoxamine
Escitalopram	Paroxetine
Fluoxetine	Sertraline
Dopamine-norepinephrine reuptake inhibitor	
Bupropion	
Serotonin-norepinephrine reuptake inhibitors	
Desvenlafaxine	Milnacipran
Duloxetine	Venlafaxine
Levomilnacipran	
Serotonin modulators	
Nefazodone	Vilazodone
Trazodone	Vortioxetine
Noradrenergic and specific serotonergic antidepressant	
Mirtazapine	
Monoamine oxidase inhibitors	
Isocarboxazid	Selegiline (transdermal)
Phenelzine	Tranylcypromine

Potential ocular adverse effects of lithium use include blurred vision, nystagmus (usually downbeat), and exophthalmos associated with lithium-induced changes in thyroid function.

Ophthalmic considerations Although behavioral disorders do not directly affect the eye, several related issues are important for ophthalmologists to be aware of. One issue is that the underlying mental disorder may cause the patient to be overly concerned about anticholinergic adverse effects such as dry eye and accommodative changes; thus, patient education and reassurance about these effects may be necessary. Poor adherence to treatment is another common problem among patients with mental health issues. Some medications used to treat eye disease, including carbonic anhydrase inhibitors, brimonidine, and oral corticosteroids, may induce or exacerbate depression. Although β-blockers were thought to increase the risk of depression, recent studies suggest that this correlation is not as strong as was previously believed.

Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. *CNS Drugs*. 2010;24(6):501–526.

Neurologic Disorders

Parkinson Disease

Parkinson disease (PD) is a neurodegenerative condition characterized by resting tremor, bradykinesia, and rigidity. The disorder usually affects persons older than 50 years, and its incidence rises dramatically after 60 years of age. *Early-onset PD* (before age 50 years) is seen in less than 10% of cases; reasons for early onset are still unclear. Worldwide, approximately 7.5 million people have PD, and this number is expected to increase to more than 9 million by 2030. There is a male predominance. The differential diagnosis for PD includes other neurodegenerative disorders such as dementia with Lewy bodies, corticobasal degeneration, multiple system atrophy, and progressive supranuclear palsy.

Etiology

The basal ganglia are a complex of deep gray matter nuclei that includes the corpus striatum, globus pallidus, and substantia nigra. These structures regulate the initiation and control of movement. Patients with PD have typically lost 80% or more of the dopamine-producing neurons in the substantia nigra. Depletion of dopamine in the complex nigrostriatal pathway produces an imbalance in inhibitory and excitatory neuronal signals, leading to the cardinal signs of PD.

Although most cases are sporadic, genetic factors are implicated in the pathogenesis, especially in early-onset cases. At least 5 possible causative genes have been identified, and the number of Parkinson-like disorders associated with specific genetic defects is increasing. Many of these defects appear to be involved in cellular protein metabolism. Overall, PD seems to have a multifactorial etiology that includes genetic predisposition, environmental factors, and age-related changes in neuron metabolism.

Features

The first symptom of PD is usually tremor of a limb at rest. As mentioned previously, bradykinesia and rigidity are characteristic symptoms. Other common symptoms are shuffling gait, postural instability, and stooped posture. Persons with PD often have reduced facial expressions and speak in a soft voice. The disease is associated with nonmotor features such as depression (in up to 50% of cases), dementia, personality changes, sexual difficulties, sleep disorders, and hallucinations.

Treatment

There is currently no cure for PD. Dopamine replacement, with medications such as *levodopa,* is the primary treatment. Dopamine itself cannot be given because it does not cross the blood–brain barrier. Although levodopa helps at least three-fourths of patients with PD, not all symptoms respond equally to the drug. Bradykinesia and rigidity respond best, whereas tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all. Patients are often given levodopa combined with *carbidopa*. The combination of the 2 medications delays the conversion of levodopa into dopamine until it reaches the brain, diminishing some of the adverse effects (such as nausea and vomiting) that often accompany levodopa therapy alone.

After years of therapy, patients may experience a "wearing-off" effect approximately 4 hours after a dose of levodopa, when symptoms may return. Catechol-O-methyltransferase inhibitors such as *entacapone* extend the duration of the levodopa effect and reduce the "off" time by inhibiting the methylation of levodopa and dopamine.

Several additional therapies for PD exist, and research is dedicated to finding more effective modalities. Dopamine agonists (*pramipexole, ropinirole, rotigotine,* and *apomorphine*) stimulate dopamine receptors in the brain and may delay the need for levodopa. The monoamine oxidase type B inhibitors *selegiline, rasagiline,* and *safinamide* modestly improve PD symptoms. The glucagon-like peptide-1 drug *exenatide,* which is used to treat type 2 diabetes, has also demonstrated some potential neuroprotective effect and is currently being studied. Anticholinergic drugs such as *trihexyphenidyl* and *benztropine* have a short-lived effect in controlling tremor and rigidity. However, only about half of patients respond to anticholinergics, and typical anticholinergic adverse effects can be problematic.

Amantadine, an antiviral drug, may be used during the early stages of the disease, either alone or in combination with anticholinergics or levodopa. However, after several months, the effectiveness of amantadine wears off in one-third to one-half of patients. Of note, several large studies indicate a potential protective effect with α_1-adrenergic receptor antagonists used to treat prostatic hypertrophy.

Modern surgical treatments consist primarily of *deep brain stimulation,* which involves implanting an electrode in the brain, and *thalamotomy.* Another surgical treatment, *pallidotomy,* carries the risk of complications such as stroke and hemorrhage, as well as the risk of irreversible adverse effects and, therefore, is seldom performed. The dopamine deficiency in patients with PD results in excitation of the globus pallidus, which in turn inhibits thalamic activity. Both surgical techniques serve to suppress this excessive globus pallidus activity. Deep brain stimulation is initially safer than pallidotomy but requires intensive adjustments and lifelong maintenance, given the risk of hardware complications and infection.

Ferreira M, Massano J. An updated review of Parkinson's disease genetics and clinicopathological correlations. *Acta Neurol Scand.* 2017;135(3):273–284.

Kalia LV, Kalia SK, Lang AE. Disease-modifying strategies for Parkinson's disease. *Mov Disord.* 2015;30(11):1442–1450.

Ophthalmic considerations Patients with PD may present with numerous ophthalmic findings, which can be divided into eyelid disorders and ocular motor abnormalities. *Eyelid disorders* include seborrheic dermatitis and blepharitis, apraxia of eyelid opening, eyelid retraction, decreased blinking (with secondary dry eye), and blepharospasm. *Ocular motor abnormalities* include convergence insufficiency, limitation of upgaze, saccadic abnormalities, square-wave jerks, and oculogyric crisis. In addition, patients commonly report difficulty with reading and symptoms related to ocular surface abnormalities.

Drug-related adverse effects may also be superimposed, especially for patients using anticholinergic medications, which may exacerbate dry eye and cause accommodative changes or precipitate angle-closure glaucoma. More

than 30% of patients with coexisting ocular disease and reduced vision may experience formed recurrent hallucinations characteristic of Charles Bonnet syndrome. However, this syndrome is not specific to PD; it can occur with other neurodegenerative and ocular conditions. Visual hallucinations can also occur as a result of treatment. This adverse effect has been reported particularly with levodopa and anticholinergic agents. The drug amantadine has been reported to cause corneal infiltrates and edema in rare cases.

Multiple Sclerosis

See BCSC Section 5, *Neuro-Ophthalmology.*

Epilepsy

Epilepsy is a brain disorder characterized by recurrent seizures, which can be focal or generalized. The prevalence of epilepsy increases with age, especially after age 65 years, and occurs in 2%–5% of adults. Patients with epilepsy may have problems with depression, driving, employment, and insurance even when the epilepsy is under control. The overall mortality rate of patients with epilepsy is approximately twice that of the general global population.

Etiology

Epilepsy can be inherited or acquired and has many possible causes. Seizures result from uncontrolled electrical activity of neuronal networks in the cerebral cortex. Any disturbance of normal neuronal activity—which can occur as a result of injury, infection, or abnormal brain development, among other causes—can lead to seizures. Cerebrovascular disease is the most common cause in older adults; however, approximately half of all seizures have no identifiable cause. Seizures may develop because of an abnormality in brain wiring, an imbalance of neurotransmitters, or some combination of these factors. Epilepsy can also be associated with a variety of developmental and metabolic disorders, including cerebral palsy, neurofibromatosis, tuberous sclerosis, and autism.

Types of seizures

Typically, seizures are divided into 2 major categories: focal and generalized. *Focal* (formerly called *partial*) *seizures* occur in only 1 part of the brain and are further divided into *simple* (without impairment of consciousness) and *complex* (with impairment of consciousness). Symptoms of simple focal seizures (also called *auras*) depend on the part of the brain from which the seizures originate and include motor symptoms, sensory symptoms (which can resemble a migraine aura), and even autonomic symptoms. Complex focal seizures are the most common type of seizures in adults with epilepsy. During the seizure, individuals may appear awake but do not interact with others around them and do not respond as they typically would to instructions or questions. They often stare into space and either remain motionless or engage in repetitive behaviors, called *automatisms,* such as facial grimacing or gesturing.

Generalized seizures cause impaired consciousness and abnormal activity in both hemispheres at the onset of the seizure. These events may follow focal seizures. They can be nonconvulsive (*absence;* formerly, *petit mal*) or convulsive (*tonic-clonic;* formerly, *grand mal*; or some variation of tonic-clonic). Absence seizures nearly always first occur in childhood or adolescence and are frequently familial, suggesting a genetic cause. Some patients make purposeless movements during seizures, such as jerking an arm or rapidly blinking their eyes. Others have no noticeable symptoms except for brief periods of "absence." Childhood absence epilepsy often stops when the child reaches puberty. A generalized tonic-clonic seizure is the most dramatic in that it begins with an abrupt alteration in consciousness, sometimes in association with a scream or shriek. All muscles stiffen, and the patient may become cyanotic during the tonic phase. Within a short time, the muscles begin to jerk and twitch; this lasts for 1–2 minutes, and then the patient goes into a deep sleep.

The end of a seizure is referred to as the *postictal period* and signifies the recovery period for the brain. This period may last from several seconds to a few days, although typically no more than a few hours. Postictal paresis is a transient focal motor deficit that lasts for hours or, in rare cases, days after an epileptic convulsion. It is thought to be related to neuronal exhaustion (from electrical overactivity during the seizure) or active inhibition.

Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. *Cold Spring Harb Perspect Med*. 2015;5(6):a022426.

Diagnosis

Electroencephalography (EEG) is the most common diagnostic test for epilepsy, although a normal EEG result does not rule out the disorder. Computed tomography, magnetic resonance imaging (MRI), positron emission tomography, and single-photon emission computed tomography are helpful tools for revealing abnormalities in the brain that cause epilepsy.

Treatment

Currently available treatments help control seizure activity in 80% of patients with epilepsy. The medication used is determined by the type of seizure, comorbidities, age of the patient, and potential drug interactions. The latter concern applies specifically to the medication's effect on patients concurrently being treated with warfarin or certain antibiotics or those taking oral contraceptives. For generalized tonic-clonic seizures, the first-line therapy includes *valproic acid, lamotrigine,* and *topiramate*. For focal seizures, *lamotrigine, carbamazepine, phenytoin,* or *oxcarbazepine* is considered. For more refractory cases, *cenobamate,* a newer drug that modulates the GABA receptor, is available.

To minimize adverse effects, monotherapy is the goal; however, a second agent is sometimes necessary to control breakout seizures. Adverse effects vary; they may include nausea, rash, anorexia, somnolence, dizziness, and confusion. The neurologic effects often become the dose-limiting factor. Some of the drugs used to treat epilepsy can also promote hyperlipidemia, which may increase the risk of cardiovascular disease. Rare but serious drug reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis.

When medications inadequately control seizure activity, surgery is a potential option. The most commonly performed procedure for epilepsy is removal of a seizure focus via lobectomy or lesionectomy. Other, less common surgical procedures for epilepsy include multiple subpial transections, corpus callosotomy, and hemispherectomy. An implanted vagus nerve stimulation device can be effective in helping to control seizures in children when medication alone is insufficient.

Ophthalmic considerations Transient unilateral or bilateral mydriasis can occur as an expression of seizure activity during or after the event; it is most common in children. Horizontal or vertical gaze deviations are commonly associated with seizure activity. The gaze tends to be directed away from the side of the cortical seizure activity during the event and then toward the side of the prior activity after the seizure. Some patients experience conjugate, convergent, or monocular nystagmus during the clonic stage of a seizure. Clonic eyelid retraction has also been described in patients with absence or myoclonic seizures. It is unusual for patients with true seizures to shut their eyes during the episode, whereas patients who feign a seizure often keep their eyes closed.

Certain antiepileptic drugs have potential ocular adverse effects. Phenytoin can cause dose-related nystagmus, and maternal use of this medication is associated with fetal hydantoin syndrome, which includes hypertelorism, epicanthal folds, glaucoma, optic nerve hypoplasia, and retinal colobomas. Carbamazepine can cause blurred vision, diplopia, and nystagmus. Topiramate has been associated with acute angle-closure glaucoma secondary to ciliochoroidal effusions and anterior chamber shallowing, usually within the first 2 weeks of starting therapy. Treatment of the glaucoma includes cessation of the drug and use of cycloplegics and topical hypotensive agents.

Stroke

See Chapter 7, Cerebrovascular Disease, in this volume.

Alzheimer Disease and Dementia

The term *dementia* refers a decline in cognitive ability to the point of interfering with daily functioning. Dementia is not one specific disease; rather, it encompasses several types caused by a variety of conditions and diseases. The most common type is Alzheimer disease; other types include vascular (multi-infarct) dementia and Lewy body dementia. Diagnosis of dementia can be challenging because its onset is insidious, and the early symptoms may be apparent only to close family members.

Globally, the prevalence of dementia in individuals 60 years and older is between 5% and 8%. Of the 50 million people affected worldwide, approximately 60% live in low- to middle-income regions.

Alzheimer disease

Alzheimer disease (AD) is the most common type of neurodegenerative dementia in people older than 65 years. Epidemiologic data from the European Community Concerted Action Epidemiology of Dementia Group found that 70% of patients with dementia have AD. After age 65 years, the incidence of AD doubles with every 5-year increase in age. Memory impairment is the cardinal feature of AD, with language and behavioral deficits occurring over time. The pathologic hallmarks of AD are extraneuronal amyloid plaques and neurofibrillary degeneration. These 2 findings are associated with neuronal death and decreased levels of the neurotransmitter acetylcholine. As the disease progresses, the basal forebrain and eventually the cerebral cortex become involved. In addition to older age, family history appears to be a risk factor for AD, suggesting a genetic link; the early-onset form of the disease seems to have the strongest genetic tie.

Diagnosis of AD is made clinically; serologic testing and neuroimaging studies are used to rule out other causes. Life expectancy in individuals with AD is shortened relative to the degree of impairment at the time of diagnosis. The disease presents considerable challenges to family and caregivers in dealing with various related issues, including emotional lability, risk of wandering, and potential for injury. Resources are available to assist patients and their families with these matters, such as the Alzheimer's Association (www.alz.org).

An atypical presentation of AD can result from neuropathologic abnormalities concentrated in particular areas of the brain. For example, posterior cortical atrophy can lead to progressive cortical impairment and ocular manifestations from pathology involving visual pathways. As a result, many of these patients may present early in the disease progression with various visual symptoms and findings, including homonymous visual field defects.

Cholinesterase inhibitors such as *donepezil* and the neuropeptide-modifying agent *memantine,* used alone or in combination therapy, can be helpful in treating patients with AD. Recently, the US Food and Drug Administration (FDA) granted approvals for monoclonal antibodies aducanumab and lecanemab for the treatment of AD. Both biologics target the underlying pathophysiology of amyloid deposition in the brain, which has been associated with cognitive decline. Studies investigating the potential benefit of *vitamin E* supplementation show mixed results.

Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules.* 2020;25(24):5789.

Vascular dementia

Vascular dementia is the second most common form of neurodegenerative dementia after AD and accounts for 10%–20% of dementia cases in North America and Europe. The disease is associated with findings on neurologic examination consistent with prior strokes; neuroimaging studies typically show evidence of multiple infarcts. As in other vascular conditions, patients with hypertension, diabetes, or abnormal lipid profiles are at increased risk. Although donepezil and memantine are sometimes used, their benefit appears limited. Management is usually directed at treating any comorbidities, including the behavioral symptoms that often accompany this disease, such as mood changes and difficulty with planning or communicating thoughts and feelings.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is another common form of neurodegenerative dementia. The disease is characterized pathologically by the presence of eosinophilic intracytoplasmic inclusions *(Lewy bodies)* in the deep cortical regions of the brain. There may be considerable clinical and pathologic overlap between DLB, AD, and PD. Ophthalmologists should be aware of DLB because 70% of patients with this disorder present with complex (or formed) visual hallucinations as an early sign. The Dementia With Lewy Body Consortium recently revised the criteria used to diagnose the disorder, including interpretation of specific biomarkers and the significance of the presence of a rapid eye movement (REM) sleep behavior disorder in the patient. There are no specific pharmacotherapy options for patients with DLB, although cholinesterase inhibitors have shown some benefit in selected cases.

McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report for the DLB Consortium. *Neurology.* 2017;89(1): 88–100.

Ophthalmic considerations Patients with dementia may report a host of visual symptoms and manifest a variety of findings depending on the extent of the disease. Reduced contrast sensitivity, depth perception, and motion perception have been reported in patients with AD. Because this disease is associated with an impaired cholinergic system, a reduced pupillary constriction response may be observed, which improves after treatment with the anticholinesterase agent donepezil.

Currently, there is no reliable, specific diagnostic test for AD. Ocular motility disorders, especially saccadic latency, have been reported. Because the retina is part of the central nervous system, optical coherence tomography of the retina is being investigated as a tool to detect neurodegenerative disease; thinning of the retinal nerve fiber layer may be an associated finding.

Prion-Associated Neurologic Disorders

Prion diseases (also known as *transmissible spongiform encephalopathies*) are chronic and progressive neurodegenerative disorders that can affect both humans and animals. *Prions* are transmissible pathogenic agents consisting of abnormal proteins on cellular surfaces; these proteins interfere with normal processes such as cell signaling and neuronal homeostasis. Known human forms of prion diseases include kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. Most prion diseases have overlapping clinical features, including tremor, ataxia, involuntary movements, and dementia.

Creutzfeldt-Jakob disease (CJD) is the most commonly recognized form of prion disease. The worldwide incidence is approximately 1 case per million population. Males and females are equally affected, and the median age at onset is 60 years. An iatrogenic form can occur after various surgical procedures, including corneal transplantation. Rapidly

progressive mental deterioration, behavioral abnormalities, and myoclonus are characteristic of the disease. Ophthalmic disturbances are not uncommon and may include diplopia, supranuclear palsies, hallucinations, and visual field deficits.

CJD is distinguished from more common causes of dementia by its rapid onset and progression and the presence of myoclonus and associated gait disturbances. Brain biopsy is the gold standard for diagnosing the disorder but is rarely necessary. MRI, EEG, and cerebral spinal fluid (CSF) analysis are generally sufficient to rule out other disease etiologies and help establish the diagnosis. The presence of the CSF protein 14-3-3 is highly specific for the disease, but the sensitivity is lower, thus limiting the test's usefulness. There is no treatment for CJD, and death often occurs within a year of onset.

Informed Consent in Patients With Behavioral or Neurologic Disorders

Every physician-patient interaction involves some assessment to determine whether the patient has adequate capacity to make an informed decision about his or her care. However, assessing the decision-making capacity in patients with mental health diseases or specific neurologic conditions can present challenges to the clinician. A patient's cognitive status is the primary determinant affecting this capacity, and patients with behavioral and neurodegenerative disorders are at risk of impaired cognitive ability. At highest risk of such impairment are patients with AD, PD, schizophrenia, depression, substance use disorder, and traumatic brain injury.

When cognitive impairment is suspected, the clinician should consider initiating a formal assessment of capacity by a trained professional. This assessment consists of open-ended questions relating to the medical decision being investigated. The questions are designed to formally evaluate the 4 decision-making attributes: understanding, appreciation, reasoning, and expression of choice. Several assessment tools are available to help determine a person's decision-making capacity, such as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), the Assessment of Capacity for Everyday Decision-making (ACED), and the Capacity to Consent to Treatment Instrument (CCTI). Clinicians must understand the potential challenges; if patients refuse to be tested, it may be an issue of trust, particularly if they feel that their ability to understand is being questioned. It may be effective to help these patients understand that this assessment is required and that all information obtained during the assessment will result in the best medical care.

When it is determined that a patient has significant impairment and lacks the capacity to make an informed decision, there is an ethical obligation to find an individual capable of making decisions for that patient. It is helpful when patient preferences are established before the patient's incapacity. Without this, local laws can determine who may serve as the patient's proxy. Generally, the order prioritizes the spouse first, followed by any adult children, and then parents, siblings, or other relatives. If the treatment dilemma is urgent and no surrogate is found, a judge can assign formal guardianship based on a legal determination of incompetence.

Fields LM, Calvert JD. Informed consent procedures with cognitively impaired patients: a review of ethics and best practices. *Psychiatry Clin Neurosci.* 2015;69(8):462–471.

CHAPTER 13

Preventive Medicine

Highlights

- Multiple studies support the lifesaving value of mammography in breast cancer screening. The frequency of mammography and other tests should be based on an assessment of the individual patient's risk of breast cancer.
- Screening for colorectal cancer can be performed through a number of procedures or through stool testing. Fecal immunochemical testing is more sensitive than guaiac-based fecal occult blood testing.
- More than 99% of all cervical cancers are positive for human papillomavirus (HPV). A vaccine against HPV is now available.
- In 2017, the US Food and Drug Administration (FDA) approved an inactivated recombinant varicella-zoster vaccine that is far more effective than the previous zoster vaccine for prevention of clinical herpes zoster (shingles) in patients older than 50 years.

Screening Procedures

The goal of preventive medicine is not only to reduce premature morbidity and mortality but also to preserve function and quality of life.

Screening techniques can be used for research and for practical disease prevention or treatment. Screening for nonresearch purposes is useful if the disease in question is

- detectable with some measurable degree of reliability
- treatable or preventable
- significant because of its impact (in prevalence or severity)
- progressive
- generally asymptomatic (or has symptoms a patient might deny or might not recognize)

Screening techniques should not be applied to a population until the following concerns have been addressed:

- sensitivity and specificity of the test
- convenience and comfort of the test
- cost of finding a problem
- cost of not finding a problem

The term *sensitivity* describes how often a test result is positive among persons with a target disease. *Specificity* measures the test's ability to exclude truly negative results. *Relative risk* is the probability of a disease based on a specific finding divided by the probability of that disease in the absence of that specific finding. (See Chapter 2 for additional discussion of these terms.)

Cost can and should be measured in both economic and human terms, including the cost of discomfort, loss of function, or death.

Screening can be performed as a one-time event or through the sequential use of screening tests. Initially, a more sensitive test is administered; when appropriate, it is followed by a more specific test (which is often more costly or difficult to use). When judging the predictive value of the screens for an individual patient, the physician should consider the patient's clinical history, current medications, and results from a physical examination.

Cardiovascular Diseases

Hypertension

The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines published in November 2017 define hypertension as blood pressure ≥130/≥80 mm Hg. Hypertension currently affects approximately 1.4 billion people worldwide, and in the United States, an estimated 116 million persons aged 20 years and older have hypertension. The consequences of uncontrolled hypertension include significantly increased risk of thrombotic and hemorrhagic stroke, atherosclerotic heart disease, atrial fibrillation, congestive heart failure, left ventricular hypertrophy, aortic aneurysm and dissection, peripheral arterial disease, and kidney failure. Approximately 30% of end-stage renal disease is related to hypertension.

Hypertension meets all 5 of the screening criteria mentioned previously: it is detectable, treatable, highly prevalent, progressively damaging, and characteristically asymptomatic until late in its course. See Chapter 4 for discussion of the classification, evaluation, and pharmacologic treatment of hypertension.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13–e115.

Atherosclerotic cardiovascular disease

In the United States, atherosclerosis is responsible for approximately one-half of deaths in individuals of all ages and for one-third of deaths in individuals between 35 and 65 years of age. Three-fourths of deaths related to atherosclerosis result from *coronary heart disease (CHD).* Atherosclerosis is the leading cause of permanent disability and accounts for more hospital days than any other illness.

The rationale for early screening emerged after it was demonstrated that a reduction in risk factors correlated to a reduction in the incidence of coronary disease events. For further discussion on identifying and modifying cardiovascular risk factors, see Chapter 5.

Screening for significant coronary artery atherosclerosis is more expensive and time-consuming than screening for associated reversible risk factors. In general, it is reasonable to screen for a history of cardiovascular symptoms and events (eg, chest pain, dyspnea, syncope, arrhythmias, claudication, or stroke) and reserve the more specific testing (eg, exercise stress testing, cardiac computed tomography [CT], or magnetic resonance imaging [MRI]) for individuals in higher-risk categories.

Cancer

In women, the most common cancers are breast, lung, and colorectal; in men, they are prostate, lung, and colorectal. The types of cancer that best meet the criteria for screening are breast cancer, cervical cancer, colorectal cancer, lung cancer, melanoma, and urologic cancer. Table 13-1 presents the American Cancer Society's 2021 recommendations for early cancer detection. See also Chapter 14.

Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2019;69(3):184–210.

Breast cancer

Though now surpassed by lung cancer as the most common cause of death in women older than 40 years, breast cancer remains the most common malignancy in women. The overall prevalence of breast cancer in women in the United States and Europe is 13%. The age-adjusted incidence of breast cancer declined by 6.7% in 2003 (12% decline in women older than 50 years). This decrease was mostly the result of a 50% reduction in the use of hormone replacement therapy (HRT). In the Women's Health Initiative, a US National Institutes of Health randomized trial, HRT with estrogen and progesterone was associated with an increased risk of invasive breast cancer and abnormal mammograms. From 1989 to 2015, the breast cancer death rate in the United States decreased by 39%, although Black women had a significantly higher death rate than White women. More than 75% of all breast cancers are cured with current therapy. Nevertheless, approximately 281,000 new cases of breast cancer and >43,000 related deaths were projected for the United States for 2021. In the European Union (EU), 355,000 new cases and 93,000 deaths are predicted.

The importance of specific screening is increased by the presence of known risk factors, all of which are identifiable by patient history: (1) first-degree relative with breast, ovarian, or tubal cancer; (2) prior breast, ovarian, or tubal cancer; (3) nulliparity; (4) first pregnancy after age 30; (5) early menarche or late menopause; (6) radiotherapy to the chest between the ages of 10 and 30 years; and (7) *BRCA* mutation (pathologic variant) status. Additional risk factors are high breast density, elevated serum estrogen or testosterone levels, a high-fat diet, obesity, Ashkenazi Jewish ancestry, and a sedentary lifestyle.

Approximately 42% of breast cancers detectable by mammography are not detectable by physical examination alone, and one-third of those found during mammographic screening are noninvasive or, if invasive, <1 cm in size. Because mammograms can yield false-negative results, the best detection strategy involves a physical examination plus mammography,

Table 13-1 American Cancer Society Recommendations for Early Cancer Detection in Asymptomatic Adult Patients, 2021

Test or Procedure, by Cancer Type	Population		Frequency
	Sex	Age, Years	
Colorectal			
Multitargeted stool DNA testing	M, F	>45	Every 3 years
Fecal immunochemical or gFOBT test	M, F	>45	Annually
Colonoscopy	M, F	>45	Every 10 years if patient not high risk
CT colonography	M, F	>45	Every 5 years
Flexible sigmoidoscopy	M, F	>45	Every 5 years
Cervical			
Papanicolaou test ("Pap smear")	F	25–65	Every 3 years
Primary HPV or co-testing with Pap smear	F	25–65	Every 5 years
Endometrial			
Endometrial tissue sample	F	Women at high risk[a]	When indicated
Breast			
Mammography	F	40–44	Individualize
		45–54	Baseline, then annually
		55+	Every 2 years
Prostate			
Serum PSA	M	>50	Discuss risks/benefits of testing
		Men at high risk[b]	Annually for high-risk patients, starting at age 40
Lung			
Low-dose helical CT	M, F	55–74, smokers	Annually if patient identified as high risk
General			
Health counseling and cancer checkup[c]	M, F	>20	At time of general checkup

CT = computed tomography; gFOBT = guaiac-based fecal occult blood test; HPV = human papillomavirus; PSA = prostate-specific antigen.
[a] History of infertility, obesity, failure to ovulate, abnormal uterine bleeding, or use of estrogen therapy.
[b] Positive family history of prostate cancer before age 65, African American race, *BRCA* carriers.
[c] To include examination for cancers of the thyroid, testis, prostate, ovary, lymph nodes, oral region, and skin.

followed by fine-needle aspiration or biopsy if either reveals an abnormality. Mammography has been shown to be safe as well as effective; the current low-dose radiation associated with it does not significantly increase the risk of radiation-induced cancer.

Counseling alone is generally recommended for women with an average risk of breast cancer until 40 years of age. According to the recommendation by the US Preventive

Services Task Force (USPSTF), mammographic screening should be performed every 2 years for average-risk women aged 50–75 years, and screening should be discussed with women from age 40. The American Cancer Society continues to recommend yearly mammography after age 45. Digital mammography and digital breast tomosynthesis are generally more sensitive than film mammography. In addition to general screening recommendations, assessment tools can help estimate an individual patient's risk of breast cancer, for example, the Gail model (BCrisktool.cancer.gov). European guidelines are similar, recommending mammography every 2–3 years from age 45 to 74 (https://healthcare-quality.jrc.ec.europa.eu/ecibc/european-breast-cancer-guidelines/screening-ages-and-frequencies). Although the ideal mammographic screening interval is not clear, the American Cancer Society and USPSTF recommendations, as well as results from large studies done in the United Kingdom and Europe (eg, EUROSCREEN), continue to support the lifesaving value of mammography.

Other modalities available for breast cancer screening include ultrasonography and MRI. Because MRI of the breast is more sensitive but less specific than other methods, it should be used primarily in high-risk younger patients or as a follow-up to abnormal screening results. Women with known mutations in the breast cancer 1 gene *(BRCA1)* or *BRCA2* are at dramatically increased lifetime risk for breast and ovarian cancer and require more intensive counseling and surveillance, including yearly mammography and breast MRI.

DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(6):438–451.

Cervical cancer

Cervical cancer is the most common gynecologic cancer in patients between 15 and 34 years of age. Overall, approximately 14,000 cases of invasive cancer of the cervix (about 4000 resulting in death) and 45,000 cases of carcinoma in situ occur each year in the United States. Worldwide, approximately 84% of the 570,000 cervical cancer cases diagnosed each year occur in developing countries. Despite advances in the diagnosis and treatment of cervical cancer, more than half of the women with the disease worldwide will die. In many developed countries (including the United States), mortality has been reduced by >70% due to the implementation of cytologic screening and HPV vaccination. Cervical cancer is the eighth most common cause of cancer mortality in the United States. The incidence of cervical cancer in the European Union varies widely by nation. The highest incidence is in countries with low HPV vaccination rates, and the European Union has established a goal of a 90% HPV vaccination rate by 2030 for girls by the age of 15 years.

The risk factors for cervical cancer include the presence of high-risk serotypes of HPV, the number of lifetime sexual partners, low socioeconomic status, positive smoking history, use of steroid contraceptive hormones, and a history of other sexually transmitted infections. More than 99% of all cervical cancers are positive for HPV. Early detection and appropriate treatment markedly reduce the morbidity and mortality from invasive cancer of the cervix. In a large randomized trial in rural India, a single lifetime screening for HPV reduced cervical cancer mortality by 50%. Cervical cancer is asymptomatic when it occurs in situ, and the most effective screening technique is testing for HPV. This virus can be

detected with polymerase chain reaction (PCR) assay techniques, and patients aged 25–65 years should receive HPV testing alone or with their Papanicolaou test ("co-testing"). The USPSTF suggests a Pap smear alone from age 21 to 29 because of higher false-positive results from HPV testing in this age group. Vaccines to prevent HPV infection and its sequelae are discussed later in this chapter. Cervical cancer survivors should have annual cervical and vaginal cytology.

US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674–686.

Colorectal cancer

Colorectal cancer is a major killer in developed countries, second only to lung cancer in incidence and mortality. In the United States, the cumulative lifetime probability of developing colon cancer is roughly 4.5%, and approximately one-third of affected individuals will die from this disease. Although the overall incidence of colorectal cancer in the United States has been declining since 1980, there has been a steady increase in the incidence of colorectal cancer in individuals younger than 50 years.

Most authorities accept the theory that colorectal cancer develops from an initially benign polyp in a mitotic process that occurs over approximately 10 years. Colonoscopic removal or ablation of all polyps has become the standard of care where facilities and trained personnel are available. Factors associated with a higher risk of development of colon cancer include increased size and number of polyps, high-grade dysplasia or villous features on biomicroscopy, and sessile polyps only partially removed during a previous colonoscopy. Increased dietary fiber intake and reduced dietary fat intake have been associated with reduced risk of colorectal cancer. In addition, calcium supplementation, multivitamins containing folic acid, and the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a moderate reduction in the risk of recurrent colorectal adenomas.

It is estimated that the mortality rate of colorectal cancer could be reduced by >50% with widespread adoption of screening studies, for example, the guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy, and colonoscopy, with aggressive follow-up of patients who have positive test results. Another stool-based screening test, *fecal DNA testing,* can detect molecular tumor markers associated with colorectal cancer. FIT and fecal DNA testing are easier to use and more sensitive than gFOBT, so patient adherence may be better. The best screening test is the one that the patient is willing to complete. More frequent testing should be considered for higher-risk patients, including those with ulcerative colitis or Crohn disease, a positive family history of colon cancer, or African American descent.

Flexible sigmoidoscopy (every 5 years) and home *gFOBT* (annually) have been recommended in asymptomatic adults between 45 and 75 years of age. Recommendations remain controversial because of a lack of randomized trials. Sigmoidoscopy offers good specificity but misses proximal cancers. FIT, fecal DNA testing, and gFOBT are now accepted screening modalities by the American Cancer Society. Home gFOBT has been shown to decrease the mortality rate of colon cancer by up to 40%. For this test, 3 gFOBT cards are completed

at home; a single gFOBT completed at the time of an annual physical examination is not sufficient.

Colonoscopy has been increasingly used as a screening test for asymptomatic patients older than 45 years. When results are negative in low-risk patients, the test is repeated every 10 years. Many of the lesions discovered with colonoscopy would not be detected with sigmoidoscopy. Yearly colonoscopy has been advocated in populations at very high risk, such as patients with familial polyposis and first-degree relatives of patients with colon cancer. The disadvantages of colonoscopy are its higher cost when compared with other screening methods, the number of trained personnel required to conduct the procedure, and the risks associated with intravenous sedation and of colonic perforation (approximately 0.1%). The advantage of colonoscopy is that it enables the examiner to detect suspicious polyps, which can then be removed, preventing progression to cancer.

CT colonography, another screening tool, may be able to screen out patients without neoplasia. Colonoscopy could then be reserved for only those patients with significant lesions. CT colonography may be preferable for those patients who are not healthy enough to undergo colonoscopy.

For persons older than 50 years, current American Cancer Society guidelines recommend a variety of screening tests, the exact method to be determined following discussion between the physician and the patient (see Table 13-1). In 2021, the European Council recommended either gFOBT or FIT screening for individuals between the ages of 50 and 74 years, but only 14% of EU citizens participate in colon cancer screening. Early detection and treatment of colon cancer, even with isolated metastatic disease, can still result in a cure. Posttreatment surveillance of these patients includes taking periodic histories and performing physical examinations; serum carcinoembryonic antigen (CEA) testing; and CT of the chest, abdomen, and pelvis.

Gini A, Jansen EEL, Zielonke N, et al. Impact of colorectal cancer screening on cancer-specific mortality in Europe: a systematic review. *Eur J Cancer.* 2020;127:224–235.

US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA.* 2021; 325(19):1965–1977.

Gastrointestinal cancer

Tobacco use and alcohol consumption are the primary risk factors for squamous cell carcinoma of the esophagus, accounting for 80%–90% of cases. The main risk factors for adenocarcinoma of the esophagus are gastroesophageal reflux disease (GERD), obesity, and a history of Barrett esophagus (a complication resulting from long-standing GERD). Treatment for esophageal cancer has poor results; thus, prevention or elimination of the risk factors is worthwhile. The incidence of adenocarcinoma of the esophagus is increasing in developed countries, but squamous cell carcinoma remains dominant in developing areas. Currently, no effective preventive screening programs are available, and most patients present with advanced or metastatic disease.

Gastric cancer appears to be associated with certain geographic areas (Japan, China, Central and South America, Eastern Europe, and parts of the Middle East), high ingestion of nitrates, loss of gastric acidity, lower socioeconomic status, and blood type A. It remains

the second most frequent and lethal malignancy worldwide. Although routine endoscopic screening is not cost-effective, widespread screening for and treatment of *Helicobacter pylori* infection in high-incidence populations could be an effective strategy for reducing gastric cancer in these groups. Further testing is recommended only for individuals in high-risk groups.

Pancreatic cancer is 2–3 times more common in heavy smokers than in nonsmokers, and it has also been associated with chronic pancreatitis, diabetes, and obesity. Familial pancreatic cancer represents only about 5%–10% of all cases but carries a higher mortality rate than sporadic pancreatic cancer. Several genetic mutations have been identified that are responsible for a small percentage of familial cases.

Hepatocellular cancer is more common in persons with preexisting liver disease, especially cirrhosis and hepatitis B or C.

Lung cancer

Lung cancer is the leading cause of cancer-related deaths in men and women in the United States and Europe. Worldwide, there were 1.8 million deaths due to lung cancer in 2020. Among male patients with lung cancer in the United States, 85% are smokers. The number and percentage of cases in women have risen with the increased incidence of smoking among women. Fortunately, with the overall decreasing incidence of smoking, the incidence of and death rate from lung cancer in the United States have also been declining. The usefulness of chest radiography and sputum cytologic screening in the general population is generally considered to be low. In high-risk patient groups, screening protocols produce a higher yield. In the US National Lung Screening Trial and the European NELSON study, lung cancer mortality in high-risk patients decreased 20%–25% when these patients were screened annually with low-dose helical chest CT. Positron emission tomography is a promising tool for identifying early malignant changes in the central airways; fluorescent bronchoscopy may also be useful for this purpose. New molecular markers detected in sputum and serum show promise in the future of lung cancer screening. Prevention through smoking cessation remains the most effective way to decrease lung cancer mortality.

de Konig HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med.* 2020;382(6):503–513.

Cutaneous melanoma

Melanoma is the deadliest form of skin cancer, and its incidence is increasing faster than that of all other cancers. In the United States, about 1 in 75 persons will develop melanoma during their lifetime. According to the American Cancer Society, an estimated 106,000 new melanoma cases and 7000 related deaths were predicted in the United States in 2021.

Most melanomas probably arise from dysplastic nevi. Risk factors for melanoma include history of melanoma or atypical moles, presence of more than 50 moles, positive melanoma family history, history of previous nonmelanoma skin cancer, giant congenital nevus (>20 cm), xeroderma pigmentosum, immunosuppression, treatment with UV-A and psoralens, frequent tanning with UV-A light, and a history of 3 or more severe (blistering)

sunburns. Other, less significant risk factors are light skin, hair, and eye color; freckles; inability to tan; indoor occupation with outdoor hobbies; and proximity to the equator.

UV damage probably causes most melanomas. Intense intermittent exposures are directly related to melanoma, whereas other skin cancers are more associated with cumulative exposure. UV radiation causes DNA damage, which is usually corrected by DNA repair enzymes; however, these DNA repair processes degrade with increasing age.

A pigmented lesion with any of the following characteristics, easily remembered by the *ABCDE* mnemonic, is suggestive of melanoma: *a*symmetric lesions, *b*order (irregular), *c*olor (variable), *d*iameter (≥6 mm), and *e*volving (change in size, shape, or color). Other characteristics suggestive of melanoma are pruritus, bleeding, changing morphology, and new lesions or scalp lesions. Everyone should perform periodic self–skin examinations; suspicious lesions require referral to a dermatologist and possible biopsy. Avoiding the sun during peak hours and using sunblock can reduce the risk of melanoma and other skin cancers. In addition to enabling simple visualization, dermoscopy (epiluminescence microscopy), when conducted by skilled examiners, can increase the specificity of clinical examination for the detection of melanomas.

American Cancer Society. Key statistics for melanoma skin cancer. Last revised January 12, 2023. Accessed October 6, 2023. www.cancer.org/cancer/types/melanoma-skin-cancer/about/key-statistics.html

Urologic cancer

In the United States, approximately 16% of new cancer cases per year are found in the prostate, bladder, kidney, and testis, with most of the common malignancies occurring in middle-aged and older men. Approximately 248,000 new cases (336,000 in Europe) of prostate cancer and nearly 34,000 related deaths are expected in 2021 in the United States. Despite a decrease in the overall incidence of prostate cancer, the incidence of more advanced disease is increasing. Although prostate cancer can sometimes be detected early by digital rectal examination (DRE) of the prostate, no effect on mortality has been demonstrated, so annual DRE is no longer recommended. Serum prostate-specific antigen (PSA) screening remains controversial, and data suggest that this screening does not affect mortality. The PSA false-negative rate varies between 15% and 38%, and only about 30% of patients with elevated PSA levels truly have prostate carcinoma. A trend of increasing PSA levels is a more sensitive indicator of prostate cancer than is an individual elevated PSA level. Because of the high rate of false-positives, minimal disease identified by PSA screening, and the potentially significant adverse effects of treating minimal disease, routine yearly serum PSA screening is no longer recommended except for higher-risk individuals, such as African American men, *BRCA* carriers, and those with a positive family history of prostate cancer. Instead, in 2017, the USPSTF recommended individualized discussion of the risks and benefits of prostate cancer screening for men between the ages of 55 and 69; this guidance is similar to that given by the European Society for Medical Oncology.

Although prostate cancer is a potentially lethal illness, many detectable prostate cancers are of little threat to life. Some studies suggest that >75% of men with screen-detected localized disease may not even need treatment. Some men with low-grade prostate cancer receive curative treatment, even though their disease may not require treatment.

More-specific screening methods are needed to allow differentiation between potentially lethal and nonlethal cancers.

Jemal A, Culp MB, Ma J, Islami F, Fedewa SA. Prostate cancer incidence 5 years after US Preventive Services Task Force recommendations against screening. *J Natl Cancer Inst.* 2021;113(1):64–71.

Infectious Diseases

The major public health screening efforts in the United States have been directed at tuberculosis (TB) and sexually transmitted infections (syphilis, chlamydia, gonorrhea, HIV, and herpes simplex virus). Hepatitis screening is used primarily for blood donation, institutionalized populations, and health care workers rather than for the general population. These disorders are discussed in more detail in Chapter 15.

Tuberculosis

One-third of the world's population is infected with *Mycobacterium tuberculosis.* The prevalence of TB in the United States has decreased since 2005. In the United States, most TB infections occur in foreign-born persons; however, other high-risk individuals include those with alcohol use disorder, the urban poor, homeless persons, persons who inject drugs, incarcerated persons, persons living in shelters, persons with HIV infection, and older adults. TB skin testing should still be performed on individuals in high-risk groups, and positive results should prompt chest radiography and consideration of chemoprophylaxis. Some experts advocate regular skin testing of all persons younger than 35 years at the time of routine health examination (for detection as well as for baseline data). The US Occupational Safety and Health Administration recommends that all health care facilities conduct a TB risk assessment, with testing performed if indicated; routine testing is no longer recommended. In addition to TB skin testing, an interferon-gamma release assay can be used to screen for TB exposure. This blood test may be preferred in some clinical situations, including screening for TB in patients who previously received the BCG vaccine. Although acid-fast smears and histopathology remain the most common approach for confirming a diagnosis of TB, a number of nucleic acid amplification assays are also now available.

Several candidate vaccines for TB are currently being investigated; they include subunit, recombinant BCG, and inactivated whole-cell vaccines. The current BCG vaccine can also provide limited protection to newborns in endemic areas.

Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis screening, testing, and treatment of U.S. health care personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep.* 2019;68(19):439–443.

Syphilis

The incidence of syphilis is increasing in the United States, particularly among men who have sexual intercourse with other men. Syphilis is almost always transmitted sexually; although congenital disease transmitted in utero still occurs, it is rare (600 cases in the United States in 2016). The incidence of congenital syphilis has dropped 90% since the 1940s because of mandatory premarital screening and pregnancy screening. Better

prenatal care and increased syphilis screening during pregnancy improve the likelihood of detecting infants at risk for congenital syphilis, thus allowing early maternal treatment.

Latent, untreated cases of syphilis in which the primary or secondary mucocutaneous lesion is no longer present can be detected only by screening. It is important to detect early latent disease: in approximately 25% of cases, infectious mucocutaneous lesions reemerge spontaneously in the first 2 years. Late latent disease should be detected and treated because of the long-term destructive effects on the central nervous system, the aorta, and the skeletal system.

Screening is generally performed with the more sensitive, but less specific, nontreponemal antigen tests (VDRL, RPR, TRUST). Positive results are then confirmed with treponemal antigen tests (FTA-ABS, MHA-TP, TPPA, TP-EIA), which were more expensive in the past; automation of these treponemal antigen tests has decreased their costs, and these tests are now sometimes used for the initial screening. ELISA, Western blot, and DNA PCR techniques may also be used.

US Preventive Services Task Force (USPSTF), Bibbins-Domingo K, Grossman DC, et al. Screening for syphilis infection in nonpregnant adults and adolescents: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315(21):2321–2327.

Immunization

The development of immunization as a means of preventing the spread of infectious disease began in 1796, when Edward Jenner injected cowpox virus, which causes a mild disease, into a child to prevent smallpox, a severe, potentially fatal illness. Immunization today still relies on Jenner's inoculation methods to protect against disease. There are 2 types of immunization: active and passive.

In *active immunization,* the recipient develops an acquired immune response to inactivated or killed viruses, viral subtractions, bacterial toxoids or antigens, or synthetic vaccines. Once the immune response to a particular pathogen has developed, it protects the host against infection. The persistence of acquired immunity depends on the perpetuation of cell strains responsive to the target antigenic stimulus; for certain immunogens, booster inoculations may be required.

In general, live, attenuated vaccines produce longer-lasting immunity; however, they are contraindicated in immunocompromised or pregnant persons because the pathogen can potentially replicate in the host. Ideally, active immunization should be completed before exposure; however, lifesaving postexposure immunity can be developed by combining active and passive immunization.

Passive immunization depends on the transfer of immunoglobulin in serum from a host with active immunity to a susceptible host. Passive immunity does not result in active immunity and sometimes even blocks the development of active immunity. Passive immunity is short-lived and does not confer long-term immunity; however, it provides immediate protection for the recipient who has been exposed to the pathogen. Pooled human globulin, antitoxins, and human globulin with high antibody titers for specific diseases are the usual products available for passive immunization.

The current recommended US immunization schedules, developed by the Advisory Committee on Immunization Practices—including immunization schedules for persons aged 0–18 years, the catch-up schedule for individuals aged 4 months–18 years, and the adult schedule—can be found on the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines/schedules/index.html). The catch-up protocols are for children who have missed some of the recommended immunization doses.

Immunization should be avoided in persons who have had allergic reactions to the vaccine or its components. Idiopathic autoantibody or cross-reacting antibody development may occur after vaccination, resulting in systemic disease such as Guillain-Barré syndrome, a rare but devastating complication of vaccination. Immunization should be avoided during a febrile illness. Multidose immunization schedules that are interrupted can be resumed; however, doses given outside the schedule should not be counted toward completion of the vaccination sequence.

For patients who are pregnant, immunization against tetanus, diphtheria, and influenza is indicated; immunization against other diseases (hepatitis, pneumococcal or meningococcal disease) is indicated if a patient is at high risk of exposure. Additional immunizations may be considered but must be weighed against rare potential risks to the fetus.

The following sections are based on the recommended immunization schedules in the United States. In other parts of the world, immunizations are performed based on World Health Organization (WHO) guidelines, national programs, or recommendations by multinational organizations such as the European Centre for Disease Prevention and Control (ECDC). As a general rule, national immunization schedules for children are quite similar, but recommended immunizations for adults vary widely between countries (Table 13-2 lists a sampling). For more information on the immunization schedules of EU nations, see the ECDC website (https://vaccine-schedule.ecdc.europa.eu).

Chlibek R, Anca I, André F, et al. Adult vaccination in 11 Central European countries—calendars are not just for children. *Vaccine.* 2012;30(9):1529–1540.

US Centers for Disease Control and Prevention. Adult immunization schedule: recommendations for ages 19 years or older, United States, 2022. Last reviewed April 27, 2023. Accessed October 6, 2023. www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

US Centers for Disease Control and Prevention. Child and adolescent immunization schedule: recommendations for ages 18 years or younger, United States, 2022. Last reviewed April 27, 2023. Accessed October 6, 2023. www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Hepatitis

There are 3 main types of hepatitis viruses. Infection with hepatitis A virus is the leading cause of viral hepatitis in the United States, while hepatitis C is the most common in Europe.

Hepatitis A

Hepatitis A virus (HAV) is usually transmitted orally and may be acquired from contaminated water supplies and unwashed or undercooked foods. Vaccination against HAV infection is recommended for children aged 12–23 months and for persons at high risk of

Table 13-2 2021 National Adult Immunization Recommendations: A Sampling[a]

Vaccine	United States	United Kingdom	Finland	Denmark	France	Spain
Influenza	Annually ≥6 months	Annually ≥65 years	Annually ≥65 years	Annually >65 years	Annually >65 years	Annually >65 years
Tetanus, diphtheria	Tdap once 19–64 years of age, then Td booster every 10 years	Catch-up only	Tetanus and diphtheria boosters	—	Tetanus and diphtheria boosters	Tetanus and diphtheria boosters at 65 years
Pertussis	Pertussis as Tdap	Pregnant females	Pertussis by age 15 years	—	Pertussis as Tdap	—
Human papillomavirus (HPV)	Males and females, 3 doses	Males and females	Females only	Males and females	Females only	Females only
Varicella-zoster virus	2 doses, ≥60 years	1 dose, >70 years	—	—	1 dose, >65 years	—
Measles/mumps/rubella (MMR)	1 or 2 doses	Catch-up only	—	—	Catch-up only	—
Pneumococcal pneumonia	1 dose, >65 years	1 dose, >65 years	1 dose, >65 years	High-risk groups	—	High-risk groups

Td = tetanus and diphtheria toxoid vaccine; Tdap = tetanus toxoid, diphtheria, and acellular pertussis vaccine.

[a] Recommendations as of October 16, 2021.

Recommendations from the Centers for Disease Control and Prevention (www.cdc.gov/vaccines/) and the European Centre for Disease Prevention and Control (https://vaccine-schedule.ecdc.europa.eu/).

exposure to HAV (eg, travelers to endemic areas, patients with blood clotting factor disorders, military personnel, people who use illegal drugs, family contacts of infected patients, laboratory workers exposed to the virus). In the United States, 2 preparations are available, each consisting of viral antigens purified from human cell cultures.

Hepatitis B

Approximately 250,000 cases of hepatitis B occur annually in the United States. Between 6% and 10% of adult patients with hepatitis B become carriers, and chronic active hepatitis occurs in 25% of these carriers. Of the patients with chronic active disease, 20% will die of cirrhosis and 5% will die of hepatocellular carcinoma. Worldwide, 250 million persons are chronic carriers.

A number of recombinant vaccines based on the hepatitis B virus (HBV) are now available in the United States and Europe. In adults, HBV vaccine is usually administered in a series of 2 or 3 doses, depending on the product, and 90% of recipients develop protective antibody levels (>10 milli-international units/mL [mIU/mL]), which persist for at least 3 years and may be protective for up to 30 years. Booster injections are advised for persons with antibody levels <10 mIU/mL. A second vaccination results in the development of protective antibodies in 50% of the initial nonresponders.

Vaccination before exposure to HBV is recommended and cost-effective for all infants and children and for individuals in certain high-risk groups: health care workers, hemodialysis patients, adults older than 60 years with diabetes, residents and staff of long-term care facilities, household and sexual contacts of chronic HBV carriers, persons with hemophilia, persons who inject illegal drugs, prison inmates, sexually active men who have sex with men, and HIV-seropositive individuals. Vaccination can be combined with passive immunization for postexposure prophylaxis without affecting the development of active immunity. The incorporation of the vaccine into childhood immunization schedules has resulted in a decrease in the number of new hepatitis B cases reported annually, and there has also been a significant reduction in the number of hepatocellular carcinoma cases reported in children. Some of the available combination vaccines protect not only against hepatitis B but also against hepatitis A, diphtheria, pertussis, tetanus, and polio.

Postexposure prophylaxis with hepatitis B immunoglobulin should be considered when there is perinatal exposure of an infant born to a carrier of HBV, accidental percutaneous or permucosal exposure to blood that is positive for the HBV surface antigen, or sexual exposure (within 14 days) to a carrier of HBV. Hepatitis B immunoglobulin should be given as soon as possible after exposure; a recombinant HBV vaccine should be concurrently administered in an accelerated dosing schedule.

Patients with chronic HBV infection and evidence of liver disease may improve after treatment with antiviral medications. If indicated, interferon or nucleoside or nucleotide analogues (entecavir and tenofovir, respectively) are effective and are associated with a lower incidence of viral resistance than lamivudine.

Hepatitis C

Hepatitis C is the leading indication for liver transplantation in the United States. The CDC has recommended that all adults in the United States born between 1945 and 1965 have a one-time test for hepatitis C. Early intervention in chronically infected individuals,

including treatment and alcohol counseling, can slow the progression of disease. Vaccines against hepatitis C and E are being developed. See Chapter 15 for additional discussion of hepatitis C.

Barrett CE, Pape BJ, Benedict KM, et al. Impact of public health interventions on drinking water–associated outbreaks of hepatitis A—United States, 1971–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(35):766–770.

Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. *MMWR Recomm Rep.* 2020;69(2):1–17.

Influenza

Although influenza is usually a self-limited disease with rare sequelae, it can be associated with severe morbidity and mortality in older persons or those with chronic diseases and obesity (body mass index ≥40). Influenza vaccines produce long-lasting immunity. However, antigenic shifts, primarily in type A rather than type B influenza virus, require yearly reformulation of the vaccine to contain the antigens of strains considered most likely to cause disease. Protection is correlated with the development of antihemagglutinin and antineuraminidase antibodies, which decrease the patient's susceptibility and the severity of the disease. The influenza vaccine is as effective in HIV-seropositive patients as it is in HIV-seronegative patients, regardless of the individual's $CD4^+$ T-cell counts.

In the United States, annual vaccination is recommended for all adults and for children older than 6 months. The influenza vaccine is well tolerated, and there has been no increased risk of neurologic complications with the vaccines administered after 1991. Trivalent and quadrivalent *inactivated influenza vaccines (IIVs)* are available, as well as a recombinant influenza vaccine. A *live, attenuated influenza vaccine (LAIV),* which is administered as a nasal spray, is also available for persons aged 2–49 years, but it may not be as effective as the IIV. Pregnant women may safely receive the IIV. Health care personnel working with severely immunocompromised patients should receive the IIV. The IIV and LAIV should not be administered to persons with anaphylactic hypersensitivity to eggs, but the recombinant vaccine Flublok or the cell culture–based Flucelvax may be used. A high-dose vaccine for patients older than 65 years is also available. Antiviral agents may be indicated to treat influenza in high-risk patients who are more likely to have serious sequelae from influenza (eg, older adults, pregnant women, individuals with certain chronic conditions). The CDC (and others) suggest treatment with neuraminidase inhibitors (zanamivir, oseltamivir, peramivir) because of emerging resistance to amantadine and rimantadine.

Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 influenza season. *MMWR Recomm Rep.* 2021;70(5):1–28.

Varicella-Zoster

Varivax, an approved live, attenuated varicella-zoster vaccine, is recommended in the United States for the prevention of *varicella (chickenpox)* in immunocompetent pediatric patients older than 12 months with no history of previous infection with varicella-zoster

virus (VZV). A second dose is given when the child is between 4 and 6 years of age. For patients older than 13 years, 2 doses of vaccine are given 4–8 weeks apart. Health care workers who have not been exposed to varicella should also be vaccinated. This vaccine is safe and provides immunity for up to 20 years. Data from the CDC confirmed a dramatic decline (87%) in the incidence of varicella in the United States from 1995 to 2000.

Shingrix, an inactivated recombinant VZV vaccine given in 2 doses, is recommended by the FDA for adults aged 50 years or older to reduce the incidence of *herpes zoster (HZ),* or *shingles.* This vaccine, approved in 2017, decreases the risk of HZ by 90% and may be safe to use in immunocompromised patients. Shingrix may not be used in place of Varivax in younger persons. *Zostavax,* a live, attenuated vaccine, was previously recommended to reduce the risk of HZ but is no longer available in the United States. See also Chapter 15.

Ophthalmic considerations The incidence of VZV reactivation, resulting in herpes zoster, increases with increasing age; it has a rate of 11 cases per 1000 person-years for patients in their 80s. In the United States, 1.2 million new cases of HZ are diagnosed each year in adults, 20% of whom have ophthalmic involvement, including keratitis and uveitis. While the incidence of HZ is plateauing in older patients, it is gradually increasing in younger age groups. Ophthalmologists should encourage their patients who are >50 years to receive the current HZ vaccine (Shingrix) even if they previously received the Zostavax vaccine.

Cornea Society and AAO Quality of Care Secretariat, Hoskins Center for Quality Eye Care. Policy Statement. Recommendations for herpes zoster vaccine for patients 50 years of age and older—2018. Revised June 2018. Accessed November 19, 2022. www.aao.org/education/clinical-statement/recommendations-herpes-zoster-vaccine-patients-50-

Measles, Mumps, and Rubella

Vaccination has dramatically reduced the incidence of measles, along with its associated encephalitis and mortality. Introduced in 1963, the initial vaccine was based on an inactivated virus that did not provide a long duration of protection. In 1967, a live, attenuated vaccine providing long-lasting immunity was introduced. Vaccination with the attenuated strain should be routine not only for individuals aged 12 months but also for persons born between 1957 and 1967 who were neither vaccinated nor infected and for persons who received the inactivated viral vaccine. Individuals born before 1957 are considered immune by virtue of natural infection. The vaccine is contraindicated for persons with allergic or previous anaphylactic reactions to gelatin or neomycin but is safe for patients with hypersensitivity to eggs. *Measles-mumps-rubella (MMR)* vaccination is recommended for all children and is usually given first at about 12 months of age and again when the child is between the ages of 4 and 6 years, but the second dose can be given sooner if necessary. It cannot be given to immunosuppressed persons because it contains a live, attenuated virus. The preservative thimerosal is no longer used in this vaccine, and multiple studies have refuted previous concerns about an association between MMR vaccines and autism.

For nonimmunized persons exposed to measles, postexposure prophylaxis with immunoglobulin should be given within 6 days of exposure.

The number of reported cases of mumps in the United States has decreased steadily since the introduction of a live mumps vaccine in 1967. Although mumps is generally self-limited, meningeal signs may appear in up to 15% of cases and orchitis in up to 20% of clinical cases in postpubertal males. Other possible complications include permanent deafness and pancreatitis. MMR vaccination is indicated for all children and susceptible adults, such as child care workers. Revaccination should be considered for patients who originally received only a single dose of the vaccine, particularly students entering college, health care workers, and individuals traveling to endemic areas.

Rubella immunization is intended to prevent fetal infection and subsequent congenital rubella syndrome, which can occur in up to 80% of fetuses of mothers infected during the first trimester of pregnancy. The number of reported cases of rubella in the United States has decreased steadily from more than 56,000 in 1969 to 10 cases in 2005. Rubella was declared eliminated from the United States in 2004, and from the Americas in 2010, although rare outbreaks still occur elsewhere in the world.

Vaccination against rubella is recommended for adults, particularly women, unless proof of immunity is available (documented rubella vaccination on or after the first birthday or a positive serologic test result) or the vaccine is specifically contraindicated. A single subcutaneously administered dose of MMR vaccine provides long-term (probably lifetime) immunity against rubella in approximately 95% of persons vaccinated. Because of the theoretical risk to the fetus, women of childbearing age should receive the vaccine only if they are not pregnant.

Polio

Before the introduction of the first polio vaccine in 1955, polio (poliomyelitis) caused thousands of cases of paralysis. Despite widespread immunization with oral vaccine since 1962, polio persists in some nations in Asia and Africa. There are 2 forms of the vaccine: an oral form containing live, attenuated poliovirus *(oral poliovirus vaccine [OPV], Sabin vaccine)* and an injectable form containing killed virus *(inactivated poliovirus vaccine [IPV], Salk vaccine),* which is administered subcutaneously. To eliminate the risk of vaccine-associated paralytic poliomyelitis, a condition that has been associated more often with OPV than with IPV, only IPV is used in the United States. However, because OPV is cheaper and easier to distribute and because it transmits the weakened virus to unimmunized contacts of those who are vaccinated, helping the former to develop immunity, the WHO suggests that OPV be used for immunization in developing countries, followed by a single dose of IPV. The currently used bivalent OPV is less likely to cause vaccine-associated polio than the older trivalent form. OPV is contraindicated in pregnant females or immunosuppressed patients, who should receive only the inactivated virus vaccine. The WHO plans to switch to the IPV once all circulating polioviruses are eradicated worldwide.

Tetanus, Diphtheria, and Pertussis

The combined *tetanus and diphtheria toxoid vaccine (Td)* is highly effective; it is used for both primary and booster immunization of adults. The prior pediatric vaccine,

diphtheria-tetanus-pertussis (DTP), has been replaced by the newer pediatric vaccine, *DTaP (diphtheria and tetanus toxoid with acellular pertussis)*. *Tdap,* which contains a lower concentration of diphtheria toxoid and acellular pertussis than does DTaP, is recommended in the United States as a one-time booster for all adults aged 19–64 years and, in particular, for all health care professionals and anyone caring for infants younger than 12 months. Young adults should also receive a booster dose of Td every 10 years. If serious doubt exists about the completion of a primary series of immunizations, 2 doses of the combined toxoids should be given intramuscularly at monthly intervals, followed by a third dose 6–10 months later. Thereafter, a booster dose of 0.5 mL should be given at 10-year intervals. Although tetanus is uncommon, >60% of cases occur in persons older than 60 years. Therefore, older adults should be given a single booster at age 65. Pregnant women should receive 1 dose of Tdap during each pregnancy.

In wound management for tetanus prevention, previously immunized persons with severe wounds should receive a Td booster if >5 years have elapsed since the last injection. The management of previously unimmunized patients with severe wounds should include tetanus immunoglobulin as well as Td.

Rotavirus

Rotavirus, a double-stranded RNA virus, is the most common cause of severe acute gastroenteritis in children and infants worldwide. In the United States, 2 live, attenuated oral rotavirus vaccines are available: one based on a bovine rotavirus strain and the other on an attenuated human rotavirus. Three oral doses of the bovine strain are given to infants at 2, 4, and 6 months of age; alternatively, 2 doses of the attenuated human vaccine are given at 2 and 4 months of age. The vaccine is not recommended in children with a history of intussusception or children receiving high-level immunosuppressive therapies.

Cortese MM, Parashar UD; Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2009;58(RR-2):1–25.

Pneumococcal Pneumonia

Pneumococcal pneumonia is the most serious and prevalent of the community-acquired respiratory tract infections. Although pneumococcal disease affects children and adults, the incidence of pneumococcal pneumonia increases in persons older than 40 years. Since 1974, penicillin-resistant pneumococci have emerged. The mortality rate from bacteremic pneumococcal infection exceeds 25% in older adults, despite treatment with antibiotics.

The current unconjugated pneumococcal vaccine contains polysaccharide antigens from the 23 serotypes of *Streptococcus pneumoniae* most commonly found in bacteremic pneumococcal disease. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been designed to induce a protective level of serum antibodies in immunocompetent adults. Adults aged 65 years and older may receive the PPSV23 either alone or in combination with PCV13 (see discussion in the following paragraph), particularly if they are in a high-risk group (eg, a history of cardiac or respiratory disease, sickle cell disease, splenic dysfunction,

renal and hepatic disease, or immunodeficiency). Those who received pneumococcal vaccine before age 65 years should be revaccinated at age 65 if >5 years have passed since the initial vaccination. PPSV23 is not effective for children younger than 2 years.

A pneumococcal conjugate vaccine (PCV) is recommended in the United States for all children younger than 5 years. In the United States, a 13-valent conjugate vaccine (PCV13) is typically used, while in Europe, a 7-valent vaccine is more commonly used. PCV13 is administered in 4 intramuscular doses, given at 2, 4, 6, and 12–15 months of age. The vaccine provides coverage for approximately 80% of the invasive pneumococcal diseases in children in the United States. PCV is recommended for all infants and toddlers younger than 2 years, all children between 2 and 5 years of age who have chronic cardiopulmonary disorders or immunosuppression, and some adults older than 65 years.

The duration of protection afforded by primary vaccination with pneumococcal vaccine appears to wane after 5–7 years.

Haemophilus influenzae

A vaccine against *Haemophilus influenzae* type b (Hib) is recommended for all children before age 24 months. The vaccine has significantly reduced the number of infections caused by encapsulated Hib. In the past, meningitis comprised approximately 60% of Hib infections, amounting to about 10,000 cases each year in the United States. The type b capsule enhances the invasive potential of *H influenzae;* thus, the presence or absence of serum antibodies to these capsular antigens is a critical factor that determines an individual's susceptibility to systemic Hib infection.

The vaccine significantly reduces the risk of contracting Hib-related epiglottitis, meningitis, and orbital cellulitis. The vaccine is available as a conjugated protein between the capsular polysaccharide PRP and other agents that increase the immunologic response (PRP-OMP and PRP-T). It is also available in combination with other vaccines, such as DTaP or meningococcus, for increased patient convenience and adherence. The vaccine is administered in 2 or 3 doses, with the first dose given at age 2 months and the final dose after age 6 months. When the full series is given, the vaccine is more than 95% effective.

Meningococcus

Three meningococcal conjugate vaccines are available for the prevention of meningococcal meningitis serotypes A, C, W, and Y: MenACWY-D, MenACWY-TT, and MenACWY-CRM. These vaccines are recommended for use in all adolescents aged 11–18 years as well in as military personnel, college students living in dormitories, travelers to endemic areas (such as sub-Saharan Africa), close contacts of infected patients, and high-risk patients (especially splenectomized and complement-deficient patients) aged 2–10 or 19–55 years and during new outbreaks of the disease. The MenACWY vaccines are approximately 70% effective in preventing the spread of group C meningococcal infections, but they will not prevent infection from strains of meningococcus not represented in the vaccine. Immunity may wane over time, so revaccination may be required.

In addition, 2 vaccines are available to protect against meningococcus group B (menB). These vaccines are recommended for persons 10 years or older who are at increased risk

of infection, including those who are asplenic, complement deficient, or in the setting of a menB outbreak.

Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: recommendations of the Advisory Committee on Immunization Practices, United States, 2020. *MMWR Recomm Rep.* 2020;69(9):1–41.

Human Papillomavirus

The human papillomavirus (HPV) is a sexually transmitted virus that causes anal and genital warts *(condylomata)*. Even more importantly, HPV is present in 99% of all cervical cancers in women and is a leading cause of penile and anal cancer in men. It is hoped that preventing HPV infection will significantly reduce the incidence of cervical and other gynecologic cancers. HPV vaccines do not eradicate existing viral disease, so they are most effective if given before the patient becomes sexually active. The 9-valent HPV vaccine is administered in a series of 3 doses over a 6-month period, beginning at age 11–12 years in boys and girls. The US CDC suggests catch-up doses to age 26 years. From age 27 to 46, inadequately vaccinated patients may consider vaccination, but it is of limited utility in this age group.

Malaria

In October 2021, the WHO recommended widespread use of a new malaria vaccine in children in endemic areas where *Plasmodium falciparum* predominates. The RTS,S vaccine, a recombinant fusion protein directed against the *P falciparum* sporozoite, has been safe and effective in a pilot study of 800,000 children in Ghana, Kenya, and Malawi. A 30% reduction in severe and deadly malarial cases was observed.

Other potential malaria vaccines include the R21/MM vaccine, which is directed against another *P falciparum* circumsporozoite protein and has a reported efficacy of 75%.

Olotu A, Fegan G, Wambua J, et al. Seven-year efficacy of RTS,S/ASO1 malaria vaccine among young African children. *N Engl J Med.* 2016;374(26):2519–2529.

COVID-19 (SARS-CoV-2)

In late 2019, a coronavirus causing a severe respiratory syndrome emerged in Wuhan, China. The subsequent worldwide COVID-19 pandemic caused by this virus led to the development of a series of vaccines, most using the SARS-CoV-2 spike protein as their antigenic target. Previous research with other coronaviruses (SARS-CoV-1 and MERS-CoV) had demonstrated that antibodies to the spike protein can prevent virus attachment to the host cell.

Although a number of approaches to vaccine development were attempted worldwide, the COVID-19 vaccines initially authorized for clinical use fall into 2 categories:

- *Messenger RNA vaccines.* These enter the cell cytoplasm and direct the production of spike proteins (BNT162b2, Pfizer-BioNTech; and mRNA-1273, Moderna). The RNA does not enter the cell nucleus or interact with the host DNA.
- *Adenovirus vector vaccines.* These vaccines utilize a replication-incompetent adenovirus expressing a spike protein (Ad26.COV2.S, Janssen/Johnson & Johnson; and ChAdOx1 nCOV-19/AZD1222, Oxford/AstraZeneca).

All 4 vaccines are effective but can have rare adverse effects: some recipients of the mRNA vaccines have developed myocarditis, while some vaccinated with the adenovirus vector vaccines have had rare thrombotic complications and a possible association with Guillain-Barré syndrome.

More recently, an emergency use authorization was granted by the FDA to a protein subunit vaccine (Novavax). There have been rare reports of myocarditis, pericarditis, and embolic events with this vaccine. See Chapter 15 for more information on COVID-19.

Krammer F. SARS-CoV-2 vaccines in development. *Nature.* 2020;586(7830):516–527.
World Health Organization. COVID-19 vaccine tracker and landscape. Updated March 30, 2023. Accessed October 6, 2023. www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Ophthalmic considerations Rare case reports have noted possible ocular side effects following COVID vaccination. These include cranial nerve palsies, uveitis, central serous retinopathy, and worsening of Graves disease and Vogt-Koyanagi-Harada syndrome. Further study is needed to assess the mechanism and any relationship to the type of vaccine.

Ng XL, Betzler BK, Testi I, et al. Ocular adverse effects after COVID-19 vaccination. *Ocul Immunol Inflamm.* 2021;29(6):1216–1224.

Travel Immunizations

Precise travel vaccination recommendations depend on the geographic destinations, duration of travel, consumption of local food and untreated water, and likelihood of close contact with local populations. Health information for travelers, including updated immunization and prevention recommendations for various regions of the world, can be found on the CDC website (www.cdc.gov/travel) and the WHO website (www.who.int/health-topics/travel-and-health).

Routine childhood vaccinations should be reviewed for all travelers and updated as needed. Children older than 6 months should be immunized against measles (MMR vaccine) prior to travel abroad. Adults should be fully vaccinated against COVID-19, influenza, pertussis, and tetanus. Following are considerations for specific conditions:

- *Yellow fever.* Vaccination may be required for anyone going to or through a yellow fever endemic area or, to prevent introduction of the disease, for travelers returning from an endemic area.
- *Hepatitis B.* Travelers who expect to have close contact with local populations known to have high rates of hepatitis B transmission should consider vaccination.
- *Cholera.* Emergency and relief workers should consider vaccination.
- *Meningococcus.* Vaccination is required to obtain a visa to Saudi Arabia and is recommended for those planning to visit sub-Saharan Africa.
- *Tick-borne encephalitis.* Immunization is available in Europe and Australia but not in the United States.
- *Japanese encephalitis.* Vaccination should be offered to travelers whose plans include prolonged trips to rural areas in Southeast Asia or the Indian subcontinent during the endemic season.

- *Typhoid fever and hepatitis A.* These immunizations are recommended for travelers who may be exposed to potentially contaminated food and water sources.
- *Monkeypox.* Travelers to West Africa and the Congo should consider vaccination.
- *Rabies.* Preexposure vaccination should be considered for travelers whose plans include a prolonged visit in a remote area or for those whose activities might involve working near animals. (In addition, the WHO provides emergency treatment recommendations in case of a bite by a suspected rabid animal; see www.who.int/news-room/fact-sheets/detail/rabies).

Travelers planning to visit areas endemic for malaria should consult the CDC or WHO website to determine appropriate chemoprophylaxis for the region. *P falciparum* is almost always resistant to chloroquine and sulfadoxine/pyrimethamine, so these drugs are no longer recommended. The drugs used for malaria prevention include atovaquone/proguanil, doxycycline, mefloquine, tafenoquine, and primaquine. All of these medications may cause serious adverse effects.

Freedman DO, Leder K. Immunizations for travel. Updated January 8, 2023. Accessed October 6, 2023. www.uptodate.com/contents/immunizations-for-travel

New and Future Vaccines

New vaccines are now available for anthrax and Ebola virus. Vaccines undergoing investigation include those for HIV, dysentery *(Shigella), Campylobacter, Clostridioides* (formerly *Clostridium*) *difficile,* respiratory syncytial virus, Zika virus, cytomegalovirus, herpes simplex type 2, Epstein-Barr virus, TB, *Pseudomonas aeruginosa, H pylori, Staphylococcus, Cutibacterium* (formerly *Propionibacterium*) *acnes*, parainfluenza virus, and leishmaniasis. Some vaccines, such as those for smallpox and plague *(Yersinia pestis),* are in development largely in anticipation of a potential future bioterrorism attack using these disease vectors.

Passive immunization with human hyperimmune globulin is currently available to treat or prevent rabies, tetanus, cytomegalovirus, hepatitis A, hepatitis B, hepatitis C, herpesvirus, and varicella-zoster infections. Respiratory syncytial virus immune globulin is no longer available, but new monoclonal antibodies show promise.

Considering the worldwide impact of infectious diseases, there is great interest in developing new vaccines for the treatment of gonorrhea, syphilis, leprosy, trachoma, and other infectious diseases. It is hoped that ongoing research will lead to the development of safe and effective vaccines for many or all of these illnesses.

Centers for Disease Control and Prevention website; www.cdc.gov/vaccines/

European Centre for Disease Prevention and Control website; www.ecdc.europa.eu/en/immunisation-and-vaccines

World Health Organization website; www.who.int/health-topics/vaccines-and-immunization

CHAPTER 14

Cancer

Highlights

- Cancer is the second-leading cause of death in the United States, but survival rates have improved with advanced treatment modalities.
- Surgical management, chemotherapy, radiation, and biologic therapies can be used in combination for curative and palliative treatment of cancer.
- Immune checkpoint inhibitors play an important role in the treatment of cancer; ophthalmologists must be aware of, and monitor for serious ocular side effects from, these medications.

Introduction

Worldwide, cancer is a leading cause of death; in 2018, there were 18.1 million newly diagnosed cancer cases and 9.5 million deaths due to cancer. In the United States, cancer is the second-leading cause of death; it accounted for approximately 18% of all US deaths in 2020. Among US children, cancer is second only to injury as the leading cause of death in children past infancy. In the United States in 2020, 1.8 million new cases were diagnosed, and 600,000 deaths occurred. It is estimated that cancer will develop in approximately 39.5% of US men and women during their lifetimes. In the European Region, it is estimated that in 2018, there were 3.9 million new cases of cancer and 1.9 million deaths from cancer, representing approximately 20% of all deaths in the region.

Early diagnosis and improved treatment have decreased the death rate for most cancers. As of 2019, there were approximately 16.9 million cancer survivors in the United States. Among US children, the 5-year survival rate for all childhood cancers combined has improved from approximately 51% in 1973 to over 80% today.

The word *cancer* refers to a group of related diseases; therefore, discussions of etiology, prevention, and treatment must address the specific type of tumor. Nonmelanotic skin cancers, including squamous cell and basal cell carcinomas, are the most common tumors, but these cancers are rarely a cause of death. After skin cancer, the most common forms of cancer in adult Americans are (in decreasing order of incidence) breast, lung, prostate, and colorectal cancers and melanoma of the skin. In 2020, prostate, lung, and colorectal cancers accounted for 43% of all cancers diagnosed in men; and breast, lung, and colorectal cancers accounted for 50% of newly diagnosed cancers in women.

The Cancer Atlas. Accessed October 31, 2022. https://canceratlas.cancer.org/the-burden/
ECIS—European Cancer Information System. Accessed October 31, 2022. https://ecis.jrc.ec.europa.eu/

Etiology

Genetic and Environmental Factors

Cancer is caused by mutations, or *pathogenic variants,* in genes that control cell division. Some of these genes, called *oncogenes,* stimulate cell division; others, called *tumor suppressor genes,* slow this process. In the normal state, both types of genes work together, enabling the body to replace dead cells and repair damaged ones. Mutations in these genes cause cells to proliferate out of control; these cells grow and divide without regard for cell death. The cell cycle is regulated biochemically, and 2 important groups of enzymes are involved in this process: *cyclin-dependent kinases (CDKs)* and *cyclin-dependent phosphatases.* (An example of CDK function involves the tumor suppressor p53 protein, which upregulates the p21 inhibitor of CDK function.)

Gene mutations can be inherited or can result from damage to DNA caused by environmental exposures. Therefore, the etiology of cancer is often multifactorial and can involve chemical, radiation-related, or viral conditions that occur in a complex milieu, including the host's genetic composition and immunobiologic status. Epidemiologic data suggest that up to 80% of cancer cases in humans may result from exogenous or environmental chemical exposure. If these chemicals could be properly identified, a major proportion of human cancers could be prevented by reducing host exposure or by protecting the host.

Radiation

The general population is exposed to both naturally occurring ionizing radiation and man-made ionizing radiation. The latter includes medical diagnostic equipment and technologically altered natural sources (such as phosphate fertilizers and building materials containing small amounts of radioactivity). The carcinogenic effects of radiation exposure result from molecular lesions caused by random interactions of radiation with atoms and molecules. Most molecular lesions induced in this way are of little consequence to the affected cell. However, DNA is not repaired with 100% efficiency, and mutations and chromosomal aberrations accrue with increasing radiation doses. Parameters that influence the response of the target tissue include the total radiation dose, the dose rate, the quality of the radiation source, the characteristics of certain internal emitters (such as radioiodine), and individual host factors.

Viruses

The role of viruses in the etiology of cancer has been studied extensively. For example, researchers have inoculated laboratory animals with specific viruses to see whether they induce tumor development. Several human cancers show a definite correlation with viral infection and the presence and retention of specific virus nucleic acid sequences and virus proteins in the tumor cells. Table 14-1 lists several viruses and their associated cancers.

Table 14-1 Virus-Associated Cancers

Type of Virus	Systemic Findings	Associated Cancers
DNA viruses		
Cytomegalovirus	Cytomegalovirus disease, transfusion mononucleosis, interstitial pneumonia	Carcinoma of the bladder and uterine cervix, Kaposi sarcoma, prostate cancer
Epstein-Barr virus	Infectious mononucleosis	Burkitt lymphoma, nasopharyngeal carcinoma
Hepatitis B virus	Cirrhosis	Hepatocellular carcinoma
Herpes simplex virus type 1	Gingivostomatitis, labialis, encephalitis, keratoconjunctivitis, neuralgia	Carcinoma of the lip and oropharynx
Herpes simplex virus type 2	Genital herpes, disseminated neonatal herpes, encephalitis, neuralgia	Cancer of the kidney, nasopharynx, uterine cervix, vulva
Human papillomavirus	Cutaneous verrucae, laryngeal papilloma	Cervical cancer, squamous cell carcinoma
RNA viruses		
Hepatitis C virus	Cirrhosis	Hepatocellular carcinoma
Human T-lymphotropic virus type 1	Arthropathy, myopathy, polyneuropathy, Sjögren syndrome, uveitis	Adult T-cell leukemia

All of the DNA virus groups have been associated with cancer, except for the parvovirus family. This is notable because the DNA viruses associated with cancer all contain double-stranded DNA, whereas the parvoviruses contain only single-stranded DNA. The papillomavirus of the papovavirus group has been associated with squamous cell carcinoma, cervical cancer, and laryngeal papilloma in humans. A vaccine against human papillomavirus is now available and may prevent most cases of cervical cancer in women; see Chapter 13 for additional discussion. Of the 9 RNA virus groups, only the retrovirus group is associated with oncogenicity.

Familial Cancers

Finally, cancers may aggregate in a nonrandom manner in certain families. These cancers may be of the same type or dissimilar. For example, in such cancer-cluster families, several children may have soft-tissue sarcoma and relatives may have a variety of other cancers, especially breast cancer in young women. Multiple endocrine neoplasia types 1 and 2 are other examples of hereditary cancer syndromes (see Chapter 3). The recognition of familial cancer syndromes permits early detection that may be lifesaving.

Ophthalmic considerations The eye and adnexa are frequently involved in systemic malignancies as well as in extraocular malignancies that extend into ocular structures (including local malignancies of the skin, bone, and sinuses). Breast and lung cancers frequently metastasize to the eye and are the most common intraocular tumors in adults. Acute myelogenous and lymphocytic leukemias often

have uveal and posterior choroidal infiltrates as part of their generalized disease. In children, these manifestations are often signs of central nervous system involvement and suggest a poor prognosis. Although malignant lymphomas do not usually involve the uveal tract, histiocytic lymphoma often involves the vitreous and presents as uveitis. The retina and choroid may also be involved.

Tumors of the eye and adnexa are discussed in several other BCSC volumes, including Section 4, *Ophthalmic Pathology and Intraocular Tumors;* Section 6, *Pediatric Ophthalmology and Strabismus;* Section 7, *Oculofacial Plastic and Orbital Surgery;* and Section 8, *External Disease and Cornea.*

Staging

After diagnosis of a cancer, most patients undergo additional imaging, procedures, and laboratory testing to determine the disease burden and stage. Staging of cancer provides an assessment of the extent of tumor dissemination, which is critical for treatment decisions. Most malignancies are staged according to the *TNM system,* which takes into account tumor type, lymph node involvement, and presence of metastasis. The T classification is based on the size and extent of local invasion. The N classification describes the extent of lymph node involvement. The M classification is based on presence or absence of distant metastasis.

Treatment

Surgical Management

Surgical resection is performed for several reasons: to effect a cure, to provide palliative care, to debulk large tumor masses, to increase the efficacy of immunotherapy, or to relieve symptoms. Chemotherapy and radiation can be used in conjunction with surgical resection.

Radiation Therapy

Radiation therapy, which uses ionizing radiation to kill cancer cells and shrink tumors, is part of the treatment plan for many patients with cancer. Radiation therapy can be used for curative or palliative care. It is often administered in combination with chemotherapy for curative treatment. Ionizing radiation interacts with tissues by means of an energy transfer and a chemical reaction, in which free radicals are released and water molecules decompose into hydrogen, hydroxyl, and perhydroxyl ionic forms. These ionic forms break atomic and molecular bonds, which in turn break the double-stranded DNA structure and cause cell death. The resulting cell death occurs in both malignant lesions and normal tissue; however, biochemical recovery and biologic repair occur in the normal host cells, maintaining the integrity of vital systems.

In radiation oncology, *therapeutic ratio* is a fundamental concept in which the potential treatment benefits of destroying targeted cancer cells are weighed against the risks of

Table 14-2 Radiation Damage to Ocular and Nonocular Tissues

Type of Tissue	Damage Produced by Radiation	Amount of Radiation, in Gy
Ocular tissues		
Cornea	Dry eye	60
Lens	Cataract development	2
Optic nerve	Neuropathy	60
Retina	Retinopathy	50
Nonocular tissues		
Central nervous system	Tissue damage	50
Lymphocytes	Cell damage	1
Fetus	Congenital abnormalities	0.5
Skin	Erythema	10

Gy = gray.

damage to surrounding tissues. Table 14-2 lists some examples of the effects of radiation on ocular and nonocular tissues.

Radiation can be delivered through the most common approach of *external beam radiotherapy (EBRT)* or through *internal radiation therapy (brachytherapy),* in which radioactive sources are placed within the body. Radiation can also be administered systemically (eg, iodine 131 is administered orally for treating thyroid cancer). In EBRT, high-energy x-ray beams generated either by linear accelerators, which produce photons or electrons, or by cobalt machines, which use radioactive decay of an isotope such as cobalt 60, are aimed at the tumor site. Planning for EBRT involves not only localizing the tumor but also determining the proper dose of radiation: one that will kill the malignant cells while minimizing damage to the surrounding noncancerous tissue. There are many other methods of EBRT, including particle therapy and stereotactic radiosurgery.

In brachytherapy, radioactive material is implanted within or adjacent to the tumor, delivering radiation while minimizing damage to the surrounding normal tissue. The term *brachytherapy* refers to various types of procedures, for example, radioactive seed implantation used in the treatment of prostate cancer and some uveal melanomas. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for more on brachytherapy and uveal melanomas.

For some conditions, monoclonal antibodies can act as a vector to deliver radiation directly to the target tissue; these antibodies are discussed in the section Biologic Therapies.

Ophthalmic considerations The ocular effects of irradiation depend not only on total dose, fractionation, and treatment portal size but also on the presence of any associated systemic diseases such as diabetes and hypertension. Concomitant chemotherapy has an additive effect.

The lens is the most radiosensitive structure in the eye, followed by the cornea, the retina, and the optic nerve. The orbit is completely included in the treatment portal for cancers such as large retinoblastomas; it is partially

included in tumors of adjacent structures such as the maxillary antrum, nasopharynx, ethmoid sinus, and nasal cavity. Radiation doses typically range from 20 to 100 Gy. The total dose is usually fractionated into smaller doses during the treatment. In brachytherapy, a low-energy isotope such as radioactive iodine delivers a high dose of radiation within a few millimeters of the tumor but does not penetrate deep into it. For example, radioactive episcleral implants can deliver a dose of 100 Gy to the apex of a tumor, but the dose will be much lower in the rest of the eye. The sclera can tolerate doses up to 400–800 Gy.

Doses to the lens as low as 2 Gy in a single fraction can induce cataract formation. However, cataracts caused by low doses may be asymptomatic and may not progress. Cataracts resulting from higher doses (7–8 Gy) may continue to progress, leading to considerable vision loss. The average latent period for the development of radiation-induced cataracts is 2–3 years.

Radiation causes damage to lacrimal glands, leading to decreased tear production, which can result in dry eye and corneal erosions. High doses of radiation (40–60 Gy) can lead to severe keratitis, corneal opacities, and limbal stem cell deficiencies.

The clinical picture of *radiation retinopathy* resembles that of diabetic retinopathy. The interval between radiation therapy and the development of radiation-induced retinopathy is usually 2–3 years. Radiation retinopathy may develop earlier in patients with diabetes or in those undergoing chemotherapy. Cotton-wool spots are usually the earliest clinical manifestation of radiation retinopathy. After several months, these spots fade away, leaving areas of capillary nonperfusion. Telangiectatic vessels grow from the retina into these areas, and microaneurysms can also develop. These ischemic changes can cause neovascularization of the iris, which in turn may lead to neovascular glaucoma. Capillary endothelial cells are the first type of cell to be damaged, followed closely by the pericytes and then the endothelial cells of the larger vessels. The new intraretinal telangiectatic vessels have thick, collagenous walls. There may be spotty occlusion of the choriocapillaris. Panretinal photocoagulation or intravitreal injection with an anti–vascular endothelial growth factor (anti-VEGF) agent is effective in treating radiation retinopathy. See BCSC Section 12, *Retina and Vitreous,* for more on this topic.

Radiation optic neuropathy may present with optic nerve head pallor with splinter hemorrhages. Injury to the more proximal part of the optic nerve resembles retrobulbar optic neuropathy. Affected patients may report unilateral headaches and ocular pain; the optic nerve head may not reveal edema or hemorrhage. For more on radiation optic neuropathy, see BCSC Section 5, *Neuro-Ophthalmology.*

Ocular manifestations of fetal irradiation in the first trimester include microphthalmos, congenital cataracts, and retinal dysplasia.

Nuzzi R, Trossarello M, Bartoncini S, et al. Ocular complications after radiation therapy: an observational study. *Clin Ophthalmol.* 2020;14:3153–3166.

Chemotherapy

The goal of cancer chemotherapy is to damage or destroy cancer cells without killing normal cells. The type of chemotherapy treatment chosen depends on the treatment goals for the type and extent of the cancer. The purpose of *curative chemotherapy* is to eliminate cancer cells, with the goal of achieving permanent remission. *Adjuvant chemotherapy* is given after surgical resection of the tumor to destroy undetectable microscopic cancer cells and thus reduce the rate of recurrence. The goal of *neoadjuvant chemotherapy* is to shrink tumors that are too large for total resection, potentially facilitating a less invasive surgical procedure. *Palliative chemotherapy* is used when it is no longer possible to eliminate all the cancer cells; this option can provide the patient with symptomatic relief, slow the progression of tumor growth, and help avoid complications from the tumor.

Natural products, meaning agents that either occur naturally or have been synthetically modified, play a significant role in cancer chemotherapy. They include a variety of drug classes, the most common of which are alkylating agents, antimetabolites, plant alkaloids, and antitumor antibiotics (Table 14-3).

Table 14-3 Chemotherapy Drugs

Drug Class	Mechanism of Action	Drug Generic Name[a]
Alkylating agents	Act directly on DNA to prevent cell division, causing crosslinking of DNA strands, abnormal base pairing, or DNA strand breaks	Busulfan, carboplatin, chlorambucil, cyclophosphamide, melphalan, thiotepa
Antimetabolites	Interfere with metabolic pathways, thereby causing cell death. Cell-cycle specific; most effective in the DNA synthesis phase of the cell cycle	Metabolic antagonists to folate (methotrexate), purine (6-mercaptopurine), and pyrimidine (5-fluorouracil)
Antitumor antibiotics	Disrupt cell survival; are not cell-cycle specific. Bind with DNA to prevent RNA synthesis, stopping protein synthesis	Anthracyclines (daunorubicin, doxorubicin), bleomycin, mitomycin C, mitoxantrone
Hormones	Bind to androgen or estrogen receptors	Estramustine, flutamide, leuprorelin, tamoxifen
Inorganic ions	Inhibit uncoiling of DNA	Cisplatin
Mitotic inhibitors/ plant alkaloids	Cytotoxic drugs that stop cell division, thereby causing cell death. Bind to tubulin, inhibiting microtubule formation during the mitotic phase of the cell cycle	Estramustine, paclitaxel, vinblastine, vincristine, vinorelbine
Nitrosoureas	Alkylate DNA, restricting DNA uncoiling and replication	Carmustine, lomustine
Topoisomerase inhibitors	Interfere with enzymes (topoisomerases) involved in copying DNA	Etoposide, teniposide, topotecan

[a]These are examples of drugs within each class; lists of drugs are not all-inclusive.

Angiogenesis Inhibitors

New blood vessels are critical for tumor formation; thus, angiogenesis is important in the growth and spread of cancers. Angiogenesis inhibitors have been shown to stop the formation of new blood vessels, causing tumors to shrink and die. The US Food and Drug Administration (FDA) has approved angiogenesis inhibitors for the treatment of many types of cancer, including breast cancer, non–small cell lung cancer, renal cell carcinoma, cervical cancer, colorectal cancer, glioblastoma, and medullary thyroid cancer.

Antibodies against VEGF, which promotes vascular proliferation, have proved effective in cancer therapy. Bevacizumab, a humanized monoclonal antibody directed against VEGF-A, has demonstrated clinical efficacy in the treatment of colorectal and other solid tumors and, on an off-label basis, in the treatment of neovascular age-related macular degeneration. Bevacizumab is also effective in treating optic nerve gliomas in children.

Biologic Therapies

Biologic therapies (sometimes called *immunotherapy, biotherapy,* or *biologic response modifier therapy*) do not target cancer cells directly but rather harness the immune system, either directly or indirectly, to fight cancer or to lessen the adverse effects of some cancer treatments. Further, because cancer may develop when the immune system is not functioning adequately, biologic therapies are designed to repair, stimulate, or enhance the immune response.

Cells in the immune system secrete 2 types of proteins: antibodies and cytokines. *Cytokines* are nonantibody proteins produced by some immune system cells to communicate with other cells. Types of cytokines include *lymphokines, interferons, interleukins,* and *colony-stimulating factors*. Some antibodies and cytokines, called *biologic response modifiers,* can be used in the treatment of cancer.

Interleukins occur naturally in the body and can also be made in the laboratory. Many interleukins have been identified; among them, *interleukin 2 (IL-2)* has been the most widely studied for use in cancer treatment. IL-2 stimulates the growth and activity of many immune cells (eg, lymphocytes) that can destroy cancer cells. The FDA has approved IL-2 for the treatment of metastatic kidney cancer and metastatic melanoma.

Monoclonal antibodies (mAbs) are produced by a single type of cell and are specific for a particular antigen. Researchers are continuing to develop mAbs targeted to different antigens found on the surface of cancer cells. Some examples of mAbs currently used in cancer treatment are bevacizumab, rituximab, and trastuzumab (the names of all monoclonal antibodies end in *-mab*).

Therapeutic mAbs are made by injecting human cancer cells into mice, which stimulates an antibody response. The cells producing antibodies are then removed and fused with laboratory-grown cells to create hybrid cells called *hybridomas.* Hybridomas can produce large quantities of these mAbs indefinitely.

Monoclonal antibodies have many potential uses in cancer treatment; for example, they could be linked to anticancer drugs, radioisotopes, other biologic response modifiers, or toxins. When these antibodies attach to cancer cells, they could deliver these agents

directly to the cells. Monoclonal antibodies carrying radioisotopes may also prove useful in the diagnosis of certain cancers, such as colorectal, ovarian, and prostate cancers.

In 2022, *tebentafusp* (indicated for metastatic uveal melanoma) became the first FDA-approved agent in a new class known as *immune-mobilizing monoclonal T-cell receptors against cancer,* or *ImmTACs*. The drug is a bispecific fusion protein (as indicated by *-fusp*) that has a target domain and an effector domain. It acts by bringing a cytotoxic T cell in proximity to a melanoma cell and causing the release of cytotoxic agents to kill the cancer cell.

Immune checkpoint inhibitors (ICIs) block checkpoint proteins on T cells, thus preventing an "off" signal and allowing T cells to kill cancer cells. ICIs include *cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1),* and *programmed cell death ligand 1 (PD-L1)*. These agents are widely used for the treatment of melanoma, non–small cell lung cancer, renal cancer, and other solid tumors and hematologic malignancies. See Table 14-4 and the "Ophthalmic considerations" at the end of this section for ocular side effects of ICIs and other biologics.

Table 14-4 Ocular Side Effects of Biologics and Targeted Drugs

Drug Class	Generic Names	Ocular Side Effects
Epidermal growth factor receptor inhibitors	Cetuximab, erlotinib, gefitinib	Corneal melting, anterior uveitis
Human epidermal growth factor receptor 2 (HER2) inhibitors	Pertuzumab, trastuzumab	Corneal infiltrates, conjunctivitis, blurred vision, macular edema, macular ischemia, serous retinal detachment
BRAF inhibitors	Dabrafenib, encorafenib, vemurafenib	Photosensitivity, dry eye, conjunctivitis, uveitis, squamous cell carcinoma of eyelid
Mitogen-activated protein kinase inhibitors	Cobimetinib, trametinib	Blurred vision, transient visual disturbances, periorbital edema, retinal vein occlusion, retinopathy
Fibroblast growth factor receptor (FGFR) inhibitors	Dovitinib, erdafitinib, ponatinib	Serous retinopathy, eyelash trichomegaly, dry eye, corneal epithelial lesions
Immune checkpoint inhibitors	Atezolizumab, ipilimumab, nivolumab, pembrolizumab	Conjunctivitis, episcleritis, blurred vision, bilateral uveitis, exudative retinal detachment, orbital inflammation
Anaplastic lymphoma kinase inhibitors	Crizotinib	Visual disturbances, optic neuropathy
Tyrosine kinase inhibitors	Imatinib, vandetanib	Periorbital edema, epiphora, subconjunctival hemorrhage, retinal hemorrhage, cystoid macular edema, optic nerve edema

Cancer treatment vaccines are a type of immunotherapy that activates the immune system to recognize and destroy tumor-associated antigens in cancer cells. These vaccines are injected after the disease is diagnosed rather than before it develops, in contrast to the vaccines against HPV or hepatitis B that are aimed at cancer prevention. The cancer treatment vaccines may help the body to reject tumors and prevent recurrence. In 2015, the FDA approved an oncolytic virus treatment vaccine (*talimogene laherparepvec,* or *T-VEC*) to treat melanoma lesions in the skin and lymph nodes.

Other uses of biologic agents in cancer therapy include *genetic profiling* of certain tumors. Current management of lung cancer and melanoma is based on such profiling. Genetic profiling may also prove more effective than classifying tumors by their organ of origin in the management of cancer. For example, genetic profiling can be used to differentiate between tumors with a normal tumor suppressor gene p53 *(TP53)* and those with an abnormal *TP53*. Tumor cells with normal *TP53* are far more sensitive to chemotherapy than those with variant *TP53*.

Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefits of immune checkpoint inhibitors—a systematic review and meta-analysis. *Cancer Treat Rev.* 2021;92:102134. doi:10.1016/j.ctrv.2020.102134

Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385(13):1196–1206.

Ophthalmic considerations Immune checkpoint inhibitors may rarely cause ocular inflammation. *Ipilimumab* is associated with episcleritis, conjunctivitis, uveitis, and orbital inflammation. Very rarely, patients on ipilimumab can present with severe bilateral uveitis leading to exudative retinal detachment (similar in presentation to Vogt-Koyanagi-Harada syndrome) that can be vision threatening. In such cases, the patient's oncologist should be consulted promptly about stopping the drug. *Pembrolizumab* or *nivolumab* can cause uveitis in approximately 1% of patients. Treatment of ocular adverse effects includes topical glucocorticoids for mild reactions or oral glucocorticoids for severe or refractory cases. Risk of ocular complications may be increased when multiple ICIs are used, and autoimmune retinopathy has also been reported.

Abdel-Rahman O, Oweira H, Petrausch U, et al. Immune-related ocular toxicities in solid tumor patients treated with immune checkpoint inhibitors: a systematic review. *Expert Rev Anticancer Ther.* 2017;17(4):387–394.

CHAPTER 15

Infectious Diseases

Highlights

- Vancomycin-resistant strains of enterococci and staphylococci are a significant cause of life-threatening infection in hospitalized patients.
- Diagnosis of gonorrhea, syphilis, and Lyme disease, as well as chlamydial, mycobacterial, fungal, and many viral infections, has been aided by the development of highly sensitive DNA probe–based polymerase chain reaction assays.
- The treatment options for cytomegalovirus retinitis include intravitreal ganciclovir or foscarnet and oral valganciclovir, or intravenous (IV) ganciclovir or IV foscarnet, depending on the situation.
- Ophthalmologists should be aware of the possibility of conjunctivitis as a presenting sign of COVID-19.
- The US Centers for Disease Control and Prevention recommends that everyone between the ages of 13 and 64 years be tested for HIV at least once as part of routine health care. Treatment of patients in the early stages of HIV infection has improved.

General Immunology

Despite formidable immune and mechanical defense systems, the human body harbors an extensive, well-adapted population of microorganisms on the skin and in the gastrointestinal, vaginal, and upper respiratory tracts. The organisms maintain their foothold on these epithelial surfaces chiefly by adherence, and they indirectly benefit the host by excluding pathogenic bacterial colonization and by priming the immune system. If antimicrobial agents alter this host-microbe interplay by eliminating the normal flora, the host's susceptibility to normally excluded pathogenic microorganisms increases. When the mechanical defenses of the epithelial layers are breached and normally sterile areas are exposed, or if a critical component of the immune system that usually prevents microbial invasion fails, severe infections can result from the normal microbial flora.

An immune response is a sequence of molecular and cellular events intended to rid the host of a threat, such as pathogenic organisms or neoplastic cells. Two types of immune responses can be triggered: innate and adaptive. *Innate immunity* is present in nearly all multicellular organisms and includes humoral and cellular immune receptors that have broad specificity. The innate immune response does not require previous exposure to an antigen; thus, the response is usually immediate.

Adaptive (also called *acquired) immunity* is found only in vertebrates and does require prior antigen exposure (*immune,* or *immunologic,* memory). Pathogens are recognized by many randomly generated B-lymphocyte and T-lymphocyte receptors, each of which binds to a specific antigen *(epitope)*. Because adaptive immunity involves a "learned" response to specific antigens, it develops more slowly than innate immunity. But upon subsequent exposure to the antigen, the host is able to mount a faster and stronger immune response because of immunologic memory. However, even when both the mechanical barrier and immune defense systems are intact, pathogenic microbes can cause infections by means of specific virulent characteristics that allow the microbes to invade and multiply. These virulent traits vary among different species and include attachment, polysaccharide encapsulation, blocking of lysosomal fusion, antigenic surface variation, immunoglobulin (Ig) A protease, endotoxins, exotoxins, and biofilm formation.

The immune system, which makes possible the host's adaptive response to microbial colonization and infection, is classically divided into the humoral and cellular immune systems. The *humoral immune system,* composed of cells derived from the B lymphocytes, is responsible for antibody-mediated opsonization, complement-mediated bacterial killing, antitoxin, and mediation of intracellular infections. The *cellular immune system,* determined by the T lymphocytes, is responsible for interaction with and stimulation of the humoral immune system, direct cytotoxicity, release of chemical messengers, and control of chronic infections. The successful interplay between the humoral and cellular immune systems mitigates and usually eradicates infections, allowing for repair and healing. See BCSC Section 9, *Uveitis and Ocular Inflammation,* for further discussion of basic concepts in immunology.

Bacterial Infections

See BCSC Section 8, *External Disease and Cornea,* Chapter 12, for images related to many of the topics discussed in this section.

Staphylococcus

Staphylococcus aureus colonizes the anterior nares and other skin sites in 15% of community isolates. Of the tertiary care hospital isolates, more than 25% are resistant to all β-lactam antibiotics. The increasing prevalence of *methicillin-resistant* S aureus *(MRSA)* in tertiary referral hospitals appears to be related to the population of high-risk patients at such centers. Unfortunately, MRSA is now an increasingly common cause of serious infection in primary care settings as well.

Acute serious staphylococcal infections require immediate IV antibiotic therapy. A penicillinase-resistant penicillin or first-generation cephalosporin is typically used, pending the results of susceptibility tests.

Since 1997, infections due to strains of *S aureus* with reduced susceptibility to vancomycin (glycopeptide-intermediate *S aureus*) have been identified, and their frequency is increasing worldwide. Vancomycin-resistant strains are a substantial cause of life-threatening infection in hospitalized patients. Some vancomycin-resistant cases have been successfully treated with various forms of combination therapy and with newer antibiotics, including

daptomycin, linezolid, ceftaroline, and quinupristin/dalfopristin. In Taiwan, isolates of MRSA have recently shown steady susceptibility to vancomycin, while resistance to teicoplanin, daptomycin, and linezolid has increased. Rigorous monitoring of antibiotic policy, regular surveillance/control of nosocomial-associated infections, and intensive surveillance of vancomycin resistance are required to prevent the emergence and further spread of resistant strains of *S aureus*.

An almost universal inhabitant of the skin, *Staphylococcus epidermidis* is present in up to 90% of skin cultures. It can cause infection when local defenses are compromised. Its characteristic adherence to prosthetic devices makes *S epidermidis* the most common cause of prosthetic heart valve infections, and it is a common infectious organism of IV catheters and cerebrospinal fluid (CSF) shunts.

Most *S epidermidis* isolates are resistant to methicillin and cephalosporins; therefore, the drug of choice is vancomycin, occasionally in combination with rifampin or gentamicin. Unfortunately, there have also been reports of vancomycin-resistant infections caused by coagulase-negative *S epidermidis.* In addition to antibiotic therapy, management usually involves removal of the infected prosthetic device or vascular catheter.

Hsieh YC, Lin YC, Huang YC. Vancomycin, teicoplanin, daptomycin, and linezolid MIC creep in methicillin-resistant *Staphylococcus aureus* is associated with clonality. *Medicine (Baltimore).* 2016;95(41):e5060. doi:10.1097/MD.0000000000005060

Wu Q, Sabokroo N, Wang Y, Hashemian M, Karamollahi S, Kouhsari E. Systematic review and meta-analysis of the epidemiology of vancomycin-resistance *Staphylococcus aureus* isolates. *Antimicrob Resist Infect Control.* 2021;10(1):101. doi:10.1186/s13756-021-00967-y

Ophthalmic considerations The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study demonstrated the prevalence of methicillin resistance among staphylococcal isolates from ocular infections, as well as a high probability of concurrent resistance to fluoroquinolones, aminoglycosides, or macrolides. All staphylococcal isolates were susceptible to vancomycin, and overall antibiotic resistance of ocular isolates did not increase during the 10-year study period.

Asbell PA, Sanfilippo CM, Sahm DF, DeCory HH. Trends in antibiotic resistance among ocular microorganisms in the United States from 2009 to 2018. *JAMA Ophthalmol.* 2020;138(5):439–450.

Streptococcus

Group A β-hemolytic streptococci *(Streptococcus pyogenes)* cause a variety of acute suppurative infections via droplet transmission. Suppurative streptococcal infections in humans include pharyngitis, impetigo, pneumonia, erysipelas, wound and burn infections, puerperal infections, and scarlet fever. Rapid identification with antigen detection tests allows prompt treatment of patients with pharyngitis due to this strain of *Streptococcus* and can reduce the risk of spread of infection.

S pyogenes remains highly susceptible to penicillin G; however, in the presence of allergy, erythromycin or (if no cross-allergy exists) a cephalosporin is substituted. Macrolide-resistant and clindamycin-resistant strains of group A β-hemolytic streptococci have been reported.

Streptococcus pneumoniae are lancet-shaped diplococci that cause α-hemolysis on blood agar. In 10%–30% of the general population, 1 or more serologic types of pneumococci are found in the throat. The incidence of and mortality from pneumococcal pneumonia increase sharply after 50 years of age, with a fatality rate approaching 25%.

Besides pneumonia, conditions caused by *S pneumoniae* include sinusitis, meningitis, otitis media, and peritonitis. Pneumococci are usually highly susceptible to penicillin, other β-lactams, erythromycin, or the newer fluoroquinolones, although penicillin-resistant strains of *S pneumoniae* have been reported with increasing frequency. For patients with meningitis, bacteremia, or other life-threatening infections, routine susceptibility testing should be performed. Treatment of highly resistant strains may require vancomycin or meropenem. Prophylaxis is available through the 23-valent pneumococcal conjugate vaccine for adults and the 13-valent vaccine for children (see Chapter 13).

Between 10% and 35% of cases of community-acquired infectious endocarditis are caused by α-hemolytic streptococci, while *S aureus* accounts for 30%–50% of cases. *S aureus* also accounts for 60%–80% of cases of nosocomial endocarditis, with the majority of these cases due to MRSA. Prophylaxis for infectious endocarditis is usually not considered necessary for routine ocular surgery. However, it can be considered for surgery involving the nasolacrimal drainage system or the sinuses or for surgical repair of orbital trauma when the patient has a high risk of adverse outcome from endocarditis (Table 15-1). These include patients with prosthetic cardiac valves or prosthetic material used to repair cardiac valves, previous endocarditis, certain types of congenital heart disease, and cardiac transplantation with valve regurgitation.

Bergman K, Härnqvist T, Backhaus E, et al. Invasive pneumococcal disease in persons with predisposing factors is dominated by non-vaccine serotypes in Southwest Sweden. *BMC Infect Dis.* 2021;21(1):756. doi:10.1186/s12879-021-06430-y

Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075–3128.

Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143(5):e35–e71. doi:10.1161/CIR.0000000000000932

Clostridioides difficile

Clostridioides (formerly *Clostridium*) *difficile* is an endemic anaerobic gram-positive bacillus that is part of the normal gastrointestinal flora. It has acquired importance because of its role in the development of pseudomembranous enterocolitis after antibiotic use. In these cases, fever and diarrhea develop 1–14 days after the start of antibiotic therapy. The diarrhea occasionally becomes bloody and typically contains a cytopathic toxin that is elaborated by *C difficile.* The most frequently implicated antibiotics include clindamycin, ampicillin,

Table 15-1 SBE Prophylaxis Regimens for Dental and Incisional Nasolacrimal Procedures

Situation	Agent	Regimen: Single Dose 30–60 Minutes Before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b]	2 g	50 mg/kg
	OR doxycycline	100 mg	Weight <45 kg: 2.2 mg/kg Weight ≥45 kg: 100 mg
	OR azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV

IM = intramuscular; IV = intravenous; SBE = subacute bacterial endocarditis.

[a] Or another first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[b] Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Modified with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in the Young; and the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* 2007;116(15):1736–1754, Table 5.
Table updated with information from *J Am Dent Assoc.* 2008 Jan;139 Suppl:3S–24S.

chloramphenicol, tetracycline, erythromycin, and the cephalosporins. Recently, new, hypervirulent strains of *C difficile* have emerged in the United States, Europe, and Japan.

Enzyme immunoassay and polymerase chain reaction (PCR) tests allow rapid detection; see BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for more on the PCR method. Initial treatment includes discontinuing the causative antibiotic and administering oral vancomycin. If oral vancomycin fails, fidaxomicin can be used. Bezlotoxumab, a human monoclonal antibody against *C difficile* toxin B, is associated with a 38% lower rate of recurrent infection compared with placebo. Fecal microbiota transplantation (also known as *stool transplantation*), a procedure in which stool from a healthy donor is placed into the gut of an infected patient, has become standard-of-care therapy for recurrent *C difficile* infection.

Cold F, Baunwall SMD, Dahlerup JF, Petersen AM, Hvas CL, Hansen LH. Systematic review with meta-analysis: encapsulated faecal microbiota transplantation—evidence for clinical efficacy. *Therap Adv Gastroenterol.* 2021;14:17562848211041004. doi:10.1177/17562848211041004

Vindigni SM, Surawicz CM. Fecal microbiota transplantation. *Gastroenterol Clin North Am.* 2017;46(1):171–185.

Haemophilus influenzae

Haemophilus influenzae, a small pleiomorphic gram-negative coccobacillus, is a common inhabitant of the upper respiratory tract in 20%–50% of healthy adults and 80% of children. *H influenzae* is 1 of the 3 organisms responsible for most cases of bacterial meningitis. Roughly 14% of patients with meningitis develop significant neurologic damage. Other infections caused by this organism include orbital cellulitis, epiglottitis, arthritis, otitis media, bronchitis, pericarditis, sinusitis, and pneumonia. A PCR assay can be used for rapid diagnosis of infections of the most virulent strain, *H influenzae* type b (Hib).

Treatment of acute *H influenzae* infections has been complicated by the emergence of β-lactamase strains, with an incidence approaching 50% in some geographic areas. The current recommendation is to treat with third-generation cephalosporins, which are highly effective against *H influenzae* infections. Alternative treatments include meropenem or combined therapy with ampicillin and chloramphenicol. Nearly all isolates of *H influenzae* are resistant to macrolides. Serious or life-threatening infections are usually treated with an IV third-generation cephalosporin with known activity against *H influenzae,* such as ceftriaxone or cefotaxime, pending results of sensitivity testing.

Hib conjugate vaccines are available (see Chapter 13) for use in infants and have shown their effectiveness in protecting infants and older children against meningitis, orbital cellulitis, and other infections caused by Hib. However, it is essential to remember that immunized patients are still susceptible to infections caused by strains of *H influenzae* other than type b.

Wahl B, O'Brien KL, Greenbaum A, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Glob Health.* 2018;6(7):e744–e757. doi:10.1016/S2214-109X(18)30247-X

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram-negative bacillus found in moist environments. Together with *Serratia marcescens, P aeruginosa* is 1 of the 2 most consistently antimicrobial-resistant pathogenic bacteria. The virulence of *P aeruginosa* is related to extracellular toxins, endotoxin, and polysaccharide protection from phagocytosis. Usual sites of infection include the respiratory system, skin, eyes, urinary tract, and bone, as well as wounds. Systemic infections caused by a resistant organism carry a high mortality rate and are usually associated with depressed immunity, often in a hospital setting.

More than half of *P aeruginosa* isolates are now resistant to aminoglycosides. Ceftazidime has been the most effective cephalosporin for the treatment of pseudomonal infections. Piperacillin-tazobactam, imipenem, and meropenem also remain highly effective against most isolates, but resistance to the carbapenems and fluoroquinolones has been increasing gradually. The initial choice of antimicrobials depends on local susceptibility prevalence and should be guided by the results of susceptibility testing.

The use of vaccines incorporating multiple *P aeruginosa* serotypes is under investigation for the treatment of patients with severe burns, cystic fibrosis, or immunosuppression.

Soriano A, Carmeli Y, Omrani AS, Moore LSP, Tawadrous M, Irani P. Ceftazidime-avibactam for the treatment of serious gram-negative infections with limited treatment options: a systematic literature review. *Infect Dis Ther.* 2021;10(4):1989–2034.

Borrelia burgdorferi

Borrelia burgdorferi, a large plasmid-containing spirochete, is transmitted to humans and domestic animals through the bite of infected ticks, *Ixodes scapularis* or *Ixodes pacificus,* depending on the region of the United States. The illness caused by this transmission, *Lyme disease,* was first recognized in 1975 and is the most common vector-borne infection in the United States. Although cases have been reported in nearly all states, clusters are apparent in the northeast Atlantic, the upper Midwest, and the Pacific Southwest areas, corresponding to the distribution of the *Ixodes* tick population. The range of the disease extends throughout Europe and Asia. Two other tick-borne zoonoses, babesiosis and human granulocytic ehrlichiosis, can be cotransmitted with Lyme disease.

Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease—United States 2008–2015. *MMWR Surveill Summ.* 2017;66(22):1–12.

Stages of Lyme disease

Lyme disease usually occurs in 3 stages after a tick bite:

- *Localized (stage 1).* Present in 86% of infected patients, it is characterized by skin involvement, initially a red macule or papule, which later expands circularly, usually with a bright red border and a central clear indurated area, known as *erythema chronicum migrans.*
- *Early disseminated (stage 2).* Can occur within days to weeks after infection. It manifests as a flulike illness with headaches, fatigue, and musculoskeletal aches.
- *Late disseminated (stage 3).* More-profound symptoms occur during this stage, as the infection localizes to the nervous, cardiovascular, and musculoskeletal systems.

Neurologic complications such as meningitis, encephalitis, cranial neuritis (including Bell palsy), radiculopathy, and neuropathy occur in 10%–15% of patients.

Late disseminated manifestations are usually confined to the nervous system, skin, and joints. Late neurologic signs include encephalomyelitis as well as demyelinating and psychiatric syndromes. Joint involvement includes asymmetric pauciarticular arthritis. Skin involvement is characterized by acrodermatitis chronica atrophicans or localized lesions resembling those of systemic sclerosis.

Other systemic manifestations during the early disseminated or the late disseminated stage include uveitis, conjunctivitis, keratitis, optic neuritis, lymphadenopathy, orbital myositis, hematuria, and orchitis. In some studies, serologic testing of patients with chronic fatigue syndrome has shown an increased incidence of positive results for *B burgdorferi* antibodies.

Diagnosis of Lyme disease

The serologic tests most commonly used to aid in the diagnosis of Lyme disease are the immunofluorescence antibody assay or the more sensitive enzyme-linked immunosorbent assay (ELISA). The ELISA has a sensitivity of 50% during the early stages of the disease, and almost all symptomatic patients are seropositive for IgG and IgM antibodies to *B burgdorferi* during the late disseminated stage. These tests should be used only to support a clinical diagnosis of Lyme disease, not as the primary basis for making diagnostic or treatment decisions. Positive IgG and IgM ELISA results are usually confirmed with Western immunoblot testing. While serologic testing is not as useful in the early stage of Lyme disease because of the low

sensitivity, it is helpful in later disease, when the sensitivity and specificity are greater. Of note, false-positive results can occur in patients with syphilis, Rocky Mountain spotted fever, yaws, pinta, *Borrelia recurrentis* infection, and various rheumatic disorders. PCR has been used to detect *B burgdorferi* DNA in serum and CSF. Although patients with Lyme disease may test positive on the fluorescent treponemal antibody absorption (FTA-ABS) test for syphilis, the result of their VDRL test should be nonreactive.

Management of Lyme disease

Treatment of *B burgdorferi* infection depends on the stage and severity of the infection. Localized Lyme disease is typically treated with oral doxycycline, amoxicillin, cefuroxime, or azithromycin. Early disseminated disease is treated with oral doxycycline or amoxicillin. Late disseminated disease (with cardiac or neurologic manifestations) is typically treated with ceftriaxone or doxycycline. Infections that do not respond to the initial regimen may require alternate or combination therapy.

Mycoplasma pneumoniae

Mycoplasma pneumoniae can cause multiple disorders, including pharyngitis, otitis media, tracheobronchitis, pneumonia, endocarditis, nephritis, encephalitis, meningitis, optic neuritis, and facial nerve palsy. It has also been implicated in some cases of chronic fatigue and fibromyalgia syndromes. In addition, recent evidence suggests that *M pneumoniae* may contribute to chronic lung disorders such as asthma. Serious *M pneumoniae* infections requiring hospital admission can occur in adults and children and may involve multiple organ systems.

PCR assays have been adapted for the direct detection of *M pneumoniae* organisms, but in clinical practice, sensitive serologic tests are usually used initially to detect antibodies. Because *M pneumoniae* lacks a cell wall, it is unaffected by antibiotics that target cell wall synthesis. Initial treatment of *M pneumoniae* infections typically involves use of a macrolide, tetracycline, or fluoroquinolone.

Neisseria

The most significant human pathogenic *Neisseria* species are *Neisseria meningitidis* and *Neisseria gonorrhoeae.* Meningococci can be cultured in up to 15% of healthy persons in nonepidemic periods. Virulence is determined by the polysaccharide capsule and the potent endotoxic activity of the cell wall, which can cause cardiovascular collapse, shock, and disseminated intravascular coagulation. Individuals who are complement deficient or asplenic are at risk for serious clinical infections. Diagnostic testing may include Gram stain, blood and CSF cultures, ELISA, and PCR. To evaluate patients with suspected meningitis, an automated fluorescent multiplex PCR assay is available that can simultaneously detect *N meningitidis, H influenzae,* and *S pneumoniae*. This test provides exceptionally high sensitivity and a specificity of 100% for each organism.

Meningococcal infections include meningitis; mild to severe upper respiratory tract infections; and, less often, endophthalmitis, endocarditis, pericarditis, arthritis, and purpura fulminans. *N meningitidis* serogroup B is the most common cause of bacterial meningitis in children and young adults. Meningitis with a petechial or purpuric exanthem is the classic presentation, although each condition may occur in isolation.

Traditionally, the treatment of choice for meningococcal meningitis has been high-dose penicillin or, in the case of allergy, chloramphenicol or a third-generation cephalosporin. Rifampin or minocycline is used as chemoprophylaxis for family members and intimate personal contacts of the infected individual. Polysaccharide vaccines are most effective in older children and adults.

Among women with gonococcal infections, 50% are asymptomatic, whereas 95% of men with such infections are symptomatic. Asymptomatic patients are infectious for several months, with a transmissibility rate of 20%–50%. Nonsexual transmission is rare. The key to prevention is the identification and treatment of asymptomatic carriers and their sexual contacts.

The range of gonococcal infections includes cervicitis; urethritis; pelvic inflammatory disease; pharyngitis; conjunctivitis; ophthalmia neonatorum; and disseminated gonococcal disease with fever, polyarthralgias, and rash. *Chlamydia trachomatis* coexists with gonorrhea in 25%–50% of women with gonococcal cervicitis and 20%–33% of men with gonococcal urethritis. Diagnosis of gonococcal infections, as well as infections caused by many other bacteria, mycobacteria, viruses, and *Mycoplasma,* has been aided by the development of highly sensitive DNA probe–based PCR assays.

Because penicillin-resistant and tetracycline-resistant gonococcal strains have become common in many areas of the United States, ceftriaxone (via intramuscular injection) is first-line treatment for *Neisseria* infection; thus far, reduced susceptibility to this antibiotic has been extremely rare. Cefotaxime may also be used for the treatment of confirmed meningococcal disease. Gonococcal isolates with reduced sensitivity to macrolides and fluoroquinolones have been reported with increasing frequency, and the US Centers for Disease Control and Prevention (CDC) recommends that clinicians no longer use fluoroquinolones as a first-line treatment for gonorrhea, leaving cephalosporins as the only class of antimicrobials available for the treatment of gonorrhea in the United States.

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep.* 2021;70(4):1–87.

Chlamydia trachomatis

Chlamydia trachomatis is the causative agent of chlamydia, a common sexually transmitted infection, with 200,000 new cases per year in the United States. More than 15% of pregnant women and 10% of men with chlamydial infections are asymptomatic. Chlamydia can be transmitted by close contact and by a pregnant woman to her newborn during delivery, resulting in pneumonia or conjunctivitis in the infant.

Chlamydial infections in humans include trachoma, inclusion conjunctivitis, nongonococcal urethritis, epididymitis, mucopurulent cervicitis, proctitis, salpingitis, infant pneumonia syndrome, and lymphogranuloma venereum. Genital *C trachomatis* infection can cause pelvic inflammatory disease, tubal infertility, and ectopic pregnancy.

Diagnostic techniques include culture, direct immunofluorescence antibody testing of exudates, enzyme immunoassay, and DNA probe–based PCR assay. The preferred method for chlamydia testing is the nucleic acid amplification test, which detects the genetic material (DNA) of *C trachomatis*.

Chlamydial infections are readily treated with doxycycline or, alternatively, with azithromycin or levofloxacin. Although single-dose azithromycin therapy for urethritis and cervicitis

has proved effective in some studies, it is usually recommended that patients continue treatment for at least 7 days to ensure complete eradication. Sexual partners of patients with chlamydial infections or other sexually transmitted infections should be examined and counseled for consideration of antibiotic treatment as well.

Neonatal chlamydial conjunctivitis is treated with oral erythromycin (50 mg/kg divided, 4 times daily) for 14 days. See BCSC Section 8, *External Disease and Cornea,* Chapter 12, for further discussion of this topic.

US Preventive Services Task Force; Davidson KW, Barry MJ, Mangione CM, et al. Screening for chlamydia and gonorrhea: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;326(10):949–956.

Treponema pallidum

The bacterium *Treponema pallidum* is the causative agent of syphilis, which is transmitted through sexual contact or transplacentally. The course of the disease is divided into 4 stages: primary, secondary, latent, and tertiary (late). Initial inoculation occurs through intact mucous membranes or abraded skin and, within 6 weeks, results in a small, ulcerated, painless papule called a *chancre (primary stage).* The spirochetes readily enter the lymphatic system and bloodstream. The chancre heals spontaneously, and signs of dissemination appear after a variable quiescent period of several weeks to months.

The *secondary stage* is heralded by a truncal rash that may spread over the entire body. Fever, malaise, lymphadenopathy, and hair loss may occur. Meningitis, uveitis, optic neuritis, and hepatitis may also occur but are less common. The secondary lesions may resolve in a few weeks or recur in the first year. Without treatment, the disease enters the latent stage.

Latent syphilis, characterized by positive serologic test results in a patient without clinical signs, is divided into 2 stages. The *early latent stage* occurs within 1 year of infection. The disease is potentially transmissible during this time because relapses associated with spirochetemia are possible. The *late latent stage* is associated with immunity to relapse and resistance to recurrence of infectious lesions.

Tertiary manifestations can occur many years after the initial untreated infection. Up to one-third of untreated cases of latent disease progress to this stage; the remaining two-thirds either are subclinical or resolve spontaneously. *Tertiary disease* is characterized by destructive granulomatous lesions with a typical endarteritis that can affect the skin, bones, joints, oral and nasal cavities, parenchymal organs, cardiovascular system, eyes, meninges, and central nervous system (CNS).

On pathologic examination, a feature of all active stages of syphilis is obliterative endarteritis with a perivascular infiltrate of lymphocytes, monocytes, and plasma cells. *Gummata* are a form of granuloma that can develop on the skin, bones, or other organs during tertiary syphilis.

Ocular syphilis and neurosyphilis can occur at any stage of syphilis. Ocular syphilis manifests most commonly as posterior uveitis or panuveitis. However, it can involve any structure of the eye (including conjunctiva, sclera, cornea, lens, uvea, retina, and optic nerve), as well as the cranial nerves and pupillomotor pathways) (see BCSC Section 8, *External Disease and Cornea,* Fig 13-20).

Diagnosis of syphilis

Most cases of syphilis are diagnosed serologically. Results of *nontreponemal tests (NTTs)* such as the VDRL or rapid plasma reagin (RPR) test are usually positive during the early stages of the disease, uniformly positive during the secondary stage, and progressively nonreactive in the later stages. NTT results become predictably negative after successful therapy and can be used to assess the effectiveness of treatment; however, in a variety of autoimmune diseases, false-positive results can occur, especially in patients with systemic lupus erythematosus or antiphospholipid syndrome.

NTTs were traditionally used for initial testing, with *treponemal tests (TTs)* reserved for confirmation of positive results. However, TTs, including the FTA-ABS test, the hemagglutination treponemal test for syphilis (HATTS), the *T pallidum* hemagglutination assay (TPHA), and the microhemagglutination test for *T pallidum* (MHA-TP) are now increasingly used for initial testing because of their improved speed and automated testing and their ability to detect disease in early or late/latent stages. In this approach, known as the *reverse sequence syphilis screening algorithm,* a positive TT is then followed by an NTT to confirm findings and guide treatment. However, false-positive TT results can occur in 15% of patients with systemic lupus erythematosus; in patients with other treponemal infections or Lyme disease; and in rare instances, in patients who have lymphosarcoma or who are pregnant.

The ELISA, Western blot, and DNA PCR techniques may allow more rapid and accurate diagnosis of congenital syphilis and neurosyphilis.

Management of syphilis

Treatment of syphilis is determined by disease stage and by whether there is CNS involvement. *T pallidum* is exquisitely sensitive to penicillin, which remains the treatment of choice for all stages. In women who are pregnant, penicillin is the only treatment option. For penicillin-allergic patients who do not have neurosyphilis or HIV coinfection, alternatives include doxycycline or tetracycline. For penicillin-allergic patients with ocular syphilis, ceftriaxone and chloramphenicol have been reported to be effective alternatives. Either penicillin G or a single oral dose of azithromycin has been recommended to treat patients recently exposed to a sexual partner with infectious syphilis.

For treatment of ocular syphilis and neurosyphilis, either aqueous crystalline penicillin G, administered intravenously; or procaine penicillin G, administered intramuscularly, plus oral probenecid is used for 10–14 days. According to the CDC, cases of ocular syphilis should be reported to the local or state health department.

Lumbar puncture with examination of CSF should be performed in the following circumstances: in cases of latent syphilis of more than 1 year's duration, suspected neurosyphilis, treatment failure, HIV coinfection, high RPR titers (>1:32), and evidence of other late manifestations (cardiac involvement, gummata).

Many reports have described an accelerated clinical course of syphilis in HIV-infected patients; furthermore, such patients may experience an incomplete response to standard therapy. A patient coinfected with HIV and syphilis often requires a longer and more intensive treatment regimen, ongoing follow-up to assess for recurrence, and a complete neurologic workup with an aggressive CSF investigation for evidence of neurosyphilis. Ceftriaxone

compares favorably with IV penicillin for the treatment of neurosyphilis in HIV-coinfected patients. Patients with any stage of clinical syphilis should be tested for HIV serostatus.

Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2019.* US Dept of Health and Human Services; 2021. Accessed August 31, 2022. https://www.cdc.gov/std/statistics/2019/std-surveillance-2019.pdf

Ghanem KG. Management of adult syphilis: key questions to inform the 2015 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis.* 2015;61(suppl 8):S818–S836.

Mycobacteria

Mycobacteria include a range of pathogenic and nonpathogenic species distributed widely in the environment. *Mycobacterium tuberculosis* is an acid-fast obligate aerobe that causes tuberculosis (TB). A total of 1.6 million people died of TB in 2021, including 187,000 people with HIV infection. Worldwide, TB is the second leading cause of death (after HIV infection) from infectious disease. Most TB cases and deaths occur in developing countries, with the highest number of new cases occurring in Asia and Africa.

Among the other diseases caused by mycobacteria is *Hansen disease (leprosy),* the etiologic agents of which are *Mycobacterium leprae* and *Mycobacterium lepromatosis.* In addition, *nontuberculous mycobacteria* (*NTM;* also called *atypical mycobacteria*) are mycobacteria that can cause lung disease resembling tuberculosis, lymphadenitis, skin disease, and bacteremia. *Multidrug-resistant NTM,* also known as *Mycobacterium abscessus complex*, is more challenging to treat because of its resistance to standard antituberculous regimens.

Tuberculosis

Infection with *M tuberculosis* usually occurs through inhalation of infective aerosolized droplets and, in rare cases, by way of the skin or gastrointestinal tract. Infection mainly involves the lungs, but it can spread systemically and involve any organ system.

The purified protein derivative (PPD) tuberculin skin test measures delayed hypersensitivity to tuberculoprotein. A positive PPD reaction is defined as a 10 mm or larger area of induration at the site of intradermal injection of 0.1 mL of PPD, read 48–72 hours after the injection. Because a false-positive test result may occur in patients who have been vaccinated with the BCG vaccine, blood tests are used in these individuals. They are also used in patients who are high risk and have a negative tuberculin skin test result. These TB blood tests include the interferon-gamma release assay. After a positive tuberculin skin test result, chest radiography, chest computed tomography, and sputum testing can be used to aid in diagnosis.

Treatment of active TB infection consists of intensive therapy with daily isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for 8 weeks. EMB may be discontinued after drug susceptibility testing. The intensive therapy is followed by continuation therapy with daily or thrice weekly INH and RIF for 18 weeks.

All currently used agents have toxic adverse effects, especially hepatic and neurologic effects; thus, patients should be carefully monitored during the course of therapy. INH and EMB can cause optic neuropathy in a small percentage of patients, and RIF can cause pink-tinged tears and blepharoconjunctivitis. In patients with suspected ethambutol-induced optic neuropathy, formal visual acuity testing, central visual field testing, fundus examination, and optical coherence tomography (OCT) of the peripapillary retinal nerve fiber layer,

as well as possibly electrophysiologic testing (eg, visual evoked potential, multifocal electroretinography), should be considered.

Outbreaks of nosocomial and community-acquired *multidrug-resistant TB (MDRTB)*—that is, TB resistant to INH and RIF—have increased, particularly in people with concurrent HIV infection. MDRTB in HIV-infected patients is associated with widely disseminated disease, poor treatment response, and substantial mortality. MDRTB infection has also been documented in health care workers exposed to these patients. Treatment of MDRTB involves using at least 5 agents from the following list: fluoroquinolone (eg, levofloxacin or moxifloxacin), bedaquiline, linezolid, clofazimine, and cycloserine/terizidone. Other drugs may be used to limit adverse effects or treat susceptible strains. These agents are used for at least 18–24 months until sputum culture converts from positive to negative for *M tuberculosis*.

Mandal S, Saxena R, Dhiman R, et al. Prospective study to evaluate incidence and indicators for early detection of ethambutol toxicity. *Br J Ophthalmol.* 2021;105(7):1024–1028.

Takwoingi Y, Whitworth H, Rees-Roberts M, et al. Interferon gamma release assays for diagnostic evaluation of active tuberculosis (IDEA): test accuracy study and economic evaluation. *Health Technol Assess.* 2019;23(23):1–152.

World Health Organization. *Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care.* World Health Organization; updated 2017. Accessed August 31, 2022. https://www.who.int/publications/i/item/9789241550000

World Health Organization. *WHO Treatment Guidelines for Isoniazid-Resistant Tuberculosis: Supplement to the WHO Treatment Guidelines for Drug-Resistant Tuberculosis*. World Health Organization; 2018. Accessed November 21, 2022. https://www.who.int/publications/i/item/9789241550079

Ophthalmic considerations Screening recommendations have been established for patients taking ethambutol (EMB) at doses >15 mg/kg/day. The initial baseline examination should include a dilated fundus examination and visual acuity, color vision, formal central visual field, and Amsler grid testing. The patient should be examined monthly; if there is any change in vision, loss of color vision, or visual field loss, the ophthalmologist should consult with the prescribing physician about adjustment or discontinuation of the medication. OCT imaging and visual evoked potential testing may help to identify optic neuropathy in its early stages.

There are no standard screening recommendations for patients taking EMB at doses <15 mg/kg/day; however, these patients should be screened regularly, including formal visual field testing. Before EMB therapy is initiated, informed consent that explains the risk of potentially irreversible vision loss associated with any dose of EMB should be obtained.

Fungal Infections

Candida albicans is a yeast that is present in the mouth and gastrointestinal tract in 40%–60% of healthy adults. In individuals with disrupted local defenses or depressed immunity, overgrowth and parenchymal invasion can occur, with the potential for systemic spread. Associated infections include oral lesions (thrush) and vaginal, skin, esophageal, and

urinary tract involvement. Chronic mucocutaneous lesions may occur in persons with specific T-lymphocyte defects. Disseminated disease can involve any organ system, most commonly the kidneys, brain, heart, and eyes, and is more common in immunocompromised patients and those with indwelling vascular catheters.

Other important invasive fungal infections are cryptococcosis, histoplasmosis, blastomycosis, aspergillosis, and coccidioidomycosis. Invasive fungal infections are a substantial problem in immunocompromised patients. Fungal PCR assays allow more rapid diagnosis of serious fungal infections and offer higher sensitivity than fungal cultures.

Treatment of serious systemic infections has traditionally involved IV amphotericin B, sometimes combined with flucytosine or an imidazole. Lipid complex and liposome-encapsulated amphotericin B formulations were developed to reduce this drug's nephrotoxic and myelosuppressive effects. Imidazoles, such as fluconazole, itraconazole, and voriconazole, are less toxic and better-tolerated alternatives. See the section Antifungal Agents later in this chapter.

Parasitic Infection

Toxoplasma

Toxoplasmosis is caused by infection with the protozoan parasite *Toxoplasma gondii,* which infects up to one-third of the world's population. Acute infections may be asymptomatic in women who are pregnant, and the infection can be transmitted to the fetus, causing severe complications, including cognitive impairment, blindness, and epilepsy. In the United States, as many as 4000 new cases of congenital toxoplasmosis occur each year. Nearly 750 US deaths are attributed to toxoplasmosis each year, and in approximately half of these cases, *T gondii* infection is believed to be caused by eating contaminated undercooked or raw meat. *T gondii* can also be transmitted to humans by ingesting oocysts, an environmentally resistant form of the organism, through exposure to cat feces, water, or soil containing the parasite or from eating unwashed contaminated fruits or vegetables.

Infection can be prevented in large part by cooking meat to a safe temperature, peeling or thoroughly washing fruits and vegetables before eating, and cleaning cooking surfaces and utensils after they have come into contact with raw meat. Also, pregnant women should avoid changing cat litter and handling raw or undercooked meat. In addition, pet owners should keep cats indoors, where they are less likely to eat infected prey and subsequently acquire *T gondii.*

Primary infection is usually subclinical, but cervical lymphadenopathy or ocular disease can be present in some patients. The ocular manifestations include uveitis and chorioretinitis with macular scarring. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* Chapter 10, for related images, and Section 9, *Uveitis and Ocular Inflammation,* for images and additional discussion of ocular manifestations. The clinical picture and histopathology of toxoplasmosis reflect the immune response. In immunocompromised patients, reactivation of latent disease can cause life-threatening encephalitis.

Diagnosis of toxoplasmosis can be established by direct detection of the parasite or by serologic techniques. Real-time PCR is a very sensitive technique for diagnosing *T gondii* infection and for determining the organism's precise genotype. In the past, the most commonly

used therapeutic regimen was pyrimethamine combined with sulfadiazine and folinic acid. This regimen has been largely replaced by trimethoprim-sulfamethoxazole (TMP-SMX), which is more readily available and less expensive. Other drugs with activity against *T gondii* include azithromycin, atovaquone, and clindamycin. See BCSC Section 12, *Retina and Vitreous,* for more details on the treatment of ocular toxoplasmosis.

Viral Infections

Herpesvirus

As a class, viruses are strictly intracellular parasites, relying on the host cell for their replication. Herpesviruses, which are large-enveloped, double-stranded DNA viruses, are some of the most common human infectious agents and are responsible for a wide variety of acute and chronic diseases. Herpesviruses of interest to the ophthalmologist are the herpes simplex viruses (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Following are the 9 recognized types of human herpesviruses:

- type 1: HSV-1
- type 2: HSV-2
- type 3: VZV
- type 4: EBV
- type 5: CMV
- types 6A, 6B, and 7: human herpesvirus (HHV)-6A, HHV-6B, and HHV-7, respectively
- type 8: HHV-8 (associated with Kaposi sarcoma)

Herpes simplex

Herpes simplex virus (HSV) types 1 and 2 are members of the family Herpesviridae. HSV type 1 and type 2 infections differ in severity and clinical manifestation; many people with HSV antibodies are asymptomatic. Latent infection of sensory and autonomic ganglia can occur. Reactivation of HSV from the trigeminal ganglia may be associated with asymptomatic excretion of virus or with the development of mucosal ulceration. Serologic testing, DNA PCR testing, and viral culture can help diagnose difficult cases, particularly CNS infections.

HSV-1 is associated with mucocutaneous infections of the pharynx, skin, oral cavity, vagina, eye, and brain. Ophthalmic infection most often manifests as corneal dendritic or stromal disease but may present as acute retinal necrosis. See BCSC Section 8, *External Disease and Cornea,* Chapter 11, for more on the ocular manifestations of HSV infection, including images; also see Section 9, *Uveitis and Ocular Inflammation.* Herpes encephalitis carries a 10%–20% mortality rate. *HSV-2* infection is an important sexually transmitted disease associated with genital infections, aseptic meningitis, and congenital infection. *Neonatal herpes infection* affects around 1 in 3500 babies born in the United States and is defined by vertical transmission from mother to infant within the first 28 days of life. Neonatal herpes infection involves multiple systems and, if untreated, has a mortality rate of approximately 25%.

The drug of choice for treating acute systemic infections is acyclovir, which is approved by the US Food and Drug Administration (FDA) to treat genital herpes and HSV encephalitis. Localized disease can be treated with oral acyclovir. Topical treatment of skin or

mucocutaneous lesions with acyclovir ointment decreases the healing time. Oral acyclovir can also be used prophylactically for severe and recurrent genital herpes. Long-term suppressive oral acyclovir (400 mg twice a day) also reduces the recurrence of herpes simplex epithelial keratitis and stromal keratitis. IV acyclovir is used to treat herpes encephalitis.

Famciclovir and valacyclovir are also approved in the United States for the treatment of herpes zoster and herpes simplex infections. Compared with acyclovir, these agents have better bioavailability, achieve higher blood levels, and require less frequent dosing. HSV is also sensitive to vidarabine. Cidofovir or foscarnet can also be used to treat acyclovir-resistant herpes simplex.

Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med.* 2009;361(14):1376–1385.

Varicella-zoster

Varicella-zoster virus (sometimes referred to as *herpes zoster virus*) produces infection in a manner similar to that of HSV. After a primary infection, VZV remains latent in dorsal root ganglia; host cellular immune interaction inhibits reactivation. Primary infection usually occurs in childhood in the form of *varicella (chickenpox),* a generalized vesicular rash accompanied by mild constitutional symptoms.

Reactivation of the latent virus in adulthood—known as *herpes zoster (HZ)* or *shingles*—may be heralded by pain in a sensory nerve distribution, followed by a unilateral vesicular eruption occurring over 1–3 dermatomic areas. HZ involvement of the ophthalmic division of the trigeminal nerve *(herpes zoster ophthalmicus)* can cause keratitis, uveitis, and increased intraocular pressure. New crops of lesions appear in the same area within 7 days. Resolution of the lesions may be followed by postherpetic neuralgia. Other neurologic sequelae of HZ include segmental myelitis, Guillain-Barré syndrome, and Ramsay Hunt syndrome. The incidence of HZ is 2 or 3 times higher in patients older than 60 years. *Postherpetic neuralgia* occurs after HZ in approximately 50% of patients older than 50 years. The pain of postherpetic neuralgia can be severe and debilitating and may persist for months or even years. Immunosuppressed persons experience recurrent lesions and an increased incidence of disseminated disease.

For immunocompetent adults with cutaneous HZ, recommended 7-day treatment regimens include famciclovir (500 mg twice a day), valacyclovir (1000 mg 3 times a day), and acyclovir (800 mg 5 times a day). Treatment of acute infection (ie, varicella) in immunocompromised patients or those with visceral involvement may include acyclovir, famciclovir, or valacyclovir. Newer drugs being evaluated for resistant VZV strains or concomitant HIV infection include sorivudine, brivudine, fialuridine, fiacitabine, netivudine, lobucavir, foscarnet, and cidofovir.

Vaccines are available for both varicella and HZ. See Chapter 13 in this volume for further discussion of VZV vaccines.

In some patients, tricyclic antidepressants, pregabalin, gabapentin, and topical capsaicin cream reduce the pain of postherpetic neuralgia. For refractory cases, transcutaneous electronic nerve stimulation, nerve blocks, or intrathecal glucocorticoid injections may be helpful.

Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: a cohort study. *Neurology.* 2016;87(1):94–102.

Cytomegalovirus

Cytomegalovirus is a ubiquitous human virus: 50% of adults in developed countries harbor antibodies, usually acquired during the first 5 years of life. For up to several years after infection, the virus can be isolated from all body fluids, even in the presence of circulating neutralizing antibodies. Serologic and PCR testing is available to assist in the diagnosis of CMV infection. The pp65 antigen assay is a sensitive and specific test used to guide antiviral therapy in transplant recipients and to detect subclinical disease in high-risk patients.

Congenital CMV disease carries a 20% incidence of hearing loss or cognitive impairment and a 0.1% incidence of various other severe congenital conditions and disorders, including jaundice, hepatosplenomegaly, anemia, microcephaly, and chorioretinitis. Infections in adults include heterophile-negative mononucleosis, pneumonia, hepatitis, and Guillain-Barré syndrome. In immunocompromised patients, CMV interstitial pneumonia carries a 90% mortality rate. Disseminated spread to the gastrointestinal tract, CNS, and eyes is common in patients with AIDS. Latent infection within leukocytes causes transfusion-associated disease. CMV retinitis has been reported after intravitreal corticosteroid injections.

Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation.* 2018;102(6):900–931.

Ophthalmic considerations CMV retinitis is most often treated with either intravitreal ganciclovir or foscarnet, combined with intravenous foscarnet or ganciclovir or oral valganciclovir, depending on the situation. These medications are typically administered for 2–3 weeks. See also BCSC Section 12, *Retina and Vitreous.*

Epstein-Barr virus

Epstein-Barr virus (EBV) antibodies are found in more than 90% of all adults. Childhood infections are usually asymptomatic, whereas EBV infection in young adults can cause infectious mononucleosis. Lymphoproliferative disorders may develop in transplant recipients taking cyclosporine and in patients with AIDS. EBV is epidemiologically associated with Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and nasopharyngeal carcinoma and has also been reported in EBV-associated hemophagocytic lymphohistiocytosis, also known as *EBV-associated hemophagocytic syndrome.* In addition, EBV has been reported as a cause of pediatric acute renal failure. Recent studies suggest that EBV may also be a leading cause of multiple sclerosis. A highly sensitive PCR assay is available for detecting primary EBV infection and infectious mononucleosis.

Treatment of acute disease is mainly supportive, although the EBV DNA polymerase is sensitive to acyclovir and ganciclovir, which decrease viral replication in tissue culture. No vaccine is currently available against EBV, but research is ongoing; it is estimated that an EBV vaccine could prevent 2% of cancers worldwide.

Aguayo F, Boccardo E, Corvalán A, Calaf GM, Blanco R. Interplay between Epstein-Barr virus infection and environmental xenobiotic exposure in cancer. *Infect Agent Cancer.* 2021;16(1):50. doi:10.1186/s13027-021-00391-2

Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science.* 2022;375(6578):296–301.

COVID-19 (SARS-CoV-2)

In December 2019, the World Health Organization (WHO) was notified of cases of atypical pneumonia of unknown etiology in Wuhan, China. In January 2020, the pathogen was identified by Chinese scientists as a novel coronavirus; in February 2020, the virus that causes COVID-19 was officially named SARS-CoV-2. An RNA virus, SARS-CoV-2 belongs to the genus *Betacoronavirus* and is of zoonotic origin. It is transmitted from human to human, primarily via respiratory droplets. The WHO declared COVID-19 a pandemic on March 11, 2020. Common symptoms of COVID-19 infection include fever, cough, and shortness of breath, but symptoms may change with new COVID-19 variants.

Ophthalmic considerations The known ocular manifestations of COVID-19 are follicular conjunctivitis with hyperemia, chemosis, light sensitivity, tearing, and discharge. Conjunctival swabs have yielded positive results for SARS-CoV-2 on reverse transcriptase PCR testing. Therefore, the virus may be transmissible from contact with the ocular surface, tears, or fomites. Ophthalmologists should be aware of the possibility of conjunctivitis as a presenting sign of COVID-19 infection and use eye protection, masks, and other personal protective equipment when examining patients who are potentially infectious. Additional information on COVID-19 and its effect on ophthalmologic practice is available at www.aao.org/headline/alert-important-coronavirus-context.

Sommer A. Humans, viruses, and the eye—an early report from the COVID-19 front line. *JAMA Ophthalmol.* 2020;138(5):578–579.

Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 2020;138(5):575–578.

Zhong Y, Wang K, Zhu Y, et al. Ocular manifestations in COVID-19 patients: a systematic review and meta-analysis. *Travel Med Infect Dis.* 2021;44:102191. doi:10.1016/j.tmaid.2021.102191

In May 2020, remdesivir (Veklury) became the first drug approved by the FDA to treat COVID-19. This broad-spectrum antiviral is a nucleotide analogue prodrug and is administered via IV infusion. Two oral antiviral medications have received emergency use authorization: nirmatrelvir with ritonavir (Paxlovid) and molnupiravir (Lagevrio). These 2 drugs, which must be taken within 5 days of symptom onset, can reduce the risk of hospitalization and death by up to 88% and 30% for Paxlovid and Lagevrio, respectively.

Currently, a number of COVID-19 vaccines are approved or authorized for use by the FDA. See Chapter 13 for more information.

Influenza

See Chapter 13 in this volume for a discussion of influenza and immunization.

Hepatitis

Hepatitis A and B

See Chapter 13 for discussion of hepatitis A and B and immunization.

Hepatitis C and other forms of hepatitis

Approximately 20%–40% of acute viral hepatitis cases reported in the United States are of the non-A, non-B type; of this group, most cases are caused by the hepatitis C virus (HCV). The prevalence of chronic HCV infection is 3.5 million individuals in the United States and 71 million worldwide. Risk factors for HCV transmission include parenteral drug use, hemodialysis, occupational exposure to HCV-infected blood, blood transfusion or organ transplant before 1992, treatment with clotting factor concentrates before 1987, and incarceration. Persons born between 1945 and 1965 have the highest incidence of HCV infection. Sexual intercourse with an HCV-infected person is not a predominant mode of HCV transmission.

Of all the hepatitis viruses, HCV causes the most damage in immunocompetent hosts because of direct hepatocyte cytotoxicity. It may cause cirrhosis, fulminant hepatitis, and hepatocellular carcinoma. Hepatitis C is the most common cause of liver cancer and the most common indication for liver transplantation in the United States.

A sensitive enzyme immunoassay has been developed to detect and quantify total HCV core antigen in anti-HCV-positive or anti-HCV-negative sera. In addition, a 1-step PCR assay is available to detect HCV RNA and provide HCV genotyping.

Treatment of acute HCV infection with interferon alfa-2a reduces the rate of conversion to chronic HCV infection. Spontaneous resolution of acute HCV infection may occur in up to 50% of patients. Numerous studies suggest that the viral proteins NS3/4A protease, NS5A polymerase, and NS5B polymerase may be promising targets for inhibiting HCV RNA replication. The combination of 2 nucleotide polymerase inhibitors, ledipasvir and sofosbuvir, has demonstrated a 94%–99% sustained virologic response in patients with hepatitis C.

Other hepatitis viruses include the following:

- *Hepatitis D virus* causes chronic delta hepatitis, a severe form of chronic liver disease. Interferon alfa-2a and lamivudine have been found to be beneficial in treating chronic hepatitis D infection.
- *Hepatitis E virus* causes sporadic as well as epidemic acute viral hepatitis and is prevalent in many developing countries. In patients with preexisting chronic liver disease, acute hepatitis E viral infection has a protracted course, with high morbidity and mortality.
- *Hepatitis G virus* often occurs as a coinfection with hepatitis B virus or HCV, but it usually does not increase their pathogenicity.
- *Transfusion-transmitted virus (TTV),* identified in a small percentage of patients with posttransfusion hepatitis, has been implicated as a potential cause of 30%–50% of cases of lymphoma and Hodgkin disease.

American Association for the Study of Liver Diseases; Infectious Diseases Society of America (AASLD-IDSA). *HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C.* Accessed November 27, 2022. https://www.hcvguidelines.org

Doi A, Hikita H, Kai Y, et al. Combinations of two drugs among NS3/4A inhibitors, NS5B inhibitors and non-selective antiviral agents are effective for hepatitis C virus with NS5A-P32 deletion in humanized-liver mice. *J Gastroenterol.* 2019;54(5):449–458.

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol.* 2018;69(2):461–511.

Human Papillomavirus

Human papillomavirus (HPV) infection is highly prevalent and is closely associated with condylomata (genital warts), cervical intraepithelial neoplasia, cervical cancer (>99% of all cervical cancers are positive for HPV), conjunctival intraepithelial neoplasia, and some cases of head and neck squamous cell carcinoma. HPV has a possible etiologic role in some cases of lung adenocarcinoma. More than 50% of all persons are infected with HPV during their lifetime through sexual or intrauterine transmission. HPV can be detected with PCR assay techniques. Papanicolaou tests combined with HPV tests, or HPV tests alone, are most useful for women aged 25 years or older. See Chapter 13 for further discussion of HPV vaccination and cervical cancer.

Harper DM, DeMars LR. HPV vaccines—a review of the first decade. *Gynecol Oncol.* 2017;146(1):196–204.

Ebola Virus

Ebola virus disease (EVD) was first discovered in 1976 when cases of hemorrhagic fever occurred near the Ebola River in the Democratic Republic of Congo. The West African Ebola outbreak of 2013–2016 involved >28,000 reported cases and >11,000 recorded deaths, mainly in the countries of Guinea, Liberia, and Sierra Leone. The presumptive reservoir hosts of Ebola virus are fruit bats. Of the 5 known viruses belonging to the genus *Ebolavirus,* 4 are known to cause disease in humans, and all are members of the family Filoviridae, which are single-stranded RNA viruses.

The Ebola virus can be contracted through contact with the blood, body fluid, or tissue of infected bats, nonhuman primates, or humans. The virus can penetrate broken skin or mucous membranes. Early symptoms of infection appear 2–21 days after exposure to the virus and include fever, chills, muscle aches, headache, and weakness. Hemorrhagic conjunctivitis is a known presentation of infection. Later symptoms include rash, nausea, emesis, diarrhea, bruising, and bleeding, with eventual multisystem organ failure and death.

Infection of blood or body fluids can be confirmed by PCR, ELISA, or *Ebolavirus* immunoglobulin testing.

Post–Ebola virus syndrome in patients who have recovered from EVD includes joint, muscle, and chest pain; neurologic problems; and ocular complications.

Ophthalmic considerations The most common ocular manifestation of EVD is uveitis, which may lead to impaired vision or loss of vision. Other known sequelae include cataract, retinal scarring, optic neuropathy, hypotony, and phthisis bulbi. The CDC recommends taking the highest-level precautions when treating patients with EVD. Ophthalmologists working in endemic areas should suspect Ebola virus infection when encountering patients with hemorrhagic conjunctivitis. The ophthalmologist treating patients with EVD or post–Ebola virus syndrome should assume the virus remains active in the eye for months after the initial infection and should consult the CDC website for the most current guidelines (https://www.cdc.gov/vhf/ebola/index.html).

Eghrari AO, Bishop RJ, Ross RD, et al. Characterization of Ebola virus–associated eye disease. *JAMA Netw Open.* 2021;4(1):e2032216. doi:10.1001/jamanetworkopen.2020.32216

Steptoe PJ, Momorie F, Fornah AD, et al. Evolving longitudinal retinal observations in a cohort of survivors of Ebola virus disease. *JAMA Ophthalmol.* 2020;138(4):395–403.

Zika Virus

The Zika virus (ZIKV) was first isolated in 1947 from a rhesus macaque from the Zika Forest in Uganda. It is a single-stranded RNA virus belonging to the family Flaviviridae and the genus *Flavivirus* and is related to the dengue, yellow fever, chikungunya, and West Nile viruses. Its vector of transmission is the female *Aedes aegypti* mosquito. Transmission between humans can occur through sexual intercourse; blood transfusion; and mother-to-child vertical transmission via pregnancy, delivery, or breast milk.

The first evidence of human infection was discovered in Uganda in 1952. However, few cases were identified until an outbreak in Yap, Micronesia, in 2007. Subsequently, the virus was documented in the Americas via the Pacific Islands when an outbreak occurred in Brazil in 2015. Since then, more than 1.5 million individuals have been infected with ZIKV in Brazil.

The symptoms of ZIKV infection in adults are mild and self-limited; many individuals infected with ZIKV are asymptomatic. Symptoms include nonspecific fever, joint and muscle pain, conjunctivitis, and rash.

In northeastern Brazil, a sharp rise in the number of newborns with microcephaly (head circumference <32 cm) occurred 6 months after the onset of the Zika outbreak. ZIKV is identified via PCR and serologic testing, which was not readily available in parts of Brazil. Therefore, the association between ZIKV and microcephaly was presumptive.

Recently, the term *congenital Zika syndrome (CZS)* was coined to describe the devastating effects of the virus on the developing fetus. The CDC defines this syndrome as having the following 5 features:

- microcephaly
- structural brain abnormalities
- ocular findings
- congenital contractures such as clubfoot
- hypertonia restricting body movement soon after birth

The most common ocular findings in infants with CZS are chorioretinal atrophy and pigment mottling in the macula, similar to that seen in eyes with toxoplasmosis. Optic nerve abnormalities, bilateral iris coloboma, and lens subluxation have also been described in these infants. Therefore, when examining infants with microcephaly in regions affected by ZIKV, ophthalmologists should be aware of the ocular manifestations of congenital ZIKV infection. ZIKV vaccines are currently in clinical trials.

Marquezan MC, Ventura CV, Sheffield JS, et al. Ocular effects of Zika virus—a review. *Surv Ophthalmol.* 2018;63(2):166–173.

Venkatesh A, Patel R, Goyal S, Rajaratnam T, Sharma A, Hossain P. Ocular manifestations of emerging viral diseases. *Eye (Lond).* 2021;35(4):1117–1139.

Human Immunodeficiency Virus

In June 1981, the CDC's *Morbidity and Mortality Weekly Report* highlighted 5 homosexual men in Los Angeles, California, who had biopsy-confirmed *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia. In 1982, the CDC used the term *AIDS* for the first time and released the first case definition; by the next year the major routes of transmission had been identified. In 1983, HIV, a newly recognized retrovirus, was identified as the cause of AIDS.

HIV is a blood-borne virus that can be transmitted via sexual intercourse, shared IV drug paraphernalia (needles and syringes), and blood transfusion and from mother to child during pregnancy, birth, or breastfeeding. Although HIV infection may be transmitted via blood or blood products, the risk of transmission by accidental needle-stick injury appears relatively low (<0.5%). In 2019, an estimated 1.2 million people aged 13 years and older were infected with HIV in the United States, and 38 million were infected worldwide. In addition, an estimated 160,000 people in the United States have not been diagnosed. In 2019, worldwide, there were approximately 1.7 million new cases of HIV infection, and 690,000 people died of AIDS-related illnesses. Approximately 33 million people have died of AIDS-related illnesses since the start of the epidemic.

Etiology and pathogenesis

HIV belongs to a family of viruses known as *retroviruses.* A retrovirus encodes its genetic information in RNA and uses a unique viral enzyme named *reverse transcriptase* to copy its genome into DNA. HIV has 2 subtypes, HIV-1 and HIV-2. HIV-1 is further classified into several groups, including M, N, and O. Thus far, there are 9 known serotypes of HIV-1 group M, and 1 each of HIV-1 groups N and O. In the United States, HIV-1 group M, serotype B, is the most common form. HIV-2, another human T-lymphotropic retrovirus, has been isolated in West African individuals and is closely related to simian immunodeficiency virus.

HIV preferentially infects T lymphocytes, especially helper T ($CD4^+$) lymphocytes. The virus infects mature T lymphocytes in vitro, although other cells can serve as targets. CD4 is the phenotypic marker for this subset, and it is identified by monoclonal antibodies OKT4 and Leu-3.

The hallmark of immunodeficiency in AIDS is a depletion of the $CD4^+$ helper-inducer T lymphocytes. HIV selectively infects these lymphocytes and macrophages; with HIV replication, the helper T lymphocytes are killed. Because the helper T lymphocytes are central to

the immune response, loss of this subset results in a profound immune deficiency, leading to the life-threatening opportunistic infections indicative of AIDS. This selective depletion of $CD4^+$ helper T lymphocytes leads to the characteristic inverted $CD4^+/CD8^+$ ratio (also known as the *T4/T8 ratio*), where the ratio drops to less than 1.0; in comparison, the normal $CD4^+/CD8^+$ ratio is approximately 2.0. Years may pass between the initial HIV infection and the development of these immune abnormalities.

In addition to cellular immunodeficiency, patients with AIDS have abnormalities of B-lymphocyte function. These patients cannot mount an antibody response to novel T-lymphocyte–dependent B-lymphocyte challenges, although B lymphocytes in these patients are hyperreactive with polyclonal B-lymphocyte activation, hypergammaglobulinemia, and circulating immune complexes. This B-lymphocyte hyperfunction may be a direct consequence of HIV infection: studies have demonstrated that in vitro infection of B lymphocytes with HIV can induce polyclonal activation.

HIV has also been documented to infect macrophages in the brains of patients with AIDS. HIV infection of the brain is thought to be responsible for the HIV encephalopathy syndrome.

Clinical syndromes

HIV infection has 3 phases: acute seroconversion, asymptomatic infection, and AIDS. In the acute seroconversion phase, viremia is high and the $CD4^+$ T-lymphocyte count falls rapidly. Symptoms, including fever, rash, lymphadenopathy, and malaise, typically occur within 2–4 weeks after infection. The second phase of infection can be asymptomatic or present with persistent generalized lymphadenopathy. Then, viral replication occurs, and the $CD4^+$ lymphocyte count steadily declines. This chronic or latent phase can last more than a decade. The final stage, AIDS, is defined by a $CD4^+$ lymphocyte count <200 cells/μL of blood or by the development of opportunistic infections or malignancy.

Diagnosis

The CDC recommends that every individual between the ages of 13 and 64 years be tested for HIV at least once and that persons at high risk for HIV infection be screened at least annually. The American College of Physicians encourages the testing of all persons. The US Preventive Services Task Force recommends screening adolescents and adults at increased risk for HIV infection and all women who are pregnant. Risk factors for exposure to HIV include unprotected sexual intercourse, large number of sexual partners, history of sexually transmitted infection, blood transfusion, needle-stick injury, sharing of IV drug paraphernalia (needles and syringes), and mucosal contact with infected blood.

All HIV diagnostic tests are guided by a common principle: screen with a highly sensitive initial test and confirm reactive results with a different test that is both sensitive and highly specific. A reactive result on the initial antigen/antibody (Ag/Ab) combination test is confirmed using an IgG-sensitive HIV-1/2 antibody differentiation supplemental assay—a faster, less labor-intensive, and highly specific replacement for the Western blot. The $CD4^+$ lymphocyte count is used for classification and to monitor for opportunistic infection. The viral load in peripheral blood is used to guide therapy; the rate of progression to AIDS and death is related to viral load.

The workup of a patient with newly diagnosed HIV infection should include an ophthalmologic examination for CMV retinopathy (cotton-wool spots) and testing for TB, CMV, syphilis, hepatitis A–C, *Toxoplasma,* chlamydia, and gonococcus.

Centers for Disease Control and Prevention. *Technical Update on HIV-1/2 Differentiation Assays.* US Dept of Health and Human Services; 2016. Accessed November 28, 2022. https://stacks.cdc.gov/view/cdc/40790/cdc_40790_DS1.pdf

Stekler JD, Violette LR, Clark HA, et al. Prospective evaluation of HIV testing technologies in a clinical setting: protocol for project DETECT. *JMIR Res Protoc.* 2020;9(1):e16332. doi:10.2196/16332

Treatment

It is recommended that all patients with early HIV infection begin antiretroviral therapy (ART) as soon as possible; initiation of ART soon after the initial HIV infection may be associated with a greater chance of immune reconstitution to normal or near-normal $CD4^+$ lymphocyte levels. The goals of ART include durable suppression of HIV viral load to <50 copies/mL, restoration of immune function (as indicated by the $CD4^+$ lymphocyte count), prevention of HIV transmission, prevention of drug resistance, and improvement in quality of life. ART regimens for treatment-naive patients are composed of a "base" medication and a "backbone" regimen. The base is an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor. The backbone typically consists of 2 nucleoside reverse transcriptase inhibitors. Treatment is based on adverse-effect profiles, comorbidities, potential drug interactions, results of drug resistance testing, virologic efficacy, allergy history, pregnancy status, pill burden, and dosing frequency.

ART has been shown to dramatically reduce the HIV viral load, increase $CD4^+$ lymphocyte counts, delay disease progression, reduce the number of opportunistic infections, decrease the number of hospital admissions, and prolong survival. Some statistics show an up to 82% decline in the number of opportunistic infections in patients on ART. These advantages translate into improved survival and enhanced quality of life for patients infected with HIV.

A small percentage of the population appears to be naturally immune to HIV infection. These persons have defective genes for CCR5, a surface receptor that HIV requires to attach to T lymphocytes. Moreover, approximately 50% of long-term survivors of HIV infection are heterozygous for the CCR5 defect. This finding has led to speculation concerning the possibilities for genetic therapy, in which anti-HIV genes could be "injected" into a patient's chromosomes with a harmless viral vector.

Preexposure prophylaxis (PrEP) with tenofovir-emtricitabine may be considered in high-risk individuals. When taken consistently and when used in combination with condoms and other preventive methods, PrEP can reduce the risk of HIV infection in high-risk patients. For postexposure prophylaxis, ART is taken within 72 hours after possible exposure to HIV. Efforts to develop a safe and effective HIV vaccine are ongoing.

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.* US Dept of Health and Human Services. Updated September 21, 2022. Accessed October 24, 2022. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv

World Health Organization. *Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach*. World Health Organization; 2021. Accessed October 24, 2022. https://www.ncbi.nlm.nih.gov/books/NBK572727/

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated inflammatory response by the reconstituted immune system to residual antigens or to pathogens after the initiation of ART. In one form of IRIS, previously diagnosed and treated opportunistic infections paradoxically worsen clinically despite improvements in the clinical markers of HIV infection. In the other form of IRIS, an underlying undiagnosed infection may flare up or be unmasked. *Immune recovery uveitis (IRU),* one of the manifestations of IRIS, occurs in nearly 10% of HIV-infected patients with immune recovery and a history of CMV retinitis. Of these patients with IRU, 46% have significant cystoid macular edema, and 49% have epiretinal membrane formation.

Ophthalmic considerations The ocular manifestations of HIV infection and AIDS are discussed in BCSC Section 9, *Uveitis and Ocular Inflammation.* HIV has been found in tears, conjunctival epithelial cells, corneal epithelial cells, aqueous humor, and the retina, including retinal vascular endothelium. Although transmission of HIV infection via eye examinations or ophthalmologic equipment has not been documented, there are several precautions that clinicians can take.

Health care professionals performing eye examinations or other procedures involving contact with tears should wash their hands immediately after the procedure and between patients. Using gloves is advisable when the hands have cuts, scratches, or dermatologic lesions.

Any instrument that comes into direct contact with external surfaces of the eyes should be wiped clean and disinfected by a 5- to 10-minute exposure to 1 of the following:

- a fresh solution of 3% hydrogen peroxide
- a fresh solution containing 5000 ppm free available chlorine—a one-tenth dilution of common household bleach (sodium hypochlorite)
- 70% ethanol
- 70% isopropanol

The device should be thoroughly rinsed in tap water after disinfection and dried before use.

Diluted bleach effectively disinfects tonometer tips to prevent the transmission of HSV, adenovirus, and SARS-CoV-2 and is recommended by the CDC and most tonometer manufacturers.

Contact lenses used in trial fittings should be disinfected between fittings with a commercially available hydrogen peroxide contact lens–disinfecting system or with the standard heat disinfection regimen (78°C–80°C for 10 minutes). The

demonstration of HIV in corneal epithelium has led to recommendations that all corneal donors be screened for antibodies to HIV and that all potential donor corneas from HIV antibody–positive persons be discarded.

For more specific recommendations, see the American Academy of Ophthalmology's Clinical Statement "Infection Prevention in Eye Care Services and Operating Areas and Operating Rooms—2012," available at https://www.aao.org/education/clinical-statement/infection-prevention-in-eye-care-services-operatin.

Junk AK, Chang TC, Vanner E, Chen T. Current trends in tonometry and tonometer tip disinfection. *J Glaucoma.* 2020;29(7):507–512.

Update on Antibiotics

For more than 60 years, the main trends in the management of infectious diseases have been the evolution and refinement of antibiotic therapy. Factors that have stimulated the development of new antibiotics include the continuous emergence of resistant bacteria, economics, and the desire to eliminate adverse effects. Over the past 30 years, emphasis has gradually shifted from aminoglycosides to β-lactams and the development of new classes of antibiotics such as carbapenems and monobactams. In addition, vancomycin, TMP-SMX, erythromycin, and rifampin have enjoyed a resurgence in popularity and new applications. Quinolones offer the possibility of treating serious infections on an outpatient basis.

Antibacterial Agents

Antibacterial agents can be separated into groups according to their specific targets on or within bacteria:

- β-Lactams and glycopeptides inhibit cell wall synthesis.
- Polymyxins distort cytoplasmic membrane function.
- Quinolones and rifamycins inhibit nucleic acid synthesis.
- Macrolides, aminoglycosides, and tetracyclines inhibit ribosome function.
- Trimethoprim and sulfonamides inhibit folate metabolism.

All antibiotics facilitate the growth of resistant bacteria consequent to the destruction of susceptible bacteria. Although the wide use of antimicrobial agents for veterinary and agricultural purposes has contributed to the emergence of multiresistant microorganisms, the excessive use of antibiotics, especially in hospitals, has been the most significant catalyst for resistance. Bacteria resist antibiotics by inactivating the antibiotic, decreasing the accumulation of the antibiotic within the microorganism by means of efflux pumps (antibacterial efflux), or altering the target site on the microbe. For example, resistance to penicillins and cephalosporins is initiated by β-lactamase enzymes that hydrolyze the β-lactam ring, thus destroying the antibiotic's effectiveness. Resistance can be mediated by chromosomal mutations or by the presence of extrachromosomal DNA, also known as *plasmid resistance.* Plasmid

resistance is essential from an epidemiologic point of view because it is transmissible and usually highly stable, confers resistance to many different classes of antibiotics simultaneously, and is often associated with other characteristics that enable a microorganism to colonize and invade a susceptible host.

Resistance-conferring plasmids have been identified in virtually all bacteria. Plasmids can pick up chromosomal genes for resistance and transfer them to species that are not currently resistant. Bacteria that have acquired chromosomal and plasmid-mediated resistance can neutralize or destroy antibiotics in 3 different ways (they can use 1 or more of these mechanisms simultaneously):

- by preventing the antibacterial agent from reaching its receptor site
- by modifying or duplicating the target enzyme so that it is insensitive to the antibacterial agent
- by synthesizing enzymes that destroy the antibacterial agent or modify the agent to alter its entry or receptor binding

Antimicrobial susceptibility testing permits a rational choice of antibiotics, although the correlation between in vivo and in vitro susceptibility is not always precise. Disk-diffusion susceptibility testing has provided qualitative data about the inhibitory activity of commonly used antimicrobials against an isolated pathogen, and these data are usually sufficient. For serious infections, it is useful to quantify the drug concentrations that inhibit and kill the pathogen. The lowest drug concentration that prevents the growth of a defined inoculum of the isolated pathogen is the *minimal inhibitory concentration (MIC);* the lowest concentration that kills 99.9% of an inoculum is the *minimal lethal concentration (MLC).* For bactericidal drugs, the MIC and MLC are usually similar.

β-Lactam antibiotics

The β-lactam group includes the penicillins, cephalosporins, and monobactams, all of which possess a β-lactam ring that binds to specific microbial binding sites and interferes with cell-wall synthesis. Although the carbapenems and carbacephems are often grouped with β-lactams, they have a slightly different ring structure. Most new agents have been created by side-chain manipulation of the β-lactam ring, which has improved resistance to enzymatic degradation. However, some of the newer antibiotics (such as third-generation cephalosporins) show diminished potency against gram-positive cocci, especially staphylococci.

Roque-Borda CA, da Silva PB, Rodrigues MC, et al. Challenge in the discovery of new drugs: antimicrobial peptides against WHO-list of critical and high-priority bacteria. *Pharmaceutics.* 2021;13(6):773. doi:10.3390/pharmaceutics13060773

Penicillins The first *natural penicillins,* types G and V, were degraded by the enzyme penicillinase. The *penicillinase-resistant penicillins,* such as methicillin, nafcillin, oxacillin, and cloxacillin, were developed for treating resistant *Staphylococcus* species and were effective except against strains of methicillin-resistant *S epidermidis*. The next generation of penicillins included the *aminopenicillins,* ampicillin and amoxicillin, which were created by placing an amino group on the acyl side chain of the penicillin nucleus. This change broadened their effectiveness to include activity against *H influenzae, Escherichia coli,* and *Proteus mirabilis.*

The next advance was the development of the *carboxypenicillins,* carbenicillin and ticarcillin, which are active against aerobic gram-negative rods such as *P aeruginosa, Enterobacter* species, and indole-positive strains of *Proteus.* The fourth-generation penicillins, known as *acyl ureidopenicillins,* include azlocillin, mezlocillin, and piperacillin. Because of the possible emergence of resistance, the newer penicillins are usually administered in combination with an aminoglycoside (the latter inhibits bacterial protein synthesis).

Allergic reactions are the chief adverse effects encountered in using penicillins. Among antimicrobial agents, penicillins are the leading cause of allergy; symptoms range from mild rashes to anaphylaxis.

Cephalosporins As previously mentioned, the cephalosporins belong to the β-lactam group of antibiotics, and cross-allergenicity may occur in 3%–5% of patients with penicillin allergies. The cephalosporins and their characteristics are outlined in Table 15-2.

Touati N, Cardoso B, Delpuech M, et al. Cephalosporin hypersensitivity: descriptive analysis, cross-reactivity, and risk factors. *J Allergy Clin Immunol Pract.* 2021;9(5):1994–2000.e5.

Monobactams Monobactams are a monocyclic class of antibiotics that use only the β-lactam ring as their core structure. Aztreonam, the first approved monobactam antibiotic, has an excellent safety profile and a good success rate in treating infections caused by aerobic gram-negative bacilli but has poor activity against gram-positive and anaerobic organisms. Aztreonam has the spectrum of an aminoglycoside antibiotic without ototoxicity or nephrotoxicity, which are the main adverse effects of aminoglycosides.

Table 15-2 Cephalosporins

Drugs	Characteristics/Comments
First generation (eg, cefazolin, cephalexin)	Active against β-lactamase gram-positive cocci and gram-negative bacilli Usually ineffective against *Bacillus, Pseudomonas, Enterobacter,* and methicillin-resistant *Staphylococcus aureus* (MRSA) Do not cross the blood–brain barrier well
Second generation (eg, cefaclor, cefamandole, cefoxitin, cefuroxime)	Expanded coverage against gram-negative bacilli and *Haemophilus*
Third generation (eg, cefotaxime, ceftazidime, ceftriaxone)	More effective against gram-negative bacilli Less effective against gram-positive cocci (eg, staphylococci) and Enterobacteriaceae Cross blood–brain barrier, more effective for treatment of meningitis Ceftriaxone effective against Lyme disease and gonorrhea; represents the best all-purpose drug of the third-generation cephalosporins
Fourth generation (eg, cefepime, cefpirome)	Good coverage against most gram-negative and gram-positive organisms and anaerobes Expensive
Fifth generation (eg, ceftaroline, ceftobiprole, ceftolozane)	Ceftobiprole effective against *Pseudomonas* Ceftolozane used for treatment of complicated intra-abdominal infections or complicated urinary tract infections

Carbapenems Carbapenems are a class of antibiotics with a basic ring structure similar to that of penicillins. The carbapenems are considered to have the broadest spectrum of activity of all existing antibiotics, including activity against *S aureus, Enterobacter* species, and *P aeruginosa.* However, carbapenem resistance is an ongoing global public health problem. Carbapenems produce a postantibiotic killing effect against some organisms, with a delay in regrowth of damaged organisms similar to that observed with aminoglycosides.

Imipenem/cilastatin combines a carbapenem, imipenem, with an inhibitor of renal dehydropeptidase, cilastatin. Cilastatin has no antimicrobial activity and is present solely to prevent the degradation of imipenem by dehydropeptidase. Imipenem/cilastatin is an appropriate compound for monotherapy for mixed infections. Up to 50% of patients allergic to penicillin are also allergic to imipenem.

Meropenem, biapenem, panipenem, ertapenem, faropenem, tomopenem, and ritipenem are penems that have increased stability against degradation by dehydropeptidases. Doripenem is a newer agent that appears to be most effective of the penem class in treating carbapenem-resistant gram-negative bacilli and penicillin-resistant streptococci.

Elshamy AA, Aboshanab KM. A review on bacterial resistance to carbapenems: epidemiology, detection and treatment options. *Future Sci OA*. 2020;6(3):FSO438. doi:10.2144/fsoa-2019-0098

Carbacephems Loracarbef is an oral carbacephem, a type of antibiotic that is structurally similar to cephalosporins but has a broader spectrum of activity due to higher stability against both plasmid and chromosomally mediated β-lactamases. Loracarbef provides good coverage against most gram-positive and gram-negative aerobic bacteria.

β-Lactamase inhibitors Clavulanate, sulbactam, and tazobactam are β-lactam molecules that have little intrinsic antibacterial activity but are potent inhibitors of many plasmid-mediated class A β-lactamases. Currently, 4 antibacterial combination medications consisting of a β-lactam antibiotic and a β-lactamase inhibitor are available in the United States: Augmentin (oral amoxicillin and clavulanate), Timentin (IV ticarcillin and clavulanate), Unasyn (IV ampicillin and sulbactam), and Zosyn (IV piperacillin and tazobactam). These drugs have excellent activity against β-lactamase–producing gram-positive and gram-negative bacteria as well as many anaerobes.

Glycopeptides

Vancomycin has regained popularity because of the emergence of methicillin-resistant staphylococci and the recognition that *C difficile* is a cause of pseudomembranous colitis. This drug has excellent activity against *Clostridioides* and most gram-positive bacteria, including methicillin-resistant staphylococci, *Corynebacterium* species, and other diphtheroids. Vancomycin has been used alone to treat serious infections caused by methicillin-resistant staphylococci.

Vancomycin-resistant enterococcal infections have recently become more common. The CDC has issued recommendations regarding the appropriate use of vancomycin to help counteract the problem of bacterial drug resistance.

Teicoplanin has several advantages over vancomycin, including a longer half-life, lower nephrotoxicity, and no requirement for monitoring drug levels. Teicoplanin is effective for

treatment of staphylococcal infections, including endocarditis, bacteremia, osteomyelitis, and septic arthritis. Teicoplanin may be preferable to vancomycin for surgical prophylaxis because of its excellent tissue penetration, lower toxicity, and long half-life, allowing single-dose administration in several surgical procedures. The antibacterial activity of teicoplanin is similar to that of vancomycin but with increased potency, particularly against *Streptococcus* and *Enterococcus.* Teicoplanin is active against many vancomycin-resistant organisms, and the newer agents oritavancin and dalbavancin are also highly active against these pathogens.

Chen Z, Xiong Y, Tang Y, et al. In vitro activities of thiazolidione derivatives combined with daptomycin against clinical *Enterococcus faecium* strains. *BMC Microbiol.* 2022;22(1):16. doi:10.1186/s12866-021-02423-8

Quinolones

The introduction of fluorine into the basic quinolone nucleus of nalidixic acid has produced compounds known as *fluoroquinolones,* which have excellent activity against gram-positive bacteria. The subsequent addition of piperazine made compounds such as norfloxacin and ciprofloxacin, which have a broad spectrum of activity, encompassing staphylococci and most of the significant gram-negative bacilli, including *Pseudomonas.* Ciprofloxacin is available in oral and parenteral forms and can be used to treat urinary tract infections, gonorrhea, and diarrheal diseases, as well as respiratory, skin, and bone infections. There is good vitreous penetration of ciprofloxacin after oral and IV administration. The other FDA-approved fluoroquinolones are ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin.

The newer fluoroquinolones possess even greater activity against gram-positive and gram-negative bacteria compared with earlier generations. Either moxifloxacin or levofloxacin appears to be a good treatment choice for pneumococcal infections resistant to penicillin and macrolides. Oral quinolones are an alternative form of therapy to β-lactams and aminoglycosides and have allowed physicians to treat more patients outside the hospital setting. Reported adverse effects of fluoroquinolones include tendon rupture (especially in older adults), retinal detachment, cardiac arrhythmias, aortic ruptures or tears, mental health effects (eg, disorientation, agitation), and peripheral neuropathy. Of the quinolones, moxifloxacin carries the highest risk of dysglycemia.

Gorelik E, Masarwa R, Perlman A, et al. Fluoroquinolones and cardiovascular risk: a systematic review, meta-analysis, and network meta-analysis. *Drug Saf.* 2019; 42(4):529–538.

Macrolides

The macrolide erythromycin is often used for the initial treatment of community-acquired pneumonia. This agent is effective against infections caused by pneumococci, group A streptococci, *M pneumoniae, Chlamydia,* and *Legionella.* Erythromycin is used to treat upper respiratory tract infections and sexually transmitted infections in patients allergic to penicillin.

Chemically related to erythromycin, clarithromycin and azithromycin are well-tolerated alternatives to erythromycin and may offer advantages in treating gonococcal and chlamydial infections and in treating *Mycobacterium avium* and other recalcitrant infections associated with AIDS and HIV infection. Clarithromycin and ethambutol are used to treat *M avium* complex (MAC) in HIV-infected patients; prophylactic therapy with azithromycin,

clarithromycin, rifabutin, or combined therapy may help prevent disseminated MAC in patients with AIDS. Azithromycin, a member of the *azalide* subclass, causes far fewer drug interactions than erythromycin. Of note, there is increasing cross-resistance among the macrolides.

Clindamycin has a gram-positive spectrum similar to that of erythromycin and is also active against most anaerobes, including *Bacteroides fragilis.* Aside from treating anaerobic infection, clindamycin is rarely the drug of choice, although it is well absorbed orally, and parenteral formulations are available. Its major adverse effect is diarrhea, which may progress to pseudomembranous enterocolitis in some patients. Macrolides, especially azithromycin, can increase the risk of cardiac arrhythmias.

Bella AL, Einterz E, Huguet P, Bensaid P, Amza A, Renault D. Effectiveness and safety of azithromycin 1.5% eye drops for mass treatment of active trachoma in a highly endemic district in Cameroon. *BMJ Open Ophthalmol.* 2020;5(1):e000531. doi:10.1136/bmjophth-2020-000531

Aminoglycosides

Aminoglycoside antibiotics inhibit protein synthesis by binding to bacterial ribosomes. Gentamicin, tobramycin, amikacin, kanamycin, streptomycin, and netilmicin have similar activity, pharmacokinetics, and toxicity. Because of poor gastrointestinal absorption, parenteral administration is necessary to produce therapeutic levels.

Aminoglycosides are used to treat serious infections caused by gram-negative bacilli. They do not cross the blood–brain barrier. Aminoglycosides are not used for most gram-positive infections because the β-lactams are less toxic.

The major adverse effects of aminoglycosides are nephrotoxicity and ototoxicity. Therefore, blood urea nitrogen, creatinine, and aminoglycoside peak and trough serum levels should be monitored, especially in patients with known renal disease. Combined administration of a loop diuretic such as furosemide with aminoglycosides has a synergistic ototoxic effect, potentially leading to permanent loss of cochlear function. Penicillins may decrease the antimicrobial effectiveness of parenteral aminoglycosides, particularly in patients with impaired renal function.

Sartini S, Permana AD, Mitra S, et al. Current state and promising opportunities on pharmaceutical approaches in the treatment of polymicrobial diseases. *Pathogens.* 2021;10(2):245. doi:10.3390/pathogens10020245

Tetracyclines

The tetracyclines are bacteriostatic agents that reversibly inhibit ribosomal protein synthesis. Although they are active against a wide range of organisms (including *Staphylococcus, Rickettsia, Chlamydia, Nocardia,* and *Actinomyces*), resistance is widespread, especially among *S aureus* and gram-negative bacilli. The principal clinical uses of tetracyclines are in treating nongonococcal urethritis, Rocky Mountain spotted fever, chronic bronchitis, and sebaceous disorders such as acne rosacea. In addition, tetracyclines are an alternative for the penicillin-allergic patient with syphilis. Tetracyclines are well absorbed when taken on an empty stomach; however, their absorption is decreased when taken with milk, antacids, calcium, or iron. Tetracyclines are distributed throughout the extracellular fluid, but CSF penetration is

unreliable. Adverse effects include oral or vaginal candidiasis with prolonged use, gastrointestinal upset, photosensitivity, elevation of the blood urea nitrogen level, and idiopathic intracranial hypertension. Tetracyclines can prolong the international normalized ratio (INR) in patients taking warfarin, and they should not be administered to women who are pregnant or to children younger than 10 years because of the potential harm to developing bone and teeth.

The *glycylcyclines,* third-generation tetracycline analogues, exhibit activity against organisms resistant to other tetracyclines, mediated by either antibiotic efflux or ribosomal protection. Thus, they represent a considerable advance within this group of antibiotics. One of the glycylcyclines, 9-t-butylglycylamido-minocycline (GAR-936, tigecycline), is currently in clinical trials.

Rusu A, Buta EL. The development of third-generation tetracycline antibiotics and new perspectives. *Pharmaceutics.* 2021;13(12):2085. doi:10.3390/pharmaceutics13122085

Miscellaneous antibacterial agents

Originally developed as an anti-TB agent, rifampin is also used to treat several intractable bacterial infections. The drug is administered orally and is usually used adjunctively because bacteria develop resistance to rifampin when it is employed as a single agent. Rifampin is effective in eradicating the carrier state of nasal *S aureus.* It is also effective prophylactically against *N meningitidis* and may be useful for treating oropharyngeal carriers of Hib.

Another oral antibiotic with the potential for treating deep-seated infections is TMP-SMX. After a single oral dose, the mean serum levels of TMP-SMX are approximately 75% of the concentration that would be achieved via IV administration. In addition to its excellent pharmacokinetics, TMP-SMX has an extremely broad spectrum of activity, including effectiveness against Enterobacteriaceae and some organisms resistant to cephalosporins. Most streptococci, staphylococci, and *Listeria monocytogenes* are susceptible to it. Beyond the broad-spectrum effect of TMP-SMX, the concomitant use of metronidazole creates an antibiotic combination with activity against microorganisms that surpasses that of a third-generation cephalosporin. TMP-SMX is also used in the treatment of and as prophylaxis for *Pneumocystis* infection and toxoplasmosis.

Chloramphenicol is a bacteriostatic agent that reversibly inhibits ribosomal protein synthesis. This drug is active against a wide variety of gram-negative and gram-positive organisms, including anaerobes. The primary concern with this agent is hematopoietic toxicity, including reversible bone marrow suppression and irreversible aplasia. Aplastic anemia is an idiosyncratic late reaction to the drug and is usually fatal. Other adverse effects include hemolysis, allergy, and peripheral neuritis.

Future directions in antibacterials

The WHO recently released a list that prioritizes antibiotic-resistant pathogens in order to guide research and development of new antimicrobial agents. The WHO's review determined that the antibiotics currently under development are insufficient to mitigate the threat of antibiotic resistance.

The WHO ranked *M tuberculosis* as the highest global priority for research and development. The critical priority pathogens are carbapenem-resistant *Acinetobacter baumannii, P aeruginosa,* and Enterobacteriaceae. The high-priority pathogens include *Enterococcus*

faecium, S aureus, Helicobacter pylori, Campylobacter, Salmonella, and *Neisseria gonorrhoeae.* Medium priority has been assigned *to S pneumoniae, H influenzae,* and *Shigella. C difficile* was not listed as a priority pathogen because the infection is addressed with infection prevention, control, and stewardship measures.

Newer antibiotics have been developed that provide expanded antimicrobial coverage over earlier antibiotics and offer treatment options for multidrug-resistant infections. These include ansamycin, ceftaroline, ceftobiprole, daptomycin, delafloxacin, linezolid, teicoplanin, telithromycin, tedizolid, telavancin, tigecycline, and quinupristin/dalfopristin.

In addition, pharmacologic research has led to the development of entirely new classes of antibiotics (eg, teixobactin) that offer additional treatment options for emerging resistant bacterial strains. Most of these newer drugs are targeted against resistant strains of gram-positive bacteria. Nonetheless, the antibacterial clinical development pipeline is still insufficient to surmount the challenge of increasing emergence and spread of antimicrobial resistance. Innovation is now driven largely by small- or medium-sized enterprises, as large pharmaceutical companies continue to move away from development of antibacterial agents. For example, one new anti-TB agent, pretomanid, was developed by a not-for-profit organization. Since 2017, 8 new antibacterial agents have been approved by the FDA; however, they have limited clinical benefits. Currently in the clinical antibacterial pipeline are 50 antibiotics and combinations (with a new therapeutic entity), and 10 biologics, of which 32 antibiotics are active against the WHO priority pathogens: only 2 of these are active against the critical multidrug-resistant gram-negative bacteria. The anti-TB and *C difficile* antibacterial agents in the pipeline are more innovative than the agents in development for use against the WHO priority pathogens, but more progress is needed in developing drugs that target metallo-β-lactamase–producing pathogens.

World Health Organization. *2019 Antibacterial Agents in Clinical Development: An Analysis of the Antibacterial Clinical Development Pipeline.* World Health Organization; 2019. Accessed November 29, 2022. https://www.who.int/publications/i/item/9789240000193

Antifungal Agents

Imidazoles and *triazoles* act by damaging fungal cell membranes through cytochrome P-450–dependent enzymes. The triazoles (eg, fluconazole, itraconazole) offer a less-toxic alternative to amphotericin B for the treatment of cryptococcal meningitis and other invasive fungal diseases. They may also play a role in the long-term suppression of *Cryptococcus* after remission of acute infection in severely immunocompromised patients. Ketoconazole, an imidazole derivative, is often less effective than the newer triazoles such as posaconazole and carries a higher risk of hepatotoxicity. The second-generation triazole voriconazole, which is available in IV and oral formulations, offers a better treatment option for invasive aspergillosis and other serious fungal infections. For more on antifungal agents, see Table 15-3.

Treatment of serious, deep-seated systemic fungal infections may require IV amphotericin B, sometimes in combination with either flucytosine or a triazole. Lipid complex and liposome-encapsulated formulations of amphotericin B are available to reduce the drug's toxicity. Nystatin, which is structurally similar to amphotericin B, is an antifungal agent administered topically, vaginally, or by mouth. Terbinafine, an allylamine oral antifungal agent,

Table 15-3 Antifungal Agents[a]

Class	Agents	Mechanism of Action	Spectrum
Allylamines	Naftifine, terbinafine	Damage cell membranes by inhibiting squalene epoxidase	Treatment of opportunistic infections in AIDS
Benzylamine	Butenafine	Blocks sterol biosynthesis	Topical antifungal
Echinocandins	Anidulafungin, caspofungin, micafungin	Damage cell wall by inhibiting the synthesis of 1,3-β-D-glucan	Excellent against yeast, broad spectrum against molds
Fluorinated pyrimidine analogue	Flucytosine	Inhibits fungal RNA and DNA synthesis	Use only in combination with other agents; relatively weak, rapid resistance
Imidazole	Ketoconazole	Damages cell membranes through cytochrome P-450–dependent enzymes	Fair against yeast, other azoles are generally more effective
Polyenes	Amphotericin B, natamycin (also called *pimaricin*), nystatin	Bind to sterols and disrupt cell walls	Better against yeasts than molds; amphotericin B safer systemically in a lipid formulation
Thiocarbamate	Tolnaftate	Blocks sterol biosynthesis	Topical antifungal
Triazoles	Fluconazole, isavuconazole, itraconazole, posaconazole, voriconazole	Similar to imidazoles	Fluconazole mostly effective against yeast; the others are broad spectrum

and butenafine, a benzylamine, are effective in controlling onychomycosis due to chronic dermatophyte infections.

Murphy SE, Bicanic T. Drug resistance and novel therapeutic approaches in invasive candidiasis. *Front Cell Infect Microbiol.* 2021;11:759408. doi:10.3389/fcimb.2021.759408

Antiviral Agents

Acyclovir is a nucleoside analogue that has selective antiviral activity. It inhibits viral DNA polymerase and replication of viral DNA. Acyclovir is active against most species of human herpesviruses, especially HSV-1, HSV-2, and VZV. One step in the phosphorylation of acyclovir is catalyzed by the enzyme thymidine kinase. Virus-induced thymidine kinase, for which acyclovir has an affinity, is far more active than host cell thymidine kinase. Because of acyclovir's affinity for a specific type of viral kinase, the agent enters only the virus-infected cells and is very active against virus within them. Acyclovir is generally well tolerated.

Acyclovir has proved effective in treating a variety of herpetic infections. Oral acyclovir effectively treats acute severe genital herpes and can be used for long-term suppression in immunocompetent patients with frequently recurring genital herpes. IV acyclovir is effective against herpes simplex encephalitis. Acyclovir in doses of 500 mg/m^2 every 8 hours has been used successfully in treating herpes zoster infections in immunocompromised patients.

Oral acyclovir may be used to treat herpes zoster ophthalmicus. Doses of 800 mg 5 times daily are usually effective in reducing the incidence of ocular complications of herpes zoster ophthalmicus. However, postherpetic neuralgia is not affected by this therapy. A randomized controlled study of acyclovir and oral corticosteroids demonstrated that the latter did not help to reduce the incidence of postherpetic neuralgia when added to oral acyclovir.

Famciclovir and valacyclovir are approved in the United States for the treatment of herpes zoster and herpes simplex infections, and studies have shown that they are effective against the latter. These newer drugs allow less frequent dosing intervals (every 8–12 hours, depending on the indication). Valganciclovir is used for the prevention and treatment of CMV infections in patients who have undergone organ transplantation or who have AIDS, and it has also been found to be effective in treating acute retinal necrosis caused by VZV.

Adefovir is a nucleoside analogue and a potent inhibitor of many viruses, such as HIV, HSV, hepatitis B, HPV, and EBV. The nucleoside analogue brivudine appears to have a more potent antiviral effect against VZV than does acyclovir or penciclovir. The efficacy of brivudine has been documented in several clinical trials in patients with herpesvirus-related infections, particularly herpes zoster and herpes simplex infections.

Ganciclovir, foscarnet, and cidofovir are additional antiviral agents used for treating CMV infections, including retinitis. The M2 protein inhibitors amantadine and rimantadine were used previously to treat influenza but are no longer recommended due to widespread resistance. Oseltamivir, peramivir, and zanamivir are oral neuraminidase inhibitors used to treat and prevent influenza.

Chow EJ, Beigi RH, Riley LE, Uyeki TM. Clinical effectiveness and safety of antivirals for influenza in pregnancy. *Open Forum Infect Dis.* 2021;8(6):ofab138. doi:10.1093/ofid/ofab138

Seley-Radtke KL, Thames JE, Waters CD 3rd. Broad spectrum antiviral nucleosides—our best hope for the future. *Annu Rep Med Chem*. 2021;57:109–132.

CHAPTER 16

Perioperative Management in Ocular Surgery

This chapter includes related videos. Go to www.aao.org/bcscvideo_section01 or scan the QR codes in the text to access this content.

Highlights

- Idarucizumab has been approved for reversal of the direct thrombin inhibitor dabigatran during emergency surgery.
- Perioperative prophylaxis with β-blockers in noncardiac surgery decreases the risk of acute myocardial infarction but may increase 30-day mortality rates and stroke risk.
- Malignant hyperthermia is a potentially lethal complication of anesthesia. Increased awareness of this complication, as well as rapid intraoperative recognition and treatment with dantrolene, has decreased patient mortality to less than 5%. A 24-hour hotline is available for expert medical advice and evaluation.

Introduction

Although morbidity and mortality rates associated with ocular surgery are generally considered to be low, the perioperative management of ophthalmic surgery patients can be challenging. Often, these patients are older and have numerous medical conditions. In addition, the ophthalmic condition requiring surgery is sometimes directly related to an underlying systemic disease, such as diabetes or thyroid disease. Finally, some delicate surgical procedures may have specific requirements about the patient's level of alertness during the procedure; thus, monitoring the level of sedation is particularly important for those patients. This chapter discusses some of the key issues to consider in the preoperative medical assessment and intraoperative management of the ocular surgery patient.

Preoperative Assessment

A complete history and physical examination are essential in the preoperative assessment of all patients. Determining a patient's perioperative risk status involves identifying any high-risk conditions and symptoms that may necessitate additional testing as well as

specific consultation and management prior to elective ophthalmic surgery. Preoperative risk determination may also influence the decision whether to perform the surgery in an ambulatory surgery center or a hospital outpatient setting.

The American Society of Anesthesiologists Physical Status (ASA-PS) classification system defines a patient's overall health status prior to surgery; a higher ASA class (ASA III or higher) is associated with increased risk of complications, increased costs, unexpected hospital admission, and increased mortality, even after a low-risk surgery. These levels include the following:

- ASA I: a healthy adult, no obesity or chronic disease
- ASA II: mild systemic disease without substantial functional limitations (eg, smoking, body mass index [BMI] 30–40, well-controlled hypertension, diabetes, lung disease)
- ASA III: severe systemic disease with functional limitations (eg, poorly controlled diabetes, hypertension, chronic obstructive pulmonary disease, atherosclerotic disease)
- ASA IV: severe systemic disease, constant threat to life (eg, recent myocardial infarction or stroke, sepsis, end-stage renal disease not receiving dialysis)
- ASA V: patient not expected to survive without surgical intervention (eg, severe trauma, ruptured aneurysm, intracranial bleed)

Further information on the ASA classification system is available at www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system.

Preoperative testing, including electrocardiography and routine blood testing, is not necessary before ophthalmic surgery in a healthy patient or an asymptomatic stable patient. Preoperative testing is performed only when indicated; that is, the tests would have been done even if surgery was not planned. Multiple clinical trials have failed to show a difference in perioperative adverse events in healthy patients undergoing elective eye surgery. The American Academy of Ophthalmology (AAO) advisory opinion on the responsibilities of the ophthalmologist, Appropriate Examination and Treatment Procedures, provides general guidance on determining the appropriateness and necessity of diagnostic procedures and perioperative treatment. Although ophthalmologists may delegate the acquisition of the data required for the preoperative history and the physical examination, the surgical planning and synthesis of information prior to surgery must be done by the operating ophthalmologist.

Avoiding surgical complications begins with the decision to operate. The risks and benefits of surgery, as well as any alternatives to it, are considered before the surgical plan is devised. Typically, the patient is involved in this process; informed consent is contingent on the patient's (or legal guardian's) receipt of a detailed, understandable explanation of the surgical plan. Open communication between the surgeon and the patient enhances patient education and ensures realistic expectations regarding the anesthesia depth, surgical procedure, anticipated recovery, and expected outcomes. If a patient is judged to have some level of cognitive impairment, an assessment should be made to evaluate the capacity of the patient to understand the treatment options and thereby provide informed consent. Multiple instruments are available to assess cognitive capacity. If the patient's level of cognitive impairment renders them unfit to provide consent, informed consent may be obtained from a legal proxy *(power of attorney)* designated to make treatment decisions for the patient. See Chapter 12 for more on informed consent in patients with neurologic or behavioral disorders.

A careful review of medication allergies, reactions to previous anesthetics, or family history of a reaction to anesthesia or muscle relaxants is critical in identifying patients at risk for malignant hyperthermia (see the section Malignant Hyperthermia later in this chapter). For a patient with an implantable cardioverter-defibrillator, the ophthalmologist and the patient's cardiologist should discuss the status and possible perioperative disabling of the device before ocular surgery to avoid surgical complications, including possible electromagnetic interference with the pacemaker.

Advanced or severe neurologic and psychiatric conditions and associated behavioral disturbances need to be considered as part of a holistic preoperative assessment. The expected functional gains from a procedure need to be clearly identified prospectively and weighed against the potential for postoperative conditions such as delirium and other confused states that could increase the risk of harm to self or others. As most procedures require some level of medical monitoring, postoperative care instructions, and new medications, a patient and/or caregivers must be able to adhere to these in order to safely proceed.

The operating physician typically provides postoperative eye care. Any transfer of management should be discussed and approved, ideally before surgery, by the referring physician, the physician assuming future care, and the patient. See Chapter 11 for a discussion of perioperative management in older adult patients.

American Academy of Ophthalmology. Advisory Opinion of the Code of Ethics. Appropriate Examination and Treatment Procedures. Revised December 16, 2021. Accessed September 5, 2022. www.aao.org/ethics-detail/advisory-opinion-appropriate-examination-treatment-2

American Academy of Ophthalmology. Advisory Opinion of the Code of Ethics. Pertinent Principles and Rules of the Code of Ethics Related to Delegation and Comanagement. March 10, 2022. Accessed September 5, 2022. www.aao.org/education/ethics-detail/code-of-ethics--delegation-comanagement

Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on Non-Cardiac Surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anesthesiology (ESA). *Eur Heart J.* 2014;35(35):2383–2431.

Children and Adolescents

If surgery is planned on a child who is healthy and does not routinely take prescribed medications, no laboratory tests are necessary, even when general anesthesia is to be used. There is no evidence that abnormalities in a complete blood count affect the choice of anesthetic management for asymptomatic children. However, African American patients should be screened for sickle cell disease or trait if they have not previously been tested because some aspects of anesthetic management will change in patients with hemoglobinopathy. Routine pregnancy testing of female patients of childbearing age, prior to anesthesia, is a complex issue that may be even more complex in minors because individual states may have statutes concerning parental notification of test results. Consent is required for a pregnancy test.

The decision whether to perform elective eye surgery in a child with an upper respiratory tract infection requires judgment and should be made after careful consideration of the patient's overall health status. A child who is already ill will likely feel even worse after surgery, and the significance of a postoperative fever may be difficult to interpret. However,

in the absence of high fever or findings that suggest a lower respiratory tract infection, many anesthesiologists elect to proceed if the child appears well except for a runny nose.

Exposure to anesthesia during vulnerable periods of development may cause impairments in learning, psychomotor speed, concept formation, and motivation. Although brief exposure to general anesthesia in children younger than 3 years does not adversely affect brain development, modest neurodevelopmental impairments may occur as a result of prolonged or repeated anesthesia. The risks and benefits of, and alternatives to, general anesthesia should be carefully considered and discussed with the patient's parents.

Vutskits L, Culley DJ. GAS, PANDA, and MASK: no evidence of clinical anesthetic neurotoxicity! *Anesthesiology.* 2019;131(4):762–764.

Management of Medical Conditions Associated With Increased Perioperative Risk

Cardiovascular Disease

Heart failure is one of the most common conditions requiring evaluation and treatment before noncardiac surgery. In stable asymptomatic patients undergoing low-risk surgery, preoperative assessment with electrocardiography, echocardiography, stress testing, chest radiography, and cardiac catheterization is not necessary. Functional status is a reliable predictor of perioperative cardiac events; it can be assessed with a questionnaire such as the Duke Activity Status Index. If results from a recent stress test are not available, patients with good functional status are generally at low risk for a cardiac event in the perioperative period. However, if the patient shows clinical signs of decompensation, appropriate evaluation and management are indicated prior to surgery.

Coronary heart disease is a risk factor for perioperative myocardial ischemia, infarction, and death. However, even patients with significant coronary heart disease have a low risk of a major adverse cardiac event when they undergo low-risk procedures such as ophthalmic surgery. The goal of perioperative management of these patients is to minimize the risk of ischemic complications. Patients who have undergone percutaneous coronary intervention require treatment with dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (eg, clopidogrel) to prevent a recurrence of occlusion of the stented artery. See Chapter 6 for further discussion of heart disease.

Although severe hypertension is associated with an increased risk of perioperative complications, the potential benefit of lowering blood pressure (BP) in terms of risk reduction is important but unclear. Optimal BP is also unclear, but the joint guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British and Irish Hypertension Society recommend a target BP <160 mm Hg systolic and <100 mm Hg diastolic before elective surgery. The guidelines allow for patients whose prior BP in the primary care setting is unknown to undergo surgery with BP <180 mm Hg systolic and <110 mm Hg diastolic. In general, if patients are asymptomatic and have taken their BP medications, and their documented BP has typically been <160/100 mm Hg prior to the day of surgery, then elective surgery may be performed regardless of the BP measurement on the morning of surgery. See Chapter 4 for further discussion of hypertension.

Atrial fibrillation is the most common sustained cardiac arrhythmia encountered in clinical practice. Atrial fibrillation increases the risk of death, heart failure, thromboembolic events, and hospital admissions. Patients with a history of stable atrial fibrillation do not require any preoperative specialized testing, but for patients with new-onset atrial fibrillation, workup by a cardiologist may be cautious, as well as delay of elective surgery. It is advisable to maintain medications for ventricular rate control, including their administration on the morning of surgery. If digoxin is used, obtaining preoperative blood levels of the drug is usually not necessary.

Illegal drug use may increase the perioperative risk of surgery. In particular, cocaine, methamphetamine, and opioids can increase the risk of myocardial infarction and arrhythmias. Therefore, the urgency of surgery should be carefully considered in consultation with the anesthesiologist assisting with the case.

Hartle A, McCormack T, Carlisle J, et al. The measurement of adult blood pressure and management of hypertension before elective surgery: joint guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society. *Anaesthesia*. 2016;71(3):326–337.

Rusk MH. Avoiding unnecessary preoperative testing. *Med Clin North Am*. 2016;100(5): 1003–1008.

Smilowitz NR, Berger JS. Perioperative cardiovascular risk assessment and management for noncardiac surgery: a review. *JAMA*. 2020;324(3):279–290.

Diabetes

Management of blood glucose is important in avoiding central nervous system dysfunction. No single regimen is appropriate for all patients with diabetes; but in general, those who are dependent on insulin should undergo surgery early in the day whenever possible to minimize disruption of their metabolic status, and their glucose levels should be monitored postoperatively. For diet-controlled patients undergoing a brief surgical procedure, management generally involves only monitoring of the blood glucose level immediately after surgery and every 3 hours until oral intake is resumed. It is imperative to provide close perioperative monitoring of glucose and electrolyte levels.

Respiratory Diseases

Pulmonary complications after surgery are a significant cause of perioperative morbidity and mortality. This is especially true in patients undergoing major intrathoracic and intraabdominal surgery. However, ophthalmic surgery is usually performed with the patient under local and intravenous (IV) sedation, is of short duration relative to thoracic or abdominal surgery, and typically does not result in considerable pain for the patient, thus obviating the need for postoperative opioids that may increase respiratory risks. Intravenous sedation under monitored anesthesia care during eye surgery can result in hypoventilation, hypercapnia, hypoxia, and atelectasis in patients with chronic obstructive pulmonary disease (COPD). It is important for the ophthalmic surgeon to ensure that the patient's respiratory status is optimized preoperatively. If a patient's history and physical examination identify a potential comorbidity that could affect pulmonary function and increase risks associated with preoperative sedation, then obtaining a chest x-ray and/or pulmonary function tests would

be of value. Medical optimization may involve an increase in the patient's inhaler regimen, administration of antibiotics (if infection is suspected), administration of corticosteroids to reduce inflammation, and/or chest physiotherapy to manage secretions. Patients who are on long-term steroid therapy should receive their usual dose on the day of the surgery; however, "stress-dose" glucocorticoid administration is generally unnecessary before ophthalmic surgery. Occasionally, general anesthesia with a laryngeal mask airway may be beneficial, for example, in patients with COPD who have severe dyspnea and cough in a supine position, are unable to lie still, or have high anxiety.

Liver Disease

Liver disease that causes coagulopathies can increase the risk of intraoperative and postoperative bleeding. An international normalized ratio ≥1.5 significantly increases in-hospital mortality; and the risks and benefits of, and alternatives to, surgery should be carefully considered.

Perioperative Medication Management

Cardiac Medications

In general, patients who take cardiac or BP medications should continue their current medical regimen, including on the morning of surgery, to minimize the risk of rebound hypertension and ischemia. However, diuretics may be held the morning of surgery and resumed when the patient begins taking oral fluids postoperatively. Digoxin, which has a long half-life, may also be withheld the morning of surgery.

Guidelines for the use of prophylactic β-blockers in the perioperative period have been revised following the publication of the POISE-2 (Perioperative Ischemic Evaluation 2) trial and a subsequent meta-analysis of clinical trials. These studies demonstrated that although perioperative administration of β-blockers resulted in reduced incidence of acute myocardial infarction, the incidence of mortality and stroke increased in the first 30 days after surgery. The American College of Cardiology, the American Heart Association, and the European Society of Cardiology currently recommend that β-blockers be continued without interruption during the perioperative period in patients already taking them, but because of the risk of harm, prophylactic β-blocker therapy should *not* be initiated for patients undergoing low-risk surgery (eg, ophthalmic surgery).

Anticoagulant and antiplatelet agents

Whether to maintain or discontinue anticoagulant or antiplatelet agents in patients planning to undergo ocular surgery depends on a number of factors. They include the nature of surgery to be performed, the risk of ocular bleeding, the potential effect of bleeding on the outcome of the proposed surgery, and the risk of a serious or fatal thrombotic event if the anticoagulant or antiplatelet agent is discontinued.

In general, because cataract surgery is usually performed through a clear corneal approach with the use of topical anesthesia, the potential benefit of stopping anticoagulants before surgery in order to prevent ocular bleeding does not outweigh the potential risk. In a published meta-analysis of 11 clinical trials, when warfarin use was continued in patients

undergoing cataract surgery, bleeding events were minor and had no effect on vision, although there was an increased risk of ocular bleeding. Continued use of aspirin or clopidogrel before cataract surgery did not result in an increased risk of ocular bleeding events.

The success of other ocular surgeries, such as trabeculectomy or drainage implant surgery, could potentially be affected by subconjunctival and scleral bleeding, although the bleeding is generally not life-threatening. Furthermore, patients with concomitant iris neovascularization are at high risk of developing postoperative hyphema. As a result, some surgeons prefer to stop therapy with antiplatelet agents, direct anticoagulants, and warfarin prior to filtering surgeries.

Considerations for the perioperative use of some frequently encountered anticoagulants include the following:

- *Aspirin.* After aspirin therapy has been interrupted, the rate of platelet function recovery is approximately 10% per day.
- *Nonsteroidal anti-inflammatory drugs (NSAIDs).* For short-acting drugs such as ibuprofen, diclofenac, and indomethacin, 50% of platelet function is restored 6 hours after the last dose.
- *Thienopyridines (clopidogrel, prasugrel).* These drugs are typically stopped 5–7 days before surgery.
- *Nonthienopyridines (ticagrelor, cangrelor).* These drugs are typically stopped 5 days before surgery.
- *Vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon).* The half-life of warfarin is 36–42 hours, but warfarin is difficult to titrate owing to numerous pharmacologic interactions and genetic variations that can affect its metabolism.
- *Direct inhibitors of factor Xa (rivaroxaban, apixaban, edoxaban, betrixaban).* The direct oral anticoagulants (DOACs) have a short half-life and rapid onset of action, as well as a lower bleeding risk compared with vitamin K antagonists. However, the pharmacokinetic properties of each DOAC can vary depending upon the individual patient's renal and liver function.
- *Direct inhibitors of thrombin (lepirudin, desirudin, bivalirudin, and argatroban).* Although the plasma half-life is approximately 12 hours, the half-life of these drugs is strongly affected by renal function, as 80% is excreted through the kidneys.
- *Fondaparinux.* The plasma half-life of fondaparinux is approximately 15–17 hours; however, anticoagulant activity persists 2–4 days after the last dose.
- *Heparins.* Unfractionated heparin can be considered for patients with poor renal function; low-molecular-weight heparins are avoided for these patients.

The risks of discontinuing anticoagulant medications before surgery should be carefully considered and discussed with the patient's prescribing physician to avoid or minimize potential complications. The risks, benefits, and alternatives should also be discussed with the patient and documented in the consent form.

In a study evaluating the risk of stroke, transient cerebral ischemia, myocardial infarction, or deep venous thrombosis, no difference was demonstrated in the number of thrombotic events experienced by continuous users of aspirin or warfarin compared with patients who discontinued these agents before cataract surgery.

In theory, the same idea should apply to patients who discontinue use of direct anticoagulants before surgery. However, in patients who are on *dual antiplatelet therapy* (aspirin *plus* clopidogrel) after a recent coronary event or placement of a cardiac stent, the risk of thrombosis of the stented artery leading to a potentially fatal outcome after withdrawal of these agents warrants a 6-month delay of the elective ocular surgery. Surgery may be performed sooner in patients undergoing cataract surgery in whom cessation of anticoagulants is unnecessary.

Studies have demonstrated a 20% lower risk of intraocular bleeding with the DOACs during eye surgery compared with warfarin. In an urgent situation, the effects of dabigatran can be reversed with idarucizumab, and rivaroxaban and apixaban may be reversed with andexanet alfa (see Chapter 6).

Sun MT, Wood MK, Chan W, et al. Risk of bleeding with novel oral anticoagulants compared with warfarin: a systematic review and meta-analysis. *JAMA Ophthalmol.* 2017;135(8):864–870.

Diabetes Medications

Oral hypoglycemic medications are usually withheld the day of surgery. These medications have a relatively long duration of action, which could lead to hypoglycemia late in the day if the patient's oral caloric intake is inadequate. For patients with relatively well-controlled insulin-requiring diabetes and reasonable glucose control (<250 mg/dL), one option is to hold all short-acting insulin and give a portion (one-third or one-half) of the usual dose of intermediate-acting or long-acting insulin the morning of the surgery.

Pulmonary Medications

Theophylline should be held the night before surgery due to potential risk of arrhythmia. In general, commonly used pulmonary medications such as anticholinergic agents (eg, ipratropium, tiotropium), β_2-adrenergic agonists (eg, albuterol, metaproterenol, salmeterol), and leukotriene inhibitors (eg, montelukast, zafirlukast) are continued according to the patient's usual regimen. If the patient is currently taking corticosteroids, the usual dose of steroids is given on the morning of surgery, but stress-dose steroids are usually unnecessary.

Pfeifer KJ, Selzer A, Whinney CM, et al. Preoperative management of gastrointestinal and pulmonary medications: Society for Perioperative Assessment and Quality Improvement (SPAQI) consensus statement. *Mayo Clin Proc.* 2021;96(12):3158–3177.

Perioperative Considerations

Preoperative Fasting

The purpose of preoperative fasting is to reduce the amount of particulate matter in the stomach and to lower the gastric fluid volume and acidity in case aspiration of stomach contents occurs. Gastric emptying times vary depending on the type and quantity of food consumed. Clear liquids (eg, water, plain tea or black coffee, pulp-free juice, and carbohydrate drinks) empty fastest; breast milk empties in up to 4 hours; nonhuman milk by 6 hours; and large meals that include meat, protein-rich foods, or fatty substances by 8 hours after consumption.

Small meals, such as dry toast with black coffee (300 mL) and pulp-free juice, have been shown to clear within 4 hours.

Perioperative fasting protocols vary between institutions and between patients and may depend on comorbidities that influence gastric emptying and on the urgency of the surgery. For example, some institutions and anesthesiologists wait only 2 hours when performing surgery on babies fed breast milk. Patients with diabetes, particularly those with autonomic neuropathy, are at risk for gastroparesis (more than 50% of patients with long-term diabetes); therefore, these patients may have a prolonged gastric emptying time. Pregnant patients have a higher than normal risk of aspiration. Patients with known gastroesophageal reflux disease and those with peptic ulcer disease may also have an increased risk of aspiration.

Pediatric patients who fast for 10–12 hours preoperatively may become hypotensive as a result of dehydration. The use of clear liquids orally up to 1 hour before surgery does not lead to a higher incidence of aspiration or other gastrointestinal complications in the setting of general or local anesthesia and is encouraged for the pediatric population.

Oral administration of an H_2 blocker such as ranitidine or famotidine 2–4 hours before surgery reduces the percentage of patients with low gastric pH or high gastric volume. Metoclopramide reduces gastric volume and decreases reflux, which may prove useful in a nonfasting patient who requires urgent surgery; however, it is associated with an increased risk of extrapyramidal adverse effects, especially in older adult and very young patients.

Latex Allergy

According to the US Centers for Disease Control and Prevention, the prevalence of latex allergy is 1%–6% in the general population and 8%–12% among health care workers. Health care workers and hospital employees can experience progressive sensitization to latex because of repeated occupational exposure. This sensitivity is accentuated in those with a history of atopy.

Certain medical populations are also at significant risk for this allergy, for example, patients with myelodysplasia or spina bifida and those who have undergone repeated urinary catheterization or frequent surgical procedures. A cross-reactivity with bananas, avocados, mangoes, and chestnuts has been demonstrated, and allergies to these foods and others have been associated with latex allergy. A history of reactivity to balloons also suggests a latex allergy.

Patients suspected of having latex allergy should be clearly identified, and the operating room environment made latex free. Latex is an aeroallergen and can be present in the operating room air for at least 1 hour after the use of latex gloves. Thus, whenever possible, a patient who is allergic to latex should be the first case of the day. Alternatively, surgery may be performed in a latex-free surgical facility.

Parisi CAS, Kelly KJ, Ansotegui IJ, et al. Update on latex allergy: new insights into an old problem. *World Allergy Organ J.* 2021;14(8):100569. doi:10.1016/j.waojou.2021.100569

Universal Protocol

The definition of *wrong-site surgery* includes operating on the wrong site, performing the wrong procedure, or performing a procedure on the wrong person. In ophthalmology, the

definition includes operating on the wrong eye or performing the wrong procedure, including implantation of an intraocular lens (IOL) whose style and/or power differs from that chosen during preoperative surgical planning. For example, inserting a monofocal IOL during cataract surgery, when the plan was to implant a premium IOL, is considered a wrong procedure.

In 2004, the Joint Commission enacted the Universal Protocol (www.jointcommission.org/standards/universal-protocol), which was developed to eliminate wrong-site surgery in the United States. The Universal Protocol includes several key elements:

- agreeing on and documenting the procedure to be performed (typically done on the surgical consent form)
- marking the surgical site in the preoperative period (done by a designated member of the team, typically the surgeon)
- pausing immediately before starting the invasive procedure or making the incision (performing a time-out) to verify that all members of the surgical team agree that
  - this is the correct patient and correct procedure
  - the necessary equipment is present, including implants
  - the patient is correctly positioned
  - the medical information on the patient, including x-rays and other imaging studies, is for the correct patient
  - appropriate preoperative antibiotics, if indicated, have been given

To reduce potential errors, including performing surgery on the wrong patient, 2 unique patient identifiers are required to be confirmed by the surgical team before the initiation of surgery. These identifiers, used during the time-out, include name, date of birth, and medical record number. For the time-out to be effective, it is important that all members of the surgical team feel empowered to speak up and invoke a hard stop if they do not agree that every element of the Universal Protocol has been satisfied. Wrong-site surgery is considered a sentinel event and, in many states, must be reported to the state board of medicine.

The AAO has a wrong-site, wrong-IOL checklist that surgeons may find useful in ensuring that all of the necessary steps are followed for each patient before cataract surgery to eliminate the risk of wrong-site surgery or wrong-IOL implantation. This type of checklist can be adapted or modified for any other type of surgery.

AAO Wrong-Site Task Force, Hoskins Center for Quality Eye Care. Patient Safety Statements. Recommendations of American Academy of Ophthalmology Wrong-Site Task Force—2014. Accessed September 5, 2022. https://www.aao.org/education/patient-safety-statement/recommendations-of-american-academy-ophthalmology-

Intraoperative Considerations

Systemic Anesthetic Agents

The use of *balanced general anesthesia,* in which small amounts of several different types of medications and IV and/or inhalational anesthetic are titrated to avoid the adverse effects of a large dose of any one type, has been effective in reducing delayed awakening and a lengthy

recovery period after anesthesia. The use of short-acting neuromuscular blocking agents administered with an infusion pump allows the anesthesiologist to fine-tune the degree of neuromuscular blockade during balanced anesthesia.

The shorter-acting narcotics such as sufentanil have potencies up to 1000 times those of morphine. These agents help provide short-term stability of hemodynamics during intensive stimulation without prolonged excessive postoperative sedation, as seen with fentanyl.

Management of postoperative nausea and vomiting after general anesthesia has become easier with the use of more powerful antinausea medications such as ondansetron. Postoperative pain can be prophylactically treated during the procedure with a dose of IV ketorolac in the range of 30–60 mg or with small, titrated doses of IV fentanyl in the range of 25–100 μg. Because of its analgesic and opioid-sparing qualities, there is evidence that IV ketorolac can also reduce the amount of postoperative nausea and vomiting in patients who have undergone strabismus surgery or other procedures requiring general anesthesia. There is no evidence that this particular NSAID increases postoperative bleeding after ophthalmic surgery. However, because of the reported gastrointestinal complications of higher doses of ketorolac, patients older than 60 years should receive a total of no more than 30 mg of IV ketorolac.

Sedation is an important part of comfortable regional or general anesthesia in a patient undergoing elective surgery (Table 16-1). Anxiolytics such as midazolam can be given intramuscularly (1–4 mg) 30–60 minutes before the procedure or intravenously (0.5–2.0 mg) 2–3 minutes before the stimulus of the anesthetic block. Midazolam is a more appropriate sedative than diazepam for outpatient surgery because its elimination half-life is 1.5–2.5 hours, whereas diazepam's half-life is 30–56 hours. The effects of midazolam can also be reversed with flumazenil. Careful IV titration of sedatives and narcotics is important in older patients to avoid oversedation or respiratory depression.

Alfentanil can be given intravenously in titrated doses with appropriate anesthesia monitoring. Its peak effect occurs in 1–2 minutes, and it lasts 10–20 minutes. Fentanyl citrate, which has a peak effect in 3–5 minutes and lasts approximately 30 minutes, is also

Table 16-1 Oral Benzodiazepine Use in Office Procedures

Benzodiazepine	Oral Dose	Initial Parenteral Dose	Onset (minutes)	Half-life (hours)
Alprazolam	0.5 mg	NA	15–30 PO	12
Diazepam	2–10 mg	0.03–0.1 mg/kg (2–10 mg/dose)	15 PO, 2–3 IV	30–56
Lorazepam	1–2 mg	0.02–0.04 mg/kg (1–4 mg/dose)	15 PO, 10–15 IV	15
Midazolam	NA	IV: 0.01–0.02 mg/kg (0.5–2.0 mg/dose); IM: 1–4 mg	1–3 IV, 30–60 IM	1.5–2.5
Oxazepam	15–30 mg	NA	60–120 PO	8
Temazepam	15–30 mg	NA	30–60 PO	11

IM = intramuscular; IV = intravenous; NA = not applicable; PO = per os (by mouth).

Modified from Acute Procedural Anxiety in Adults. TIME OF CARE: Online Medicine Notebook. Accessed October 12, 2022. https://www.timeofcare.com/acute-procedural-anxiety-in-adults/

given in titrated doses during regional or topical anesthesia. These agents are used for sedation as well as for their analgesic properties. Naloxone, an IV antagonist drug, can reverse the effects of narcotics.

Thiopental sodium, a barbiturate used for rapid sequence induction, is no longer available in the United States. Propofol is the drug of choice for inducing anesthesia in most patients due to its rapid hypnotic and antiemetic effect, rapid clearance, and fast recovery properties. It is advisable to inject propofol into a large vein or after a lidocaine flush to avoid significant burning on administration. Propofol is a lipid-based medication that supports rapid bacterial growth at room temperature. Extrinsically contaminated propofol has been associated with postoperative infections, including endogenous endophthalmitis. It is therefore imperative that hospital personnel involved in the preparation, handling, and administration of this drug adhere to strict aseptic technique during its use and discard any unused portion after 6 hours.

Local Anesthetic Agents

Local anesthetic injection into the retrobulbar space can lead to perforation of the ocular globe, retrobulbar hemorrhage, apnea, respiratory arrest, seizure, and cranial nerve palsies on the injected side, or even on the opposite side. Anatomical studies of the position of the retrobulbar needle in relation to the optic nerve during injection show that it is possible to inject anesthetic into the subdural space with a standard Atkinson-type needle. Cases of cranial nerve palsies associated with respiratory difficulties represent actual brainstem anesthesia from injection of the anesthetic agent into the subdural space, with subsequent diffusion into the circulating cerebrospinal fluid.

Several suggestions have been made to avoid such complications, including changing the traditional positioning of the eye during the retrobulbar anesthetic injection so that the nerve is rotated away from the track of the needle (ie, having the patient look straight ahead, rather than up). Using a blunt, disposable retrobulbar needle <1¼ inches long also reduces the chance of perforating the optic nerve sheath. Although 1 case series implicated the concentration of anesthetic as the cause of respiratory arrest, it is more likely that a larger volume and, therefore, a larger total dose of anesthetic was delivered to the brainstem through an inadvertent subdural injection. If apnea, respiratory arrest, or cranial neuropathies occur after a retrobulbar injection, the patient's airway must be secured and assisted ventilation provided, if necessary. Apnea seldom lasts more than 30–50 minutes, but it is important that experienced medical personnel stabilize the patient's condition during this time. The peribulbar technique was devised, in part, to avoid such complications. See Videos 16-1 and 16-2.

VIDEO 16-1 Retrobulbar injection: technique and tips.
Courtesy of Julian D. Perry, MD; Alexander D. Blandford, MD; Joseph D. Boss, MD; and Rishi P. Singh, MD.

VIDEO 16-2 Modified sub-Tenon block.
Courtesy of John R. Chancellor, MD, and Ahmed A. Sallam, MBBCh.

Respiratory distress and dysphagia can result from the Nadbath facial nerve block, an injection into the stylomastoid foramen that is used to provide facial akinesia. These complications occur when the anesthetic agent is injected deeply into the area of the facial nerve as it exits the stylomastoid foramen, and the anesthetic bathes cranial nerves IX, X, and XI as they exit the jugular foramen, leading to paralysis of these nerves. The patient becomes dysphagic, begins to cough or has a hoarse voice, and may develop stridor or severe respiratory insufficiency. These complications tend to occur in thin persons, in whom it is easier to bury the needle deeply. Managing the respiratory distress requires suctioning the pharynx, positioning the patient on his or her side, and supplementing the patient's inspired gases with oxygen or even intubation. This complication can be avoided by using a short hypodermic needle, advancing it only partway into the area to be injected, and injecting a small volume (<3 mL).

Anesthetic toxicity can occur when high concentrations of anesthetic agent are given. For example, if lidocaine, 4% is used for a peribulbar injection, the total volume that can be safely given to a 154-lb (70-kg) patient is limited to 8 mL. A smaller patient would be able to tolerate no more than 5 mL of lidocaine, 4% without risking complications of systemic toxicity, including confusion, cardiac arrhythmias, and respiratory depression.

Seizures have occurred from the intra-arterial injection of local anesthetic agent into the ophthalmic artery. Such seizures are nearly instantaneous with injection; supportive measures should include airway maintenance and BP support. The seizures are of short duration.

Given the current opioid addiction crisis, all physicians who prescribe medications to relieve postoperative pain should be aware of and carefully consider the risks of and alternatives to opioid medications, particularly for long-term pain control.

Malignant Hyperthermia

Malignant hyperthermia (MH) susceptibility is a complex genetic disorder characterized by hypermetabolic activity leading to crisis following skeletal muscle exposure to a triggering agent. The triggering agent leads to a sharp increase in unbound intracellular calcium from the sarcoplasmic reticulum, stimulating sustained muscle contracture. When the oxygen supply to the muscle is depleted, anaerobic metabolism shift develops, resulting in lactic metabolic acidosis. Finally, after all energy stores are depleted, rhabdomyolysis occurs, resulting in hyperkalemia and myoglobinuria, the latter of which causes acute renal failure. Hyperthermia results from the increased metabolic state and persistent muscle rigidity.

The earliest signs of MH include tachycardia and elevated respiratory end-tidal carbon dioxide level. Labile BP, tachypnea, sweating, muscle rigidity, blotchy discoloration of skin, cyanosis, and dark urine all signal progression of the disorder. Elevation of temperature, which can reach extremely high levels, is a relatively late sign. Ultimately, respiratory and metabolic acidosis, hyperkalemia, hypercalcemia, elevated creatine kinase myoglobinuria, and renal failure can occur, as can disseminated intravascular coagulation and death.

Genetics, risk factors, and triggering agents

Malignant hyperthermia susceptibility is usually inherited as an autosomal dominant trait; a smaller, though unknown, proportion of cases results from a de novo pathogenic variant. According to the Malignant Hyperthermia Association of the United States (MHAUS;

www.mhaus.org), the prevalence of genetic variants predisposing to MH is 1 in 2000 individuals, but the actual number of cases is far lower because of variable expressivity and penetrance. The affected genes are those that code for proteins involving the calcium channel in the sarcoplasmic reticulum.

In addition to known familial susceptibility, diagnosis of certain muscle disorders raises suspicion for MH susceptibility, especially those disorders associated with ryanodine receptor mutations. Conditions formerly associated with MH that are no longer thought to confer a greater risk include Noonan syndrome, osteogenesis imperfecta, and myotonias. The preoperative history can also help determine whether a patient is at risk for MH. However, a negative history *does not* rule out MH susceptibility: nearly 50% of patients who develop MH have had 1 or 2 prior uneventful exposures to a triggering agent. Patients with a history of unexpected exertional or heat-induced rhabdomyolysis, as well as those with a history of severe statin-induced myopathy, are at increased risk for MH.

Triggering agents for MH include volatile halogenated inhalational anesthetics such as halothane, sevoflurane, isoflurane, desflurane, and enflurane, as well as a depolarizing muscle relaxant, succinylcholine.

Susceptibility testing

Patients determined to be at high risk for MH may require a muscle biopsy for muscle contracture evaluation (caffeine halothane contracture test) or genetic testing. A negative contracture test essentially rules out MH susceptibility. However, the false-positive rate is 20%, and a positive contracture test should be followed by genetic analysis. Even if no DNA variation or a DNA variation of undetermined significance is found, however, this does not definitively rule out MH susceptibility. Treatment is indicated based on the preoperative clinical impression.

Litman RS, Griggs SM, Dowling JJ, Riazi S. Malignant hyperthermia susceptibility and related diseases. *Anesthesiology.* 2018;128(1):159–167.

Prevention and treatment

Patients who are deemed susceptible to MH can be anesthetized safely with nontriggering agents. The anesthesia machine should be cleaned of any traces of volatile anesthetics and activated charcoal filters added to the ends of both the inspiratory and the expiratory portions of the anesthesia machine breathing circuit. Safe, nontriggering agents include all IV anesthetics and sedative agents (eg, propofol, ketamine, and barbiturates), all local anesthetics (eg, lidocaine, bupivacaine, and ropivacaine), nondepolarizing muscle blockers (vecuronium and rocuronium), analgesics (fentanyl, morphine, and hydromorphone), and anxiolytics (eg, midazolam). Prophylactic use of dantrolene is not recommended.

When MH occurs, it is treated as a medical emergency. Before dantrolene became available in the late 1970s, mortality was as high as 70%–80%; now, the rate is less than 5%. MHAUS staffs a 24-hour hotline to advise medical personnel on the diagnosis and treatment of MH: 800-644-9737 (within North America) or 001-209-417-3722 elsewhere.

Hopkins PM, Girard T, Dalay S, et al. Malignant hyperthermia 2020: guideline from the Association of Anaesthetists. *Anaesthesia.* 2021;76(5):655–664.

Prevention of Intraoperative Fire

Fire is often described as requiring 3 components: an oxidizer, an ignition source, and a fuel. Whenever these 3 items are in close contact in the appropriate conditions and proportions, a fire will occur. The key to prevention is altering 1 or more of these components so that combustion is not possible. Fire risk reduction strategies include the following:

- Avoid open oxygen delivery during procedures on the head and face.
- Limit supplemental oxygen use during procedures on the head and face.
- Include a preoperative time-out to assess fire risk potential.
- Utilize bipolar cautery rather than unipolar cautery.

Hart SR, Yajnik A, Ashford J, Springer R, Harvey S. Operating room fire safety. *Ochsner J.* 2011;11(1):37–42.

CHAPTER 17

Medical Emergencies and Adverse Effects of Ophthalmic and Systemic Medications

This chapter includes related videos. Go to www.aao.org/bcscvideo_section01 or scan the QR codes in the text to access this content.

Highlights

- In 2015, guidelines for cardiopulmonary resuscitation (CPR) changed; the emphasis switched to chest compressions and the immediate use of an automated external defibrillator.
- The availability of portable defibrillators in public places increases the probability of survival for patients with out-of-hospital ventricular fibrillation.
- When no breathing device is available, compression-only CPR can be performed. This method can be lifesaving and is preferable to no CPR.
- Persons with suspected ischemic stroke should be transported to a facility capable of initiating fibrinolytic therapy within 1 hour of arrival and within 3 hours of onset of symptoms.

Introduction

Although only occasionally called on to manage a medical emergency, the ophthalmologist must be aware of the diagnostic and therapeutic steps necessary for proper care of a patient in acute distress. Infrequent use of these life-support steps makes it particularly important to review them periodically. Also, it is advisable for a member of the office staff to be trained in basic life support. The American Red Cross and the American Heart Association offer courses in basic life support (BLS), advanced cardiac life support (ACLS), and pediatric advanced life support (PALS). In addition to a review of life-support techniques, it is appropriate to periodically review office procedures, medications, and the equipment needed for each category of medical emergency.

Cardiopulmonary Arrest

Cardiopulmonary resuscitation (CPR) is intended to rescue patients with acute circulatory failure, respiratory failure, or both. The most important determinant of short-term and long-term neurologically intact survival is the interval from onset of the arrest to restoration of effective spontaneous circulatory and respiratory function. Numerous studies have shown that early defibrillation is the most important factor influencing survival and the minimization of sequelae. The sequences included here have been developed to optimize treatment. They are useful guidelines for most patients but do not preclude other measures that may be indicated for individual patients. The most crucial aspects of treatment are contained in the mnemonic *CAB*—*c*hest compressions, *a*irway maintenance, and *b*reathing. The *2020 American Heart Association* (AHA) *Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care* (ECC) are the most recently published CPR and ECC protocols; these basic CPR steps for adults, children, and infants can be found online (https://eccguidelines.heart.org/circulation/cpr-ecc-guidelines/), along with extensive resources, including training programs and kits, course supplies, and video demonstrations of CPR techniques.

A critical goal of the most recent AHA guidelines is to improve bystander CPR rates, automated external defibrillator (AED) use, and timely emergency response system activation during an out-of-hospital cardiac arrest. Eliminating disparities in CPR training among minority individuals and women can improve bystander CPR rates; it is known that communities with predominantly Black and Hispanic populations and those with lower socioeconomic status have lower rates of bystander CPR and CPR training. Notably, women are less likely to receive bystander CPR because of fear of accusations of inappropriate touching, sexual assault, or injuring a woman. Targeted training can help overcome these barriers.

The following are steps for CPR using CAB; they are performed with an unconscious patient (Table 17-1, Video 17-1):

1. Determine the level of responsiveness. Attempt to rouse the patient by tapping on their shoulder and shouting, "Are you all right?" Do not allow the head or neck to move unnecessarily until this area has been evaluated for trauma. Quickly note if breathing is absent or abnormal (eg, the patient is gasping).
2. Activate the Emergency Medical Services (EMS) system if there is no patient response (in the United States, call 911 where available). Rescuers should "phone first" for unresponsive patients and give the location and nature of the emergency.
3. Retrieve an AED or send someone to retrieve an AED.
4. Position the patient supine on a firm, flat surface.
5. If the patient is unresponsive and respiration cannot be detected, initiate chest compressions. (Determination of a pulse is no longer indicated.) Place the heel of 1 hand at the midsternal region, with the bottom of the hand 1–2 fingerbreadths above the xiphoid process.
6. "Push hard and push fast." The recommended cardiac compression rate is at least 100 compressions per minute (100–120/min). The depth of chest compression is critical; optimal compression depths are 1.5 inches in infants (one-third of body depth), 2.0 inches in children (one-third of body depth), and at least 2.0 inches

Table 17-1 Quick-Reference Chart: 2015 CAB Guidelines

	Adults and Children Older Than 8 Years	Children Aged 1–8 Years	Newborns and Infants
Recognition	No breathing or abnormal breathing (ie, only gasping) Initiate for ALL presumed cardiac arrest because harm risk is LOW if not in cardiac arrest	Unresponsive	Unresponsive
Pulse	No pulse palpated within 10 seconds		
CPR sequence	CAB (chest compressions, airway maintenance, breathing)		
Compression rate	100–120 per minute		
Compression depth	At least 2 inches or 5 cm Avoid >2.4 inches or 6 cm	At least ⅓ body depth (approximately 2 inches)	At least ⅓ body depth (approximately 1.5 inches)
Chest wall recoil	Allow complete chest recoil between compressions. Health care providers should switch chest compression duties every 2 minutes.		
Compression interruptions	Minimize interruptions in chest compressions. Attempt to limit interruption lengths to less than 10 seconds.		
Airway	Head-tilt, chin-lift maneuver (if neck injury is suspected, use modified jaw thrust without head extension)		
Compression-to-ventilation ratio (until the advanced airway is placed)	30:2, with 1 or 2 rescuers	30:2, with 1 rescuer 15:2, with 2 rescuers	30:2, with 1 rescuer 15:2, with 2 rescuers Note: If 1 rescuer, thumbs on the central chest below the nipple line while using other fingers to encircle back
Defibrillation	Attach and use the AED as soon as available. Minimize interruptions and chest compressions before and after shock; resume CPR, beginning with compressions, immediately after each shock. If pediatric pads are unavailable, adult pads may be used on children, infants, and newborns (put 1 pad on the back and 1 pad on the chest).		
Adults: Activate the EMS system/phone for help first.			
Children, infants, and newborns: If alone, perform 5 cycles of 30 compressions and 2 breaths before leaving the child to call 911.			
Rescue Breathing (For Patients With Pulse Present but *No* Breathing)			
	1 breath every 5 seconds	1 breath every 3 seconds	1 breath every 3 seconds

AED = automated external defibrillator; CPR = cardiopulmonary resuscitation; EMS = Emergency Medical Services.

in adults. The chest must be allowed to recoil fully between compressions; therefore, leaning on the chest between compressions should be avoided.

7. Deliver 30 chest compressions.
8. As soon as an AED is available, the unit should be connected to the patient, and instructions should be followed for assessing the heart rhythm. Interruptions to chest compressions should be minimized by having a second rescuer (eg, the person who retrieved the AED) charge and apply the AED. Resume chest compressions immediately after the shock and continue until 30 compressions are given.
9. Open the airway. Rescue breathing (see step 10 for technique) should be performed at a rate of 10–12 ventilations per minute. Use the head-tilt, chin-lift maneuver to provide a good airway: apply firm pressure to the forehead while placing the fingers of the other hand under the chin, supporting the mandible. If a neck injury is suspected, the modified jaw thrust without head extension should be used; this maneuver displaces the mandible forward by pushing the posterior aspects of the lower jaw without moving the neck.
10. Pinch the nose closed. Cover the patient's mouth with yours, making a tight seal, and ventilate twice with full breaths (1 second each). A 2-second pause should be observed between breaths. A visible chest rise should be seen with each breath. Resume chest compressions immediately. The "Help" button on the AED can be pressed for guidance with compression and rescue breathing frequency.
11. For 1- and 2-rescuer CPR: When the patient's airway is unprotected, 30 compressions should be performed before the patient is ventilated twice. Approximately 4 seconds should be taken for 2 ventilations, including the pause between ventilations.
12. If 2 rescuers are present, chest compression duties should be switched every 2 minutes or 5 compression/ventilation cycles.
13. Continue with compression/ventilation cycles until EMS arrives.

VIDEO 17-1 CPR and use of AED in an office setting.
Courtesy of A. Luisa Di Lorenzo, MD.

CPR is most effective when started immediately after cardiac arrest. If cardiac arrest has persisted for more than 10 minutes, CPR is unlikely to restore the patient's central nervous system (CNS) to prearrest status. If there is any question about the exact duration of cardiac arrest, the patient should be given the benefit of the doubt, and resuscitation should be started.

The risk of disease transmission through mouth-to-mouth ventilation is very low, but a variety of face shields and masks are available for health care professionals. Masks are more effective than face shields in delivering adequate ventilation. Alternative airway devices (eg, a laryngeal mask airway or an esophageal/tracheal dual lumen airway device) may also be acceptable for rescuers trained in their use. When no CPR mask is available, compressions can be done without giving breaths, as compression-only CPR saves lives compared with no CPR. Other protective measures include having fewer personnel involved in the CPR effort, using personal protective equipment (PPE), and using a PPE monitor. The most recent AHA

guidelines prioritize oxygenation and ventilation strategies with lower aerosolization and a move to early intubation.

Patients with suspected stroke should be rapidly transported to a hospital capable of initiating fibrinolytic therapy within 1 hour of arrival and within 3 hours of the onset of symptoms. These patients merit the same priorities for dispatch as patients with acute myocardial infarction or major trauma. See Chapter 7 in this volume for further discussion of stroke.

The following adjuncts are helpful in CPR and are suggested components for a medical emergency tray or crash cart:

- oxygen, to enhance tissue oxygenation and to prevent or ameliorate a hypoxic state
- airway devices, oral and nasal, in sizes appropriate for patients of all ages, to be used on unconscious or sedated patients
- a bag-valve device to help secure the airway
- a barrier device, such as a face shield or mask-to-mouth unit, to prevent disease transmission (this can be used with supplemental oxygen and is especially useful if the rescuer is inexperienced in using a standard bag-valve device)
- intravenous (IV) drugs (for use by those with ACLS training)
- IV solutions: dextrose 5% and water, D5 Ringer lactate, normal saline
- syringes (1, 5, and 10 mL), hypodermic needles (20, 22, and 25 gauge), and venous catheters
- a suction apparatus, tourniquet, taped tongue blade, and tape
- a laryngoscope and endotracheal tubes (in sizes appropriate for adults, children, infants, and newborns)

If there is no 911 community emergency telephone system, it is essential to have the telephone number of the local paramedic emergency squad posted near all office telephones.

BLS also outlines methods for aiding persons who are choking. These methods include the Heimlich maneuver and appropriate manual techniques for removing foreign bodies from the oral pharynx. Epigastric thrusts should be attempted; up to 10–12 thrusts may be necessary. Ventilation should be attempted if these techniques fail to restore effective respiratory function. Using a finger sweep to clear a foreign body from the oral pharynx is recommended by the American Medical Association but is not indicated in many modern protocols. Transtracheal ventilation through cricothyrotomy may be necessary if other techniques fail to clear the airway.

The AHA has established guidelines and procedures for ACLS. ACLS includes intubation, defibrillation, cardioversion, pacemaker placement, administration of drugs and fluids, and communication with ambulance and hospital systems. Because of the comprehensive and changing nature of ACLS algorithms, these procedures are beyond the scope of this chapter.

Competency in pediatric emergency care may be enhanced with training in pediatric life support (PLS) and PALS. In addition, ophthalmologists should be familiar with the ophthalmic manifestations of child abuse and abusive head trauma (shaken baby syndrome). These are discussed in BCSC Section 6, *Pediatric Ophthalmology and Strabismus.*

Merchant RM, Topjian AA, Panchal AR, et al. Part 1: Executive summary: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2020;142(16_suppl_2):S337–S357.

Syncope

Vasovagal episodes (syncope) are common, usually benign, events. These reactions are centered around the "fight or flight" response, such as when a person experiences a perceived or actual danger or threat. Common scenarios that can trigger a vasovagal attack in an ophthalmology office include dilation, applanation tonometry, contact lens insertion, and foreign-body removal. Often, the patient has premonitory signs and symptoms before the episode; these include lightheadedness, nausea, the sensation of changes in temperature, and tinnitus. Physiologically, during an episode, the vagus nerve is stimulated, causing peripheral blood vessels to dilate, which lowers blood pressure and slows the heart rate. Cerebral hypoperfusion and subsequent loss of consciousness can occur. Fortunately, these episodes are short-lived; the patient typically recovers within seconds. If these episodes occur in older persons, cardiac abnormalities should be considered. Patients with a history of cardiac problems who experience a syncopal episode have a higher risk of morbidity and mortality and should be evaluated thoroughly. A person experiencing a syncopal episode should be placed supine—preferably in a cool, quiet place—and the legs should be elevated.

Video 17-2 depicts the management of a vasovagal episode in the office setting.

VIDEO 17-2 Management of a vasovagal episode.
Courtesy of A. Luisa Di Lorenzo, MD.

Hypoglycemia

Ophthalmologists treat patients with diabetes daily and therefore should be familiar with managing a hypoglycemic episode. There are 2 types of hypoglycemia: postprandial hypoglycemia and fasting hypoglycemia. Causes of hypoglycemia are varied but include

- diabetes treated with insulin or insulin secretagogues
- adrenal insufficiency
- presence of pheochromocytoma
- hyperthyroidism
- substance use disorder, including alcohol, cocaine, and salicylate toxicity
- nutritional deficiency
- eating disorders
- liver disease such as cirrhosis
- medications such as insulin, insulin secretagogues, methadone, and tramadol

Symptoms include perspiration, tremor, tachycardia, anxiety, hunger, dizziness, changes in vision, confusion, convulsions, and syncope. Management of these episodes depends on the severity of the hypoglycemia. Therefore, it is important to recognize the signs of hypoglycemia; if possible, blood glucose levels should be tested, but treatment should not be delayed. Mild to moderate hypoglycemia can be treated orally with glucose gel or tablets, fruit juice,

soft drinks (not diet varieties), milk, honey or corn syrup, and crackers. Unconscious patients with severe hypoglycemia should be treated with IV dextrose and intramuscular glucagon.

Shock

Shock is a state of tissue hypoperfusion that leads to impaired cellular metabolism and—if uncorrected—progresses to multiple organ failure and death.

Classification

Shock is classified according to the 4 primary pathophysiologic mechanisms involved:

- oligemic, also called *hypovolemic* (eg, hemorrhage, diabetic ketoacidosis, burns, and sequestration)
- cardiogenic (eg, myocardial infarction and arrhythmia)
- obstructive (eg, pericardial tamponade, pulmonary embolus, and tension pneumothorax)
- distributive, characterized by maldistribution of the vascular volume secondary to altered vasomotor tone (eg, sepsis, anaphylaxis, spinal cord insult, beriberi, and arteriovenous fistula)

The type of shock can often be determined by the history and physical examination and appropriate diagnostic tests. Regardless of the event that precipitated the state of shock, microcirculatory failure is the common factor that eventually leads to death in individuals in advanced shock. Ventilatory failure appears to be the most significant factor in the morbidity and mortality of shock, with subsequent hypoxemia and metabolic acidosis leading to many complications.

If vasovagal syncope is ruled out (because of its short duration and one's familiarity with the situations that produce this condition), the BLS measures for the initial emergency care of the unconscious patient are similar to the measures used in treatment of patients with shock. The most important aspects of treatment are CAB, the same principles used in CPR (see the section Cardiopulmonary Arrest).

Failure of respiratory gas exchange is the most frequent single cause of death in patients with shock; thus, respiratory obstruction must be ruled out first. Oxygen is then given by mask; if respiratory movements are shallow, mechanical ventilation is necessary. Respiratory obstruction can be assumed if there is stridor with respiratory movements or if cyanosis persists even when adequate ventilatory techniques have been applied. A conscious patient in distress who cannot speak and is developing cyanosis may be choking on food or a foreign body.

Assessment

The patient's vital signs must be monitored. The clinical syndrome is usually characterized by an altered sensorium, relative hypotension, tachycardia, tachypnea, oliguria, metabolic acidosis, weak or absent pulse, pallor, diaphoresis, and cool skin (however, in cases of septic shock,

the skin may be warm). Decreased pulse pressure is often an early sign of shock, and systolic blood pressure readings of <90 mm Hg are often associated with vital organ hypoperfusion. However, blood pressure is not always a reliable indicator of tissue perfusion.

Treatment

Specific guidelines for the treatment of shock, which is often quite complex, are beyond the scope of this text. However, general guidelines are as follows:

- The EMS system should be activated, or the patient should be transferred to an emergency department.
- The patient should be positioned supine, with the legs elevated.
- Supplemental oxygen should be administered to enhance tissue oxygenation. Mechanical ventilation may be necessary to maintain the Po_2 at normal levels and to prevent respiratory acidosis.
- Fluid resuscitation with IV infusion of a crystalloid solution (ie, normal saline or lactated Ringer solution) should be administered rapidly.
- Vasopressor drugs (norepinephrine is usually administered first) may be necessary for augmentation of systemic vascular tone and/or cardiac output to help perfuse vital organs after an adequate circulating volume is established. Vasopressin, or antidiuretic hormone, has been suggested for septic shock because of its potent vasoconstrictor effect, but it should be reserved for salvage therapy only. In 2017, the US Food and Drug Administration, and in 2019, the European Union, approved synthetic human angiotensin II (Giapreza) for adults with septic or other distributive shock.
- When sepsis is suspected, blood cultures should be drawn and antibiotic therapy initiated promptly.
- Sodium bicarbonate, given intravenously, is indicated for correction of severe metabolic acidosis.

Experimental drugs used in the treatment of septic shock include polyclonal IV immunoglobulin, which can bind endotoxin; however, no existing studies substantiate its use.

Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021;47(11):1181–1247.

Anaphylaxis

One subtype of distributive shock is anaphylaxis, which is an acute allergic reaction following antigen exposure in a previously sensitized person. It requires immediate and specific therapy. It is usually mediated by immunoglobulin E antibodies and involves the release of chemical mediators from mast cells and basophils. *Anaphylactoid reactions,* which are more common and less severe, are triggered by nonantigenic agents and result from the direct release of these chemical mediators. Anaphylaxis or anaphylactoid reactions may occur after exposure to pollen, drugs, foreign serum, insect stings, diagnostic agents (eg, iodinated contrast materials or fluorescein), vaccines, local anesthetics, and food products. The most important parameter for predicting such an attack is a history of a previous allergic reaction to any other drug or possible antigen; however, a history of known sensitivity may

not always be elicited. Pretreating high-risk patients with an antihistamine, corticosteroids, or both before fluorescein angiography may reduce the risk of an allergic reaction. Studies indicate that the prevalence of anaphylaxis has been increasing steadily since 2008.

Anaphylaxis is particularly important to the ophthalmologist because of the increasing number of surgical procedures and fluorescein angiograms performed in the office setting. It is estimated that patients experience allergic reactions to fluorescein (including urticaria) in up to 1% of all angiograms. In 1 survey, the overall risk of a severe reaction was 1 in 1900 patients, including a risk of respiratory compromise in 1 in 3800 patients. If diaphoresis, apprehension, pallor, a rapid and weak pulse, or any combination thereof develops in a patient after administration of a drug, the patient should be considered to have an allergic reaction until proven otherwise. The diagnosis is confirmed if there is associated generalized itching, urticaria, angioedema of the skin, dyspnea, wheezing, or arrhythmia. Anaphylaxis may rapidly lead to loss of consciousness, shock, cardiac arrest, coma, or death.

Once an acute allergic reaction is suspected, prompt treatment is indicated:

- Oxygen should be administered to patients in respiratory distress.
- Epinephrine (0.3 mL of a 1:1000 solution) injected intramuscularly is usually effective for maintaining circulation and blood pressure. (In the case of insect stings, it is injected into the limb opposite to the site of injury.)
- IV volume expansion may be necessary to restore and maintain tissue perfusion. For serious or prolonged reactions, methylprednisolone is administered. When given early, corticosteroids help limit possible long-term sequelae.
- Antihistamines are helpful in slowing or halting the ongoing allergic response but are of limited value in acute anaphylaxis.
- Tracheotomy or cricothyrotomy is indicated when laryngeal edema is unresponsive to the previous methods or when oral intubation cannot be performed.
- All patients with anaphylaxis or anaphylactoid reactions should be kept under observation for at least 6 hours.

In cases of mild allergic reactions, the physician can administer 25–50 mg of diphenhydramine hydrochloride orally or intramuscularly and observe the patient closely to determine whether further treatment is necessary. In all cases of anaphylaxis, supportive treatment should be maintained until the emergency medical team arrives.

For patients with a known history of anaphylaxis, personal emergency kits containing epinephrine are available and can be used until medical help arrives. The kits are designed to allow self-treatment by the patient or administration by a family member or an informed bystander. One commercially available emergency allergy kit contains a syringe and needle preloaded with 0.6 mL of 1:1000 epinephrine. The physician who prescribes this kit must give detailed instructions concerning the use of the device. Epinephrine autoinjectors such as EpiPen (Viatris, Inc), a generic version of Adrenaclick (Amneal Pharmaceuticals), and Auvi-Q (Kaléo, Inc) are also available. Each spring-loaded automatic injector, which does not permit graduated doses to be given, automatically injects 0.3 mg of epinephrine (0.15 mg in the pediatric version) when the device is triggered by pressure on the thigh. The epinephrine ampules in these self-treatment kits have a limited shelf life and should be replaced when the expiration date is reached or if the solution becomes discolored. Any

person given epinephrine requires 4–6 hours of observation to ensure that there is no rebound effect.

In recent years, there has been renewed interest in the treatment of allergic reactions with sublingual immunotherapy, in which the patient is exposed to the offending antigen via the gastrointestinal system to improve tolerance. A custom-mixed vial of drops is prepared for the patient, who takes the drops under the tongue daily. The dose is gradually increased over the first 4 months (the *escalation phase*); this is followed by the *maintenance phase,* during which the patient takes the same dose of drops.

Seizures and Status Epilepticus

A *seizure* is a paroxysmal episode of abnormal electrical activity in the brain that results in involuntary transient neurologic, motor activity, behavioral, or autonomic dysfunction. Typically, seizures are divided into 2 major categories, *focal* (formerly called *partial*) and *generalized.* Although seizures can present with many different clinical manifestations, most fit into the subcategories of simple focal, complex focal, or generalized tonic-clonic. See Chapter 12 for a detailed discussion of these categories.

Status epilepticus is defined as a prolonged seizure (lasting at least 30 minutes) or as multiple seizures that occur without intervening periods of normal consciousness. Like seizures, status epilepticus may have a focal onset with secondary generalization or may be generalized from the onset. This condition often occurs concomitantly with hyperthermia, acidosis, hypoxia, tachycardia, hypercapnia, and mydriasis and, if persistent, may be associated with irreversible brain injury. Status epilepticus that is completely stopped within 2 hours usually has relatively minor morbidity compared with episodes lasting longer than 2 hours.

Major causes of seizures and status epilepticus include the following:

- drug withdrawal, such as from anticonvulsants, benzodiazepines, barbiturates, or alcohol
- metabolic abnormalities, such as hypoglycemia, hyponatremia, hypocalcemia, and hypomagnesemia
- conditions that affect the CNS, such as infection, trauma, stroke, hypoxia, ischemia, and sleep deprivation
- toxic levels of various drugs

Emergency *medical* management of seizures is best left to physicians who perform this routinely. However, the clinician should be aware of some general considerations in treating seizures. The first priority is the maintenance of circulation as opposed to airway maintenance. Maintenance of circulation becomes particularly important if the seizure progresses to status epilepticus.

During seizure management, it is important not only to stop the seizure activity but also to identify and treat the underlying cause when possible. Additional steps include noting the time of seizure onset, monitoring and maintaining an airway, and monitoring vital signs. Activation of the emergency response (911) team is indicated in all cases of acute seizure onset. In the setting of an ophthalmology office, it may be appropriate to check blood glucose levels because many seizure patients have diabetes.

Refractory cases of status epilepticus have responded successfully to repeated electroconvulsive therapy sessions, IV sedatives such as ketamine or propofol, surgical ablation and stimulation procedures, and topiramate and levetiracetam.

Rossetti AO, Alvarez V. Update on the management of status epilepticus. *Curr Opin Neurol.* 2021;34(2):172–181.

Toxic Reactions to Local Anesthetic Agents and Other Drugs

Toxic overdose can cause acute distress and unconsciousness. Clinicians should be prepared to respond to this emergency whenever a patient is undergoing a procedure that requires local anesthesia. Table 17-2 lists commonly used local anesthetics and the maximum doses at which they may be safe for adults.

Reactions after administration of local anesthetics are almost always toxic and only rarely allergic. A high blood level of local anesthetic can be produced by the following: too large a dose, unusually rapid absorption (including inadvertent administration directly into a vein), and unusually slow detoxification or elimination (especially in individuals with liver disease). Although rare, hypersensitivity (ie, decreased patient tolerance) and idiosyncratic reactions to local anesthetic agents may occur, as with any drug. True allergic or anaphylactic reactions are also uncommon but may occur, particularly with agents belonging to the amino ester class (eg, tetracaine).

Toxic reactions cause overstimulation of the CNS, which may lead to excitability, restlessness, apprehension, disorientation, tremors, and convulsions (cerebral cortex effects), as well as nausea and vomiting (medulla effects). Cardiac effects initially include tachycardia and hypertension. Ultimately, depression of the CNS and the cardiovascular system occurs, which may result in drowsiness or coma (cerebral cortex effects), as well as in irregular respirations, sighing, dyspnea, and respiratory arrest (medulla effects). Cardiac effects of CNS depression are bradycardia and hypotension.

Injected local anesthetic can have a direct toxic effect on muscle tissue. In peribulbar or retrobulbar injections, this can result in muscle weakness, which in some patients is followed by muscle contracture. In addition, extraocular motility can be affected, resulting in diplopia (usually hypertropia) that may require surgical revision. Hyaluronidase may be partially protective by allowing more rapid diffusion of the anesthetic agent after injection. Increased metabolic activity of the CNS and poor ventilation can lead to cerebral

Table 17-2 Maximum Recommended Local Anesthetic Doses

Agent	Commercially Available Concentrations (%); 1% = 10 mg/mL	Plain Solutions, mg	Epinephrine-Containing Solutions, mg
Chloroprocaine	1, 2, 3	800	1000
Lidocaine	0.5, 1, 1.5, 2, 4, 5	300	500
Mepivacaine	1, 1.5, 2	300	225
Bupivacaine	0.25, 0.5, 0.75	175	225
Tetracaine	1	100	100

hypoxia. Treatment consists of oxygenation, supportive airway care, and titrated IV administration of midazolam, which is used to suppress cortical stimulation.

Other emergency procedures that must be applied in cases of toxic overdose include suctioning if vomiting occurs and using a taped tongue blade if convulsions develop. If shock develops, the appropriate drugs can be administered by IV infusion.

The addition of *epinephrine* to the local anesthetic can also cause adverse reactions. Reactions to epinephrine can produce symptoms similar to those of early CNS overstimulation by a local anesthetic, such as anxiety, restlessness, tremor, hypertension, and tachycardia. However, unlike local anesthetic toxicity, epinephrine overdose does not cause convulsions or bradycardia as the toxic reaction progresses. Oxygen is useful in the treatment of epinephrine overdoses.

Although rare, death can occur as a result of retrobulbar or peribulbar local anesthetic; for example, the administration of retrobulbar *bupivacaine* has been associated with respiratory arrest. This reaction may be caused by intra-arterial injection of the local anesthetic, with retrograde flow to the cerebral circulation. It can also result from puncture of the dural sheath of the optic nerve during a retrobulbar block, with diffusion of the local anesthetic along the subdural space in the midbrain. Initial symptoms are a gradual or sudden change in consciousness, such as coma with tonic-clonic seizures; apnea; and blood pressure lability. A large prospective study that compared retrobulbar injection of a mixture of 0.75% bupivacaine and 2.0% lidocaine with a mixture of 0.75% bupivacaine and 4.0% lidocaine found that the patients receiving the 4.0% lidocaine and bupivacaine mixture had an almost 9 times greater risk of respiratory arrest than did patients receiving the 2% lidocaine and bupivacaine mixture. Ophthalmologists should be prepared for these possible adverse effects by having the proper resuscitative equipment at hand and training office staff in CPR.

The use of IV *edrophonium chloride* in the diagnosis of myasthenia gravis can have toxic adverse effects. The signs and symptoms result from cholinergic stimulation and may include nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, muscle fasciculations and weakness, and bradycardia. Some of these signs may be transient and self-limited because of the very short half-life of IV edrophonium. Nevertheless, whenever the test is to be performed, a syringe containing 0.5 mg of atropine sulfate—an anticholinergic drug that reverses possible adverse effects such as heart arrhythmias and respiratory arrest—must be immediately available. Some physicians routinely pretreat with atropine all patients undergoing such testing.

As noted, if signs of excess cholinergic stimulation occur, 0.5 mg of atropine sulfate should be administered intravenously. This dose may be repeated every 3–10 minutes if necessary. The total dose of atropine necessary to counteract the toxic effects is seldom more than 2 mg. If toxic signs progress, the treatment described earlier for toxic overdose may be required.

Anker R, Kaur N. Regional anaesthesia for ophthalmic surgery. *BJA Education*. 2017;17(7): 221–227.

Guo S, Wagner R, Gewirtz M, et al. Diplopia and strabismus following ocular surgeries. *Surv Ophthalmol.* 2010;55(4):335–358.

Palte HD. Ophthalmic regional blocks: management, challenges, and solutions. *Local Reg Anesth.* 2015;8:57–70.

Opioid Overdose

The opioid crisis is a national public health and socioeconomic issue with which every ophthalmologist should be familiar. Opioid misuse includes the improper use of and addiction to prescription pain relievers, heroin, and synthetic opioids such as fentanyl. In the United States, 115 individuals die of opioid overdose daily. The Centers for Disease Control and Prevention estimates the economic burden of this crisis to be $78.5 billion per year. This figure includes the cost of health care for individuals with addiction, productivity loss, addiction treatment, and the criminal justice system's involvement in many of these cases.

The cause of this epidemic is multifactorial; its origins can be traced to the late 1990s, when pharmaceutical companies assured the medical community that patients would not become addicted to prescription opioid pain relievers. Prescription of these medications to patients led to their widespread use and subsequent misuse, and it soon became apparent that these drugs were indeed highly addictive. Opioid overdose rates began to increase; in 2015 alone, more than 33,000 individuals in the United States died as a result of overdose from prescription painkillers, heroin, and illegally manufactured synthetic fentanyl. Also in 2015, it was determined that approximately 2 million people had developed opioid use disorder and that more than half a million people were addicted to heroin. This addiction emerged in conjunction with prior opioid pain medication use in some cases.

Approximately 21%–29% of patients prescribed opioid-based chronic-pain medications ultimately misuse them. Of these, 8%–12% develop an opioid use disorder, and 4%–6% of those who misuse prescription opioids transition to heroin. In fact, 80.5% of individuals with a heroin addiction once misused prescription pain medicine. In addition to the devastating public health issues created by this crisis, there is an increase in neonatal abstinence syndrome due to the misuse of opioids during pregnancy. Increased injection drug use has also led to an increased incidence of blood-borne infections, such as HIV and hepatitis C, resulting from the use of contaminated injection drug equipment.

The US Department of Health and Human Services and the National Institutes of Health (NIH) have aggressive strategies to manage this far-reaching problem by improving access to treatment and recovery programs, promoting the use of overdose-reversing drugs such as the opioid antagonist naloxone, advocating for better public health surveillance, improving research on pain and addiction, and finally, improving prescribing patterns in the medical community for patients experiencing pain. The NIH is also exploring formal partnerships with pharmaceutical companies and academic centers to develop safe, effective, nonaddictive approaches to managing long-term pain; develop new medications and technologies to treat opioid use disorder; and improve prevention and reversal interventions to save lives and support recovery.

In Europe, the struggle centers on the over-the-counter misuse of codeine, which affects persons of all ages, across all social classes. Codeine is less dangerous than fentanyl or heroin but turns into morphine in the liver and can be toxic at high doses. Some individuals use codeine for pain relief and anxiety, while those with heroin and morphine addiction often use it as a substitute. The demand for codeine has increased 27% in the last decade across Europe. Implementing an online tracking system would allow pharmacists to share data on purchasers and cap sales accordingly. In addition, physicians can play a

crucial role in identifying dependency and educating patients on the dangers of codeine and the risk of opiate addiction.

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Adverse Effects of Ophthalmic and Systemic Medications

Because of the advancement of medical specialties and the proliferation of specific therapeutic agents, patients frequently have multiple simultaneous drug regimens. Drug interactions are always a concern in patients who use multiple topical and systemic medications, but often, no single physician is aware of all the drugs the patient is taking. The clinical problem is compounded by several factors. The physician may not be familiar with the types of drugs or the properties of drugs used outside their specialty. The patient may also have a drug interaction that affects a bodily system not usually monitored by the specialist. Finally, the patient might not associate a symptom with a particular drug if that symptom is unrelated to the system for which the drug was given. The growing use of electronic medical records has helped physicians become more aware of their patients' multiple drug regimens, but it has not eliminated the problem. The spectrum of systemic side effects of drugs commonly used in the treatment of ocular conditions is covered extensively elsewhere in the BCSC series (see BCSC Section 9, *Uveitis and Ocular Inflammation,* and Section 10, *Glaucoma*) and is summarized in Table 17-3.

The effects of some systemic drugs are widely known. For example, the commonly prescribed erectile dysfunction agent sildenafil has been noted to block photoreceptor signals, causing electroretinographic changes, visual disturbances (including changes in color perception), and increased light sensitivity. The ocular adverse effects of several commonly prescribed systemic medications are presented in Table 17-4.

The ophthalmologist can minimize adverse effects from multiple-drug therapy by doing the following:

- maintaining a high level of suspicion for drug interactions
- questioning the patient closely about other drug therapy and general symptoms
- encouraging all patients to carry a card listing the drugs they use
- keeping in close communication with the patient's primary care physician
- consulting with a clinical pharmacologist or internist whenever a question of drug interaction arises
- using the resources that may be available through electronic medical records (eg, electronic medical record systems that link to pharmacy records)

Unrecognized adverse effects of topical or systemic medications should be reported to the National Registry of Drug-Induced Ocular Side Effects, either via its website (www.eyedrugregistry.com) or in correspondence with the registry's director,

Table 17-3 Side Effects of Medications Commonly Prescribed in the Treatment of Ocular Conditions

Drug	Side Effects and Comments
Antibiotics	
Sulfonamide, sulfacetamide Tobramycin, gentamycin	Skin irritation, itching, rashes, contact allergic reactions
Fluoroquinolone	Taste disturbance
Corticosteroids	Increased intraocular pressure, cataract, ptosis Systemic toxic effects, hyperglycemia
Sympathomimetic	
Phenylephrine	Increased hypertension, cardiac arrhythmias, myocardial infarction, especially with corneal epithelial compromise 10% phenylephrine not recommended in children or older adults
Sympatholytics	
Clonidine	Pronounced reduction in blood pressure
Apraclonidine	Conjunctival hyperemia, itching, foreign-body sensation, eyelid/conjunctival edema Dry mouth, dizziness, fatigue, and drowsiness, especially in patients predisposed to bradycardia Avoid in patients with cerebral or coronary conditions, Raynaud phenomenon, orthostatic hypotension, or thromboangiitis
β-Blockers	Transient monocular vision loss Alopecia, contact dermatitis, psoriasiform rashes, bradycardia, arrhythmias, syncope, hypotension, transient cerebral ischemia, bronchoconstriction
Parasympathomimetic agents	Contact dermatitis, sweating, bronchospasm, vomiting, diarrhea, bradycardia, hypotension, confusion, memory disorders, emotional lability, agitation, and behavioral disorders
Carbonic anhydrase inhibitors	Fatigue, loss of appetite, paresthesia, depression, hypokalemia, metabolic acidosis, kidney stones Avoid in patients allergic to sulfonamides
Prostaglandins	Increased lacrimation; increased pigmentation of the iris, orbital tissue; thickening, darkening, and lengthening of eyelashes Rash (rarely), facial flushing, increased perspiration, increased asthmatic symptoms Preservative-free prostaglandins preferred because of the toxic effects of preservatives on the ocular surface
Antihistamines and antiallergics	In rare cases, GI symptoms (dry mouth feeling or nausea), headache, or drowsiness
Nonsteroidal anti-inflammatory agents (NSAIDS)	GI symptoms (rarely), contact dermatitis, triggering of acute asthma attack (due to bronchoconstrictor leukotriene synthesis)

GI = gastrointestinal.

Information from Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol*. 2016;10:2433–2441.

Table 17-4 Potential Ocular Adverse Effects of Popular Drugs

Drug	Adverse Effects
Antibiotics	
Cefaclor	Mild inflammation of ocular surface (rare), eyelid problems, nystagmus, visual hallucinations
Cefuroxime axetil	Mild inflammation of the ocular surface (rare)
Ciprofloxacin	Eyelid problems, exacerbation of myasthenia gravis, visual sensations, retinal detachment
Moxifloxacin (oral)	Iris transillumination, sphincter paralysis, retinal detachment
Rifampin	Conjunctival hyperemia, exudative conjunctivitis; increased lacrimation
Tetracycline, doxycycline, minocycline	Papilledema secondary to IIH; transient myopia; blue-gray, dark blue, or brownish pigmentation of the sclera; hyperpigmentation of eyelids or conjunctiva; diplopia
Antidepressants/anxiolytics	
Alprazolam	Diplopia, decreased or blurred vision, decreased accommodation, abnormal extraocular muscle movements, allergic conjunctivitis
Fluoxetine	Blurred vision, photophobia, mydriasis, dry eye, conjunctivitis, diplopia
Imipramine	Decreased vision, decreased accommodation, slight mydriasis, photosensitivity
Antiepileptic	
Topiramate	Conjunctivitis, abnormal accommodation, photophobia, strabismus, mydriasis, anterior uveitis, acute myopia, anterior chamber shallowing, secondary angle-closure glaucoma (bilateral), visual field defects, suprachoroidal effusions
Analgesics, anti-inflammatory drugs	
Aspirin	Transient blurred vision, transient myopia, hypersensitivity reactions
Hydroxychloroquine	Retinopathy (bull's-eye maculopathy), with decreased vision and color perception
Ibuprofen	Blurred vision, decreased vision, diplopia, photosensitivity, dry eye, decrease in color vision, optic or retrobulbar neuritis
Naproxen	Decreased vision, changes in color vision, optic or retrobulbar neuritis, papilledema secondary to IIH, photosensitivity, corneal opacities
Disease-modifying agents	
Bisphosphonates	Anterior uveitis, conjunctivitis, scleritis, blurred vision
Interferon	Cotton-wool spots
Isotretinoin	Corneal opacities, night blindness, decreased color vision, sicca syndrome, papilledema
Drugs used in the treatment of asthma and allergy	
Antihistamines	Decreased vision, pupillary changes, decreased accommodation, blurred vision, decreased mucoid or lacrimal secretions, diplopia; may induce or aggravate dry eye
Corticosteroids	Decreased vision, posterior subcapsular cataracts, increased intraocular pressure
Cardiovascular drugs	
Amiodarone	Photophobia, blurred vision, corneal deposits, anterior subcapsular lens opacities, optic neuropathy
β-Blockers	Decreased vision, dry eye, visual hallucinations, decreased intraocular pressure, decreased lacrimation

Table 17-4 *(continued)*

Drug	Adverse Effects
Selective α_{1a}-receptor antagonists	Intraoperative floppy iris syndrome with a sluggish hypotonic iris, miosis, iris prolapse
Calcium channel blockers	Decreased or blurred vision, periorbital edema, ocular irritation (general), progression of glaucoma
Captopril, enalapril	Angioedema of the eye and orbit, conjunctivitis, decreased vision
Digitalis glycosides	Decreased vision, color vision defects, glare phenomenon, flickering vision
Diuretics (thiazide-type)	Decreased vision, myopia, color vision abnormalities, retinal edema, progression of glaucoma
Flecainide	Blurred vision, decreased vision, decreased accommodation, abnormal visual sensations, decreased depth perception, nystagmus
Warfarin	Retinal hemorrhages in susceptible persons, hyphema, allergic reactions, conjunctivitis, lacrimation, decreased vision
Drugs used in the treatment of impotence	
Sildenafil, tadalafil	Possible retinal vascular occlusions, decreased color perception, conjunctivitis, photophobia
Hormones, hormone-related drugs	
Clomiphene	Visual sensations, decreased vision, mydriasis, visual field constriction, photophobia, diplopia
Danazol	Decreased vision, diplopia, papilledema secondary to IIH, visual field defects
Estradiol	Decreased vision, retinal vascular disorders, papilledema secondary to IIH, fluctuations of corneal curvature and corneal steepening, color vision abnormalities
Leuprolide	Blurred vision, papilledema secondary to IIH, retinal hemorrhage and branch vein occlusion, eye pain, eyelid edema
Oral contraceptives	Decreased vision, retinal vascular disorders, papilledema secondary to IIH, color vision abnormalities
Tamoxifen	Decreased vision, corneal deposits, retinal edema or hemorrhage, papilledema, retinopathy, decreased color vision, optic neuritis or neuropathy
Immmunomodulators	
Cyclosporine	Posterior reversible encephalopathy syndrome causing bilateral vision loss
Tacrolimus	Potential stroke; blurry vision: dose-dependent aqueous tear deficiency
Antituberculosis drug	
Ethambutol	Optic nerve toxicity: slow, progressive, irreversible
Anticholinergics	
Dicyclomine	Accommodative difficulty
Tamsulosin	Intraoperative floppy iris syndrome
Herbal medicines	
Black bitter licorice	Scintillating scotomas, migraines
Canthaxanthin	Crystalline retinal deposits, potentially causing changes on electroretinograms

IIH = idiopathic intracranial hypertension.

Frederick T. Fraunfelder, MD, at eyedrug@OHSU.edu. In the European Union, the European Medicines Agency operates the EudraVigilance system, which monitors the safety of medicines and allows electronic reporting of suspected adverse drug reactions. By effectively analyzing data, this process enables early detection of potential safety issues with medications.

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Additional Materials and Resources

Related Academy Materials

The American Academy of Ophthalmology is dedicated to providing a wealth of high-quality clinical education resources for ophthalmologists.

Print Publications and Electronic Products

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The **Resident Knowledge Exchange** (resident-exchange.aao.org) provides peer-generated study materials, including flash cards, mnemonics, and presentations that offer unique perspectives on complex concepts.

Find comprehensive **resources for diversity, equity, inclusion, and accessibility** in ophthalmology on the ONE Network at aao.org/diversity-equity-and-inclusion.

Access free, trusted articles and content with the Academy's collaborative online encyclopedia, **EyeWiki,** at aao.org/eyewiki.

Get mobile access to *The Wills Eye Manual* and *EyeWiki,* watch the latest 1-minute videos, challenge yourself with weekly Diagnose This activities, and set up alerts for clinical updates relevant to you with the free **AAO Ophthalmic Education App.** Download today: search for "AAO Ophthalmic Education" in the Apple app store or in Google Play.

Basic Texts and Additional Resources

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Study Questions

Please note that these questions are not part of your CME reporting process. They are provided here for your own educational use and for identification of any professional practice gaps. The required CME posttest is available online (see "Requesting Continuing Medical Education Credit"). Following the questions are answers with discussions. Although a concerted effort has been made to avoid ambiguity and redundancy in these questions, the authors recognize that differences of opinion may occur regarding the "best" answer. The discussions are provided to demonstrate the rationale used to derive the answer. They may also be helpful in confirming that your approach to the problem was correct or, if necessary, in fixing the principle in your memory. The Section 1 faculty thanks the Resident Self-Assessment Committee for developing these self-assessment questions and the discussions that follow.

1. What percentage of people in the United States are uninsured?
   a. 2%
   b. 10%
   c. 15%
   d. 20%

2. The National Eye Institute Visual Function Questionnaire 25 (VFQ-25) asks patients to rate their difficulty with certain tasks, such as reading street signs, on a scale from 1 to 5, with 1 being "No difficulty at all" and 5 being "Stopped doing this because of your eyesight." In terms of statistics, what type of variable is being collected?
   a. ordinal
   b. categorical
   c. dichotomous
   d. continuous

3. What is the mechanism of action of teprotumumab in the treatment of thyroid eye disease?
   a. inhibits thyroid-stimulating hormone (TSH) secretion
   b. competitively binds the TSH receptor
   c. competitively binds thyroid-stimulating immunoglobulin
   d. inhibits the insulin-like growth factor I receptor

4. What is the most common cancer in multiple endocrine neoplasia syndromes 2 and 3?
   a. gastrinoma
   b. medullary thyroid cancer
   c. ganglioneuroma
   d. pheochromocytoma

5. In the 2017 American College of Cardiology/American Heart Association guidelines for the treatment of hypertension, which class of drugs is listed as a first-line treatment for Black patients?
   a. thiazide type diuretics
   b. angiotensin-converting enzyme (ACE) inhibitors
   c. angiotensin receptor blockers
   d. β-blockers

6. What is the role of injectable PCSK9 inhibitors such as evolocumab and alirocumab in the treatment of hyperlipidemia?
   a. initial treatment for children and adolescents with low-density-lipoprotein cholesterol (LDL-C) levels of ≥190 mg/dL
   b. adjunctive therapy for high-risk patients who cannot achieve LDL-C goal with statins alone
   c. initial treatment for diabetic patients with LDL-C levels of 70–189 mg/dL
   d. adjunctive therapy for diabetic patients with LDL-C levels of ≤70 mg/dL

7. What is the focus of treatment for a patient with congestive heart failure with a reduced ejection fraction (HFrEF)?
   a. Reduce preload by decreasing circulating blood volume with diuretics.
   b. Reduce afterload by lowering blood pressure.
   c. Treat associated cardiac ischemia with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
   d. Treat associated hyperlipidemia with statins.

8. What is the preferred first-line therapy for patients who have survived a cardiac arrest?
   a. implantable cardioverter-defibrillator (ICD)
   b. PCI with drug-eluting stenting
   c. CABG
   d. digoxin therapy

9. A 65-year-old man with diabetes and hypertension is brought to the emergency department 2 hours after the onset of weakness on the right side. What imaging study is the most important in guiding urgent management?
   a. brain magnetic resonance imaging
   b. cerebral angiography
   c. noncontrast computed tomography of the brain
   d. transcranial Doppler ultrasonography

10. What antithrombotic therapy is most effective in the early treatment of ischemic stroke?
    a. aspirin
    b. aspirin/clopidogrel
    c. enoxaparin
    d. heparin

11. What ocular condition is associated with obstructive sleep apnea?
    a. proliferative diabetic retinopathy
    b. nonarteritic anterior ischemic optic neuropathy
    c. diplopia
    d. posterior subcapsular cataract

12. What type of stem cell is the precursor of red blood cells?
    a. myeloid
    b. mesenchymal
    c. lymphoid
    d. induced pluripotent

13. What is the treatment for sideroblastic anemia?
    a. iron supplementation
    b. parenteral vitamin B_{12} supplementation
    c. vitamin B_6 and iron-chelating agents
    d. systemic immunosuppression

14. What is the most common hypercoagulable state implicated in retinal vein occlusions in young White patients?
    a. activated protein C resistance (factor V Leiden mutation)
    b. prothrombin G20210A mutation
    c. protein C deficiency
    d. protein S deficiency

15. During a routine eye examination, multiple telangiectatic lesions are found on a patient's palpebral conjunctiva. Some lesions are also present on the lips. The patient reports that the lip lesions sometimes bleed spontaneously or with minimal trauma. What disorder is consistent with these findings?
    a. hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
    b. Ehlers-Danlos syndrome
    c. osteogenesis imperfecta
    d. pseudoxanthoma elasticum

16. A 65-year-old woman with symmetric bilateral arthritis presents with ulnar deviation and a positive anti–cyclic citrullinated peptide antibody test result. What ocular manifestation is commonly associated with this systemic disease?
    a. retinal vasculitis
    b. optic neuritis
    c. scleritis and episcleritis
    d. trabeculitis

17. What form of juvenile idiopathic arthritis is most likely to have ocular involvement?
    a. oligoarticular
    b. polyarticular
    c. psoriatic
    d. systemic

18. A 40-year-old man presents with mild bilateral conjunctivitis with a mucopurulent discharge. He has dysuria, which started a few weeks ago and was followed by pain in his left knee and ankle. Laboratory testing is performed, revealing that he is HLA-B27 positive. What is the most likely diagnosis?
    a. reactive arthritis
    b. relapsing polychondritis
    c. ankylosing spondylitis
    d. rheumatoid arthritis

19. What test is most confirmatory for the diagnosis of Sjögren syndrome in a patient without autoantibodies?
    a. Schirmer testing
    b. ocular surface staining
    c. salivary gland biopsy
    d. buccal mucosal biopsy

20. According to the latest recommendations, how should hydroxychloroquine be dosed to reduce the risk of retinal toxicity?
    a. daily dose ≤200 mg
    b. daily dose ≤400 mg
    c. daily dose ≤5.0 mg/kg ideal body weight
    d. daily dose ≤5.0 mg/kg actual body weight

21. An 89-year-old patient with a history of frequent bruises, repeated trips to the emergency department, and poor adherence to follow-up instructions presents for an ophthalmic examination. What initial management is appropriate?
    a. Refer the patient for low vision evaluation.
    b. Examine the patient for retinal hemorrhages.

c. Obtain a history with only the patient present.
d. Call the patient's primary care physician.

22. What ocular finding may be present in patients with bulimia nervosa?
    a. pinpoint conjunctival hemorrhages
    b. papilledema
    c. traumatic mydriasis
    d. corneal ectasia

23. A 74-year-old man has had trouble reading for 18 months. He underwent uncomplicated cataract surgery in both eyes with no noticeable improvement. His family reports some gradual cognitive decline over the past year. His visual acuity is normal at near and distance. The posterior chamber intraocular lenses are well centered, with clear posterior capsules. Fundus examination results are normal. Humphrey visual fields show a left homonymous hemianopia. Magnetic resonance imaging findings are unremarkable. What diagnosis would explain his symptoms?
    a. cancer-associated retinopathy
    b. melanoma-associated retinopathy
    c. posterior cortical atrophy
    d. right occipital stroke

24. According to the US Preventive Services Task Force, in which group of individuals should yearly prostate-specific antigen testing be done to screen for prostate cancer?
    a. all 55-year-old men
    b. men of Asian descent
    c. 60-year-old men with a positive family history
    d. 70-year-old men regardless of family history

25. What is the leading cause of viral hepatitis in the United States?
    a. hepatitis A
    b. hepatitis B
    c. hepatitis C
    d. hepatitis D

26. What is the target of the initial vaccines to prevent COVID-19?
    a. SARS-CoV-2 mRNA
    b. SARS-CoV-2 spike protein
    c. SARS-CoV-2 nucleocapsid
    d. SARS-CoV-2 envelope protein

27. What does TNM refer to in cancer staging?
    a. time course of diagnosis, lymph node involvement, presence of metastasis
    b. tumor type, neoplastic syndromes, presence of metastasis
    c. tumor type, lymph node involvement, presence of metastasis
    d. tumor type, neoplastic syndromes, method of treatment

28. A healthy 52-year-old former nuclear submarine engineer asks whether his previous occupation exposed him to any health risks. What ocular complication associated with radiation exposure is most likely to be observed on slit-lamp examination?
    a. punctate epithelial erosions
    b. posterior subcapsular cataract
    c. cotton-wool spots
    d. optic nerve head hemorrhages

29. What is the term for chemotherapy given before surgical resection, with the goal of tumor shrinkage and, therefore, a less invasive surgical procedure?
    a. adjuvant
    b. curative
    c. neoadjuvant
    d. palliative

30. What is the most serious ocular adverse effect of ipilimumab and other immune checkpoint inhibitors in the treatment of cancer?
    a. neurotrophic keratitis
    b. uveitis
    c. optic neuritis
    d. nonarteritic anterior ischemic optic neuropathy

31. What was a key finding of the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study?
    a. Methicillin resistance in staphylococcal isolates was rare.
    b. Fluoroquinolones remained effective against nearly all isolates.
    c. Vancomycin was effective against all staphylococcal isolates.
    d. Antibiotic resistance of ocular isolates increased during the 10-year study period.

32. A 73-year-old man presents with mild preseptal cellulitis of the left lower eyelid, for which he is prescribed oral clindamycin. Two days later, the patient is seen for a follow-up appointment, and there is significant improvement in eyelid erythema and edema. Five days later, the patient calls the ophthalmologist's office and reports having a fever and nonbloody diarrhea. What diagnostic test would be most appropriate?
    a. blood culture
    b. stool ova and parasites (O&P)

c. stool enzyme-linked immunosorbent assay (ELISA)
d. stool cultures

33. What intervention has been shown to decrease the incidence of *Haemophilus influenzae* infection, which can cause orbital cellulitis?
    a. isolation of infected individuals
    b. improved sanitation
    c. treatment of otitis media with antibiotics
    d. vaccination

34. What stage of *Treponema pallidum* infection is characterized by fever, malaise, lymphadenopathy, and hair loss?
    a. primary
    b. secondary
    c. latent
    d. tertiary

35. What testing should be included when screening for ethambutol optic neuropathy?
    a. central visual field testing
    b. fluorescein angiography
    c. macular optical coherence tomography
    d. Goldmann kinetic perimetry

36. For which patients should preoperative testing, such as electrocardiography and routine blood testing, be done prior to ophthalmic surgery?
    a. patients who have not seen their primary care physician within 1 year
    b. patients for whom the tests would be indicated even if they were not planning surgery
    c. patients with American Society of Anesthesiologists Physical Status class II
    d. patients with American Society of Anesthesiologists Physical Status class III

37. You are trying to make a diagnosis of myasthenia gravis in clinic and administer intravenous edrophonium chloride to a patient. The patient then becomes diaphoretic, nauseated, and bradycardic. What is the next step in management?
    a. Administer intramuscular epinephrine 1:10,000.
    b. Administer 0.5 mg intravenous (IV) atropine sulfate.
    c. Administer 0.4 mg IV naloxone.
    d. Administer 25 g IV dextrose.

38. An 80-year-old man has had binocular diplopia, worse with upgaze, since he underwent otherwise uncomplicated left-eye cataract surgery with retrobulbar anesthesia 6 months ago. His pupils and eyelids are normal. The left eye has poor elevation with positive forced duction testing. What is the most likely cause of his diplopia?
    a. ocular neuromyotonia
    b. anesthetic myotoxicity
    c. myasthenia gravis
    d. decompensated phoria

Answers

1. **b.** Although the rates of uninsured Americans have decreased under the Affordable Care Act, approximately 10% of people in the United States are uninsured. Vulnerable populations, such as underrepresented racial and ethnic groups and low-income individuals, are at highest risk of being uninsured.
2. **a.** Ordinal variables have 2 or more categories that can be ordered or ranked. For example, a variable with response data ranging from "strongly agree" to "strongly disagree" would be considered ordinal; a Likert scale is a well-known example of this type of variable. Many visual function questionnaires use ordinal data. Categorical variables are those that have discrete categories or levels. Examples include blood type, eye color, and educational level. Dichotomous variables are categorical variables with 2 levels, such as yes/no or high/low. Continuous variables are measured numerically and have an infinite number of possible values.
3. **d.** Teprotumumab, approved by the US Food and Drug Administration in 2020, has been shown to slow the progression of ophthalmopathy in patients with moderate to severe thyroid eye disease (TED). It inhibits insulin-like growth factor I receptor and represents a new therapeutic strategy for treating the underlying autoimmune pathogenesis of TED.
4. **b.** The most common cancer in multiple endocrine neoplasia syndrome (MEN) 2 (formerly MEN2A) and MEN3 (formerly MEN2B) is medullary thyroid cancer, which occurs in 90%–100% of patients and is the main cause of morbidity.
5. **a.** The 2017 American College of Cardiology/American Heart Association guidelines for the treatment of hypertension list thiazide-type diuretics and calcium channel blockers (CCBs) as the drug classes for the initial drug choice in Black patients. For patients who are not Black, the initial drug choice may be selected from 4 drug classes, on the basis of clinical setting and comorbidities: thiazide-type diuretics, CCBs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.
6. **b.** Evolocumab and alirocumab are injectable monoclonal antibodies to proprotein convertase subtilisin kexin 9 (PCSK9). These PCSK9 inhibitors are used as adjunctive therapy when maximal statin therapy fails to reduce low-density-lipoprotein cholesterol (LDL-C) to the desired level in high-risk patients. For nearly all patients whose LDL-C goals cannot be met by therapeutic lifestyle changes alone, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or *statins,* are the initial choice for medical therapy. Individuals with LDL-C levels of ≤70 mg/dL do not need therapy.
7. **b.** The most effective way to manage congestive heart failure with a reduced ejection fraction (HFrEF) is to reduce afterload to decrease the burden on the left ventricle. Regardless of the baseline values, reducing blood pressure (while maintaining adequate tissue perfusion) is the mainstay of treatment. Heart failure with preserved ejection fraction (HFpEF) can be improved by reducing preload. If medical therapy fails in patients with HFpEF, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is considered. Statins are beneficial in HFpEF but not in HFrEF.
8. **a.** Implantable cardioverter-defibrillators (ICDs) are the preferred first-line treatment for patients who have survived a cardiac arrest or an episode of hemodynamically unstable ventricular tachycardia. ICDs are associated with a 20%–30% relative reduction in the risk of death. Most patients with ICDs require concomitant antiarrhythmic therapy with

amiodarone or a β-blocker. PCI and CABG are revascularization procedures that can be used for cardiac ischemia. Digoxin is an inotropic agent used in the treatment of HFrEF.

9. **c.** Multiple studies have shown that administering the fibrinolytic agent recombinant tissue plasminogen activator (rtPA) within 3 hours of acute ischemic stroke results in lower morbidity. Imaging with noncontrast computed tomography (CT) of the brain is critical in evaluating for the presence of intracranial hemorrhage, which would be a contraindication to rtPA use. Magnetic resonance imaging, while more sensitive than noncontrast CT in detecting an evolving stroke within hours of its onset, is too time intensive given the limited window during which rtPA can be administered. Although cerebral angiography can provide detailed information about vascular abnormalities, it is not indicated in the acute care setting and would not reveal either stroke or hemorrhage. Transcranial Doppler ultrasonography may reveal stenosis of the intracranial arteries, but it is not helpful for guiding initial management.
10. **a.** Aspirin is the only antiplatelet agent that is effective in the early treatment of ischemic stroke. Two large clinical trials showed a benefit of treatment with aspirin over placebo in short-term mortality and recurrent stroke risk when aspirin is initiated within 48 hours of onset of an ischemic stroke. Early use of combination antiplatelet agents such as aspirin with clopidogrel may be beneficial, but the evidence is not consistent. Heparin and related agents such as enoxaparin are associated with higher mortality and worse outcomes in patients with cardioembolic or noncardioembolic stroke.
11. **b.** Ocular conditions associated with obstructive sleep apnea include floppy eyelid syndrome, dry eye, glaucoma, papilledema, central serous chorioretinopathy, and nonarteritic anterior ischemic optic neuropathy.
12. **a.** Myeloid stem cells are the precursors of red blood cells, granulocytes, monocytes, and platelets. Lymphoid stem cells become T cells, B cells, natural killer cells, and innate lymphoid cells. Mesenchymal stem cells are multipotent stem cells that are present in various tissues, including bone marrow, and have the ability to differentiate into a variety of cells (bone, cartilage, fat). Adult cells such as skin fibroblasts can be induced to produce pluripotent stem cells by using transcription factors. Induced pluripotent stem cells hold great promise in the field of regenerative medicine and can be used to create every type of cell.
13. **c.** If iron is not incorporated properly into the heme molecule, hemoglobin synthesis is reduced; this condition is called *sideroblastic anemia.* Treatment includes pyridoxine (vitamin B_6), iron-chelating agents such as deferoxamine, and hematopoietic stem cell transplantation (also called *bone marrow transplantation*).
14. **a.** Most patients with activated protein C (APC) resistance harbor a single specific point mutation in the factor V gene, called *factor V Leiden,* which renders both forms of factor V (active and inactive) insensitive to APC proteolysis. This mutation occurs with remarkable frequency (3%–7%) in healthy White populations but appears to be far less prevalent or even absent in certain Black and Asian populations. Factor V Leiden mutation and subsequent APC resistance are implicated in central and branch retinal vein occlusions.
15. **a.** A number of inherited and acquired disorders of blood vessels and their supporting connective tissues result in pathologic bleeding. Many of these disorders also have ocular findings. Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) is an autosomal dominant condition characterized by localized dilatation of capillaries and telangiectasias

(actually small arteriovenous malformations) of the skin and mucous membranes. The telangiectasias are often located on the lips and tongue and increase in size and number over a period of decades.

Ehlers-Danlos syndrome is characterized by hyperplastic fragile skin and hyperextensible joints. In patients with osteogenesis imperfecta, bone fractures and otosclerosis (leading to deafness) are common. Pseudoxanthoma elasticum is rare and is often complicated by gastrointestinal hemorrhage.

16. **c.** This patient has rheumatoid arthritis (RA). Ocular involvement may include dry eye; scleritis; episcleritis; and corneal inflammation, melting, and infection. Anti–citrullinated peptide antibody testing, specifically anti–cyclic citrullinated peptide and anti–mutated citrullinated vimentin, is as sensitive as rheumatoid factor (RF) but has a higher specificity for RA (>95%).

17. **a.** In patients with juvenile idiopathic arthritis, ocular involvement is most common in those with the oligoarticular form and least common in those with the systemic form. Patients with oligoarticular or polyarticular (especially RF-negative) disease should be periodically screened for ocular involvement because it is often asymptomatic. Furthermore, antinuclear antibody positivity in patients with oligoarticular, polyarticular, or psoriatic arthritis is associated with an increased risk of developing uveitis.

18. **a.** The classic triad of reactive arthritis consists of arthritis, urethritis, and conjunctivitis. Human leukocyte antigen–B27 and genetics appear to be involved in susceptibility to developing reactive arthritis after an infection. The arthritic symptoms typically have their onset from days to weeks after the antecedent infection. Joint involvement is typically asymmetric and episodic, primarily affecting the knees and ankles.

    Up to 40% of patients with either ankylosing spondylitis or reactive arthritis develop the typical manifestations of acute nongranulomatous iridocyclitis, which can be recurrent and bilateral. Ocular involvement tends not to correlate with the activity of the joint disease. Culture-negative bilateral conjunctivitis, which is typically self-limited, is also a common manifestation of reactive arthritis.

19. **c.** Labial salivary gland biopsy can be helpful for confirming a diagnosis of Sjögren syndrome in patients lacking evidence of autoimmunity (absent or low titers of autoantibodies or the absence of an associated autoimmune disorder). An abnormal Schirmer test result and abnormal ocular surface staining are less specific. Buccal mucosal biopsy is indicated when oral mucosal lesions are present.

20. **d.** Updated recommendations state that daily hydroxychloroquine dosing should not exceed 5.0 mg/kg actual body weight. Actual body weight is thought to be more predictive than ideal body weight in assessing risk of retinopathy from hydroxychloroquine.

21. **c.** In cases of suspected elder neglect or abuse, it is helpful to obtain the patient's history with the caregiver out of the room. Directed questions such as "Has anyone at home tried to harm you?" may yield information. Any suspected case of neglect or abuse should prompt a written report. Documentation of any suspicious injuries is mandatory. Requirements for reporting elder abuse vary from state to state, and many areas have abuse hotlines for reporting maltreatment. The physician should be aware of local services for adult protection, community social services, and law enforcement agencies.

22. **a.** Bilateral pinpoint conjunctival hemorrhages can occur in patients with bulimia. Other ocular findings in patients with eating disorders include lagophthalmos from orbital fat

atrophy, nystagmus or ophthalmoplegia from vitamin B_1 deficiency, and nyctalopia from vitamin A deficiency.

23. **c.** The features (normal visual acuity, normal ocular examination findings, inability to read) are suggestive of dementia, specifically the visual variant of Alzheimer disease, posterior cortical atrophy. Patients with posterior cortical atrophy may present early in the disease course with visual symptoms and findings, including homonymous visual field defects.

24. **c.** Because of the high rate of false-positives, minimal disease identified by prostate-specific antigen (PSA) screening, and the potentially significant adverse effects of treating minimal disease, routine yearly serum PSA screening is no longer recommended except for higher-risk individuals, such as African American men, *BRCA* carriers, and those with a positive family history of prostate cancer. Instead, in 2017, the US Preventive Services Task Force recommended individualized discussion of the risks and benefits of prostate cancer screening for men between the ages of 55 and 69.

25. **a.** Infection with hepatitis A virus (HAV) is the leading cause of viral hepatitis in the United States. HAV is usually transmitted orally and may be acquired from contaminated water supplies and unwashed or undercooked foods. Vaccination against HAV infection is recommended for children aged 12–23 months and for persons at high risk of exposure to HAV (eg, travelers to endemic areas, patients with blood clotting factor disorders, military personnel, people who use illegal drugs, family contacts of infected patients, laboratory workers exposed to the virus).

26. **b.** The vaccines initially authorized for the prevention of COVID-19 target the SARS-CoV-2 spike protein. Two of the initial vaccines, produced by Pfizer-BioNTech and Moderna, are mRNA vaccines. The other vaccines, such as those made by Janssen/Johnson & Johnson and Oxford/AstraZeneca, are adenovirus vector vaccines.

27. **c.** The TMN system takes into account tumor type, lymph node involvement, and the presence of metastasis. The T classification is based on the size and extent of local invasion; the N classification describes the extent of lymph node involvement; and the M classification is based on presence or absence of distant metastasis.

28. **b.** Cataract—specifically, posterior subcapsular cataract—is the most likely complication of radiation exposure that would be found in this patient. The lens is the most radiosensitive structure in the eye, followed by the cornea, the retina, and the optic nerve. Radiation doses to the lens as low as 2 Gy in a single fraction can induce cataract formation, while higher doses (7–8 Gy) can cause progressive cataracts. The average latent period for the development of radiation-induced cataracts is 2–3 years.

29. **c.** The goal of neoadjuvant chemotherapy is to shrink tumors that are too large for total resection, potentially facilitating a less invasive surgical procedure. Adjuvant chemotherapy is given after surgical resection in order to destroy undetectable microscopic cancer cells and thus reduce the rate of recurrence. Curative chemotherapy is given to eliminate cancer cells, with the goal of achieving permanent remission. Palliative chemotherapy is used to provide the patient with symptomatic relief and to slow tumor growth in the presence of incurable disease.

30. **b.** Immune checkpoint inhibitors such as ipilimumab can be associated with episcleritis, conjunctivitis, and orbital inflammation. The most serious ocular adverse effect is severe bilateral uveitis, which can lead to exudative retinal detachment. The risk of ocular complications may be increased when multiple immune checkpoint inhibitors are used.

31. **c.** All staphylococcal isolates were susceptible to vancomycin. There was a high prevalence of methicillin resistance among staphylococcal isolates and a high probability of concurrent resistance to fluoroquinolones. Overall antibiotic resistance of ocular isolates did not increase during the 10-year study period.

32. **c.** With this patient's history of fever and recent antibiotic use, the diagnosis is most likely pseudomembranous enterocolitis *(C diff).* The causative organism, *Clostridioides* (formerly *Clostridium*) *difficile,* is an anaerobic gram-positive bacillus that is part of the normal gastrointestinal flora. Fever and diarrhea develop 1–14 days after the start of antibiotic therapy. The diarrhea occasionally becomes bloody. The most frequently implicated antibiotics include clindamycin, ampicillin, chloramphenicol, tetracycline, erythromycin, and the cephalosporins. The bacterium elaborates cytopathic toxins (A and B), which can be detected by enzyme-linked immunosorbent assay (ELISA). A polymerase chain reaction assay is also sometimes used in the diagnosis. Initial treatment includes discontinuing the causative antibiotic and prescribing oral vancomycin.

33. **d.** Prior to the 1990s, a common etiology of orbital cellulitis in children younger than 9 years was *Haemophilus influenzae* infection. However, since *H influenzae* type b (Hib) vaccination in infants became widespread, the incidence of *H influenzae* infection has decreased dramatically. Orbital cellulitis does not typically develop from otitis media.

34. **b.** The secondary stage is heralded by a truncal rash that may spread over the entire body. Fever, malaise, lymphadenopathy, and hair loss may occur. Initial inoculation occurs through intact mucous membranes or abraded skin and, within 6 weeks, results in a small, ulcerated, painless papule called a *chancre* (primary stage). Latent syphilis is characterized by positive serologic test results in a patient without clinical signs. Tertiary disease is characterized by destructive granulomatous lesions with a typical endarteritis that can affect the skin, bones, joints, oral and nasal cavities, parenchymal organs, cardiovascular system, eyes, meninges, and central nervous system.

35. **a.** Ethambutol is associated with optic neuropathy in a small percentage of patients. In patients with suspected ethambutol-induced optic neuropathy, formal visual acuity testing, central visual field testing, fundus examination, and optical coherence tomography of the peripapillary retinal nerve fiber layer, as well as possibly electrophysiologic testing (eg, visual evoked potential, multifocal electroretinography), should be considered.

36. **b.** Preoperative testing, including electrocardiography and routine blood testing, should be performed only when indicated; that is, the tests would be done even if the patient was not planning surgery. Multiple clinical trials have failed to show a difference in perioperative adverse events in healthy patients undergoing elective eye surgery, whether or not preoperative testing was obtained. However, a complete history and physical examination are required for all patients as part of the preoperative assessment.

37. **b.** The use of intravenous edrophonium chloride in the diagnosis of myasthenia gravis can have toxic adverse effects. The signs and symptoms result from cholinergic stimulation and may include nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, muscle fasciculations and weakness, and bradycardia. Whenever the test is to be performed, a syringe containing 0.5 mg of atropine sulfate—an anticholinergic drug that reverses possible adverse effects such as heart arrhythmias and respiratory arrest—must be immediately available. The drug should be administered if the aforementioned signs and symptoms occur; this dose may be repeated every 3–10 minutes if necessary.

38. **b.** This patient has restrictive strabismus, as demonstrated by forced duction testing. Causes to be considered include thyroid eye disease, traumatic inferior rectus entrapment, and anesthetic myotoxicity. While the first 2 entities are possible causes, the history is more consistent with direct toxic effects of anesthetic on extraocular muscles, which can occur from inadvertent injection of local anesthetic into 1 of the rectus muscles (typically the inferior rectus). Initially, the patient may have no symptoms or a transient hypertropia of the affected eye due to muscle weakness. Over time, contraction or fibrosis develops, causing a restrictive strabismus.

    Patients with decompensated phoria should have full ductions. Patients with myasthenia gravis would not have positive forced duction tests. Ocular neuromyotonia is a rare cause of transient diplopia, usually occurring months or years after skull base irradiation, and is not consistent with the clinical picture.

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(*f* = figure; *t* = table)