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GOLDMAN'S
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西氏内科学

第24版

感染性疾病分册

LEE GOLDMAN
ANDREW I. SCHAFER

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GOLDMAN'S CECIL MEDICINE

24TH EDITION

西氏内科学

（第24版）

感染性疾病分册

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PREFACE

The 24TH Edition of *Goldman's Cecil Medicine* symbolizes a time of extraordinary advances in medicine and in technological innovations for the dissemination of information. This textbook and its associated electronic products incorporate the latest medical knowledge in formats that are designed to appeal to learners who prefer to access information in a variety of ways.

The contents of *Cecil* have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying normal physiology and pathophysiology of disease, now at the cellular and molecular as well as the organ level) and the *how* (now frequently based on Grade A evidence from randomized controlled trials). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert. Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient have diminished the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to counteract this tendency with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter. In addition to the information provided in the textbook, the Cecil website supplies expanded content and functionality. In many cases, the full articles referenced in each chapter can be accessed from the Cecil website. The website is also continuously updated to incorporate subsequent Grade A information, other evidence, and new discoveries.

The sections for each organ system begin with a chapter that summarizes an approach to patients with key symptoms, signs, or laboratory abnormalities associated with dysfunction of that organ system. As summarized in Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 100 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases but also for patients who may have undiagnosed abnormalities that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous editors of *Cecil Medicine* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, and Dennis Ausiello. As we welcome new associate editors—Wendy Levinson, Donald W. Landry, Anil Rustgi, and W. Michael Scheld—we also express our appreciation to Nicholas LaRusso and other associate editors from the previous editions on whose foundation we have built. Our returning associate editors—William P. Arend, James O. Armitage, David Clemmons, Jeffrey M. Drazen, and Robert C. Griggs—continue to make critical contributions to the selection of authors and the review and approval of all manuscripts. The editors, however, are fully responsible for the book as well as the integration among chapters.

The tradition of *Cecil Medicine* is that all chapters are written by distinguished experts in each field. We are also most grateful for the editorial assistance in New York of Theresa Considine and Silva Sergenian. These individuals and others in our offices have shown extraordinary dedication and equanimity in working with authors and editors to manage the unending flow of manuscripts, figures, and permissions. We also thank Faten Aberra, Reza Akari, Robert C. Brunham, Ivan Ciric, Seema Daulat, Gregory F. Erikson, Kevin Ghassemi, Jason H. Huang, Caron Jacobson, Lisa Kachnic, Bryan T. Kelly, Karen Krok, Heather Lehman, Keiron Leslie, Luis Marcos, Michael Overman, Eric Padron, Bianca Maria Piraccini, Don W. Powell, Katy Ralston, James M. Swain, Tania Thomas, Kirsten Tillisch, Ali Turabi, Mark Whiteford, and Y. Joseph Woo, who contributed to various chapters. At Elsevier, we are most indebted to Dolores Meloni and Linda McKinley, and also thank Cathy Carroll, Taylor Ball, Virginia Wilson, Linda Van Pelt, Suzanne Fannin, and Steve Stave, who have been critical to the planning and production process under the direction of Mary Gatsch. Many of the clinical photographs were supplied by Charles D. Forbes and William F. Jackson, authors of *Color Atlas and Text of Clinical Medicine*, Third Edition, published in 2003 by Elsevier Science Ltd. We thank them for graciously permitting us to include their pictures in our book. We have been exposed to remarkable physicians in our lifetimes and would like to acknowledge the mentorship and support of several of those who exemplify this paradigm—Robert H. Gifford, Lloyd H. Smith, Jr., Frank Gardner, and William Castle. Finally, we would like to thank the Goldman family—Jill, Jeff, Abigail, Mira, Daniel, and Robyn Goldman—and the Schafer family—Pauline, Eric, Pam, John, Evan, and Kate—for their understanding of the time and focus required to edit a book that attempts to sustain the tradition of our predecessors and to meet the needs of today's physician.

LEE GOLDMAN, MD
ANDREW I. SCHAFER, MD

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XXIII

INFECTIOUS DISEASES

286 INTRODUCTION TO MICROBIAL DISEASE: HOST-PATHOGEN INTERACTIONS

W. MICHAEL SCHELD

Infectious diseases have profoundly influenced the course of human history. The "black death" (caused by *Yersinia pestis*) changed the social structure of medieval Europe, in the process eliminating approximately a third of the population. The outcomes of military campaigns have been altered by outbreaks of diseases such as dysentery and typhus. Examples include Napoleon's retreat from Russia, after typhus did more damage to his army than the opposition forces did; the decision by the French to sell the Louisiana Territory after French soldiers died from yellow fever in Cuba and the Gulf Coast; and the introduction of smallpox to the nonimmune population of the New World by Europeans, thus facilitating the "conquest" and the dawn of the colonial age. Malaria influenced the geographic and racial pattern and distribution of hemoglobins and erythrocyte antigens in Africa. The development of *Plasmodium falciparum* is inhibited by the presence of hemoglobin S, and Duffy blood group–negative erythrocytes are resistant to infection with *Plasmodium vivax*. Thus, populations with these erythrocyte factors are found in areas where malaria is common.

Infections are a major cause of morbidity and mortality in the world. Of the approximately 53 million deaths worldwide in 2009, at least a third were due to infectious diseases. In the United States, pneumonia is the fifth leading cause of death overall and the most common cause of death related to infection. In addition, invasive disease caused by *Streptococcus pneumoniae* and community-acquired pneumonia overall have increased in incidence over the past decade. Acquired immunodeficiency syndrome (AIDS) threatens to disrupt the social fabric in many countries of Africa and is severely distressing the health care system in the United States and other parts of the world. The year 2006 marked the 25th "anniversary" of the AIDS epidemic. Approximately 33 million people worldwide are currently infected with human immunodeficiency virus (HIV), and since 1981, approximately 25 million have died (≈ 600,000 in the United States alone). AIDS is now the leading cause of death in sub-Saharan Africa.

Infection can be defined as the multiplication of microbes (from viruses to multicellular parasites) in the tissues of the host. The host may or may not be symptomatic. For example, HIV infection may cause no overt signs or symptoms of illness for years. The definition of infection should also include the multiplication of microbes on the surface or in the lumen of the host that causes signs and symptoms of illness or disease. For example, toxin-producing strains of *Escherichia coli* may multiply in the gut and cause a diarrheal illness without invading tissues. Microbes can cause diseases without actually coming in contact with the host by virtue of toxin production. *Clostridium botulinum* may grow in certain improperly processed foods and produce a toxin that can be lethal on ingestion. A relatively trivial infection such as that caused by *Clostridium tetani* in a small puncture wound can cause devastating illness because of a toxin released from the organism growing in tissues. It has now become apparent that multiple virulence factors of microorganisms can be carried in tandem on so-called pathogenicity islands of the genome (the "virulome").

We live in a virtual sea of microorganisms, and all our body surfaces have indigenous bacterial flora. This normal flora actually protects us from infection. Reduction of gut colonization increases susceptibility to infection by pathogens such as *Salmonella enteritidis* serovar *typhimurium*. Bacteria that constitute the normal flora are thought to exert their protective effect by several mechanisms: (1) utilizing nutrients and occupying an ecologic niche, thus competing with pathogens; (2) producing antibacterial substances that inhibit the growth of pathogens; and (3) inducing host immunity that is cross-reactive and effective against pathogens. These conclusions appear to be oversimplistic, however. For example, colonization of the gastrointestinal tract with *Bacteroides fragilis* expressing an immunodominant bacterial polysaccharide, through dendritic cell activation and induction of a T_H1-mediated response, leads to a splenic response characterized by normal numbers of $CD4^+$ T cells, lymphoid architecture, and systemic lymphocytic expansion. Thus, a single bacterial molecule in our gut is necessary to make us "immunologically fit." In addition to the normal flora, transient colonization may be seen with known or potential pathogens. This may be a special problem in hospitalized patients because it can lead to nosocomial infection (Chapter 290).

Only a small proportion of microbial species can be considered primary or professional pathogens, and even among these species, a relatively small number of clones have been shown to cause disease. For example, epidemic meningococcal meningitis and meningococcemia are due to a small number of clones of *Neisseria meningitidis*, and the worldwide explosion of penicillin-resistant *S. pneumoniae* can be traced to a few clones originating in South Africa and Spain. This observation supports the concept that pathogenic organisms are highly adapted to the pathogenic state and have developed characteristics that enable them to be transmitted, attach to surfaces, invade tissue, avoid host defenses, and thus cause disease. In contrast, opportunistic pathogens cause disease principally in impaired hosts, and these organisms, which may be harmless members of normal flora in healthy persons, can act as virulent invaders in patients with severe defects in host defense mechanisms. Although opportunistic infection has traditionally been viewed as the exploitation of a weakened host through physiologic stress or immunocompromise (or both) by relatively "avirulent" pathogens, this is an oversimplification. For example, *Pseudomonas aeruginosa* recognizes host immune activation, specifically by binding interferon-γ to a cell surface protein OprF, which in turn, through a quorum-sensing signaling system, leads to the overexpression of virulence determinants such as PA-I (lecA) and pyocyanin. Thus, bacteria have developed a "contingency system" that recognizes immunologic perturbations in the host and counters this response by the expression of virulence factors.

Pathogenic organisms may be acquired by several routes. Direct contact has been implicated in the acquisition of staphylococcal disease. Airborne spread, usually by droplet nuclei, occurs in respiratory diseases such as influenza and in severe acute respiratory syndrome (SARS). Contaminated water is the usual vehicle in *Giardia* infection and typhoid fever. Food-borne toxic illnesses may be caused by extracellular toxins produced by *Clostridium perfringens* and *Staphylococcus aureus*. Blood and blood products may be vectors for transmitting hepatitis B and C viruses, as well as HIV. Sexual transmission is also important for these agents and for a variety of other pathogens, including *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), and *Chlamydia trachomatis* (nonspecific urethritis). The fetus may be infected in utero, and the infection may be devastating if the agent is rubella virus or cytomegalovirus. Arthropod vectors may be important, as illustrated by mosquitoes for malaria and dengue, ticks for Lyme disease and ehrlichiosis, and lice for typhus.

Pathogens are able to cause disease because of a finely tuned array of adaptations, including the ability to attach to appropriate cells, often mediated by specialized structures such as the pili on Gram-negative rods. Microbes such as *Shigella* species have the ability to invade cells and cause damage. Toxins may act at a distance or may intoxicate only infected cells. Pathogens have the ability to thwart host defenses by a variety of ingenious maneuvers. The antiphagocytic coat of the pneumococcus is an example. Organisms may change their surface antigen display at an astonishingly rapid rate to outmaneuver the host immune system. Examples include influenza virus and trypanosomes. Certain pathogens have the ability to inhibit the respiratory burst of phagocytes *(Toxoplasma gondii)*, and others can destroy phagocytic cells that have engulfed them (e.g., *Streptococcus pyogenes*). The environment plays an important role in infection, both in transmission and in the host's ability to combat the invader. The humidity and temperature of air may affect the infectivity of airborne pathogens. The sanitary state of food and water, woefully lacking in many areas of the developing world, is an important factor in the acquisition of enteric pathogens, one of the major causes of mortality and morbidity, such as physical and mental developmental delay leading to poor performance in school and other consequences. The malaria associated with the "bad air" of swamps is, in fact, due to the mosquitoes there, but the environmental association was appropriate. The nutritional status of the host is clearly a significant factor in certain infectious diseases. It is likely that micronutrient deficiency contributes to the invasion and multiplication of certain pathogens. A new concept is the possibility that infectious diseases cause malnutrition through a vicious circle of diarrhea leading to dehydration and poor oral intake, resulting in secondary diarrhea with a propensity for "stunting" and delaying intellectual development. Establishment of infection is a complicated interplay of factors involving the microbe, the host, and the environment.

Host reaction to infection may result in illness. For example, previous infection with *Campylobacter jejuni* is responsible for about 40% of cases of Guillain-Barré syndrome. The mechanism is thought to be the production of antibodies against *C. jejuni* lipopolysaccharides that cross-react with gangliosides in peripheral nerves. Similarly, much of the damage resulting from meningitis is due to the host's response to invading bacterial pathogens.

With some exceptions, infectious diseases are often treatable and curable. Thus, it is important to make an accurate etiologic diagnosis and institute appropriate therapy promptly. In acute infections such as pneumonia, meningitis, or sepsis, rapid institution of therapy may be life-saving; thus, a presumptive etiologic diagnosis should be established before a definitive diagnosis. This presumptive diagnosis is based on the history, physical examination, epidemiology of illness in the community, and rapid techniques such as microscopic examination of appropriate Gram-stained specimens. Antimicrobial therapy can then be instituted for the presumptive etiologic agents, but it must be reevaluated as more definitive diagnostic information becomes available.

The study as well as the understanding of infectious diseases is a dynamic process. A number of factors or themes of current interest contribute to this conclusion, including the following:

EMERGING INFECTIONS. The most obvious is AIDS, but recent examples with a major impact on the public health in the United States include community-associated methicillin-resistant *S. aureus*, a hypervirulent strain of *Clostridium difficile*, and the 2009 H1N1 influenza. More than 300 new, emerging infectious diseases have been described in the last 70 years; approximately 60% are zoonoses associated with geographic "hotspots." Their emergence is driven largely by ecologic, socioeconomic, and environmental factors.

GENOMICS AND OTHER "OMICS." The exact sequence of the genome of more than 2000 microbes relevant to humans has been determined. This new information, in concert with genomic information from multicellular organisms such as the *Anopheles* mosquito, offers significant promise for the development of new therapies and vaccines. Careful analysis of the genomes of pathogens will continue to yield important information about the pathogenesis of infection. For example, genome sequencing of group A streptococci, collected over time with relevant robust clinical information, has detected the acquisition of new determinants (often by prophage) responsible for increased virulence and resulting in toxic shock syndrome, necrotizing fasciitis, or both. Proteomics, transcriptomics, metabolomics, and virulomics have transformed research on infectious diseases and promise significant improvements in diagnostics and therapeutics in the future.

GENETIC FACTORS ALTERING SUSCEPTIBILITY TO INFECTION AND THE RESPONSE TO INFECTIOUS DISEASES. This field promises new and significant information relevant to the wide variety of responses to infectious diseases in humans. For example, an overvigorous response, with generation of tumor necrosis factor-α, may accentuate the development of cerebral complications in falciparum malaria. Analysis of single-nucleotide polymorphisms of the human genome will lead to an enhanced understanding of two fundamental issues in infectious diseases: why invasive, overt disease develops in only a small fraction of individuals colonized with a given microbe, and why infections are more severe in some people than in others. Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, and innate and adaptive immunity are being identified at an astonishing rate.

INNATE IMMUNITY. This is the most active field in immunology. The identification of pattern recognition receptors (e.g., Toll-like receptors [TLRs] and nucleotide oligomerization domain [NOD]-like receptors) that recognize pathogen-associated molecular patterns, as well as endogenous substances reflecting tissue injury (e.g., alarmins), has revolutionized our understanding of the early host response to infection. Agonists or antagonists of TLRs have already entered clinical trials as adjuvant therapies (e.g., editoran for sepsis) or to improve the immunogenicity of vaccines. The other area that has exploded recently is the study of antimicrobial peptides (e.g., defensins, cathecidins, histatins, galectins) and their role in the early response to infectious disorders.

ANTIMICROBIAL RESISTANCE. The development of new antimicrobial agents has slowed despite the burgeoning problem of antimicrobial resistance. This disconnect has been the focus of meetings among the pharmaceutical industry, the Infectious Diseases Society of America, the Food and Drug Administration, and others. Multiresistant pneumococci, vancomycin resistance in *S. aureus*, vancomycin-resistant enterococci, and, perhaps most important, multidrug-resistant gram-negative bacilli (MDR-GNB) are just a few examples. Some MDR-GNB are susceptible to only a few agents of "last resort," such as colistin or tigecycline; others are truly untreatable (Chapter 313). Unfortunately, new agents active against these strains are years, if not decades, away from introduction.

THE ROLE OF INFECTIOUS AGENTS IN CHRONIC DISEASES. Many so-called idiopathic diseases may in fact have an infectious basis. Conditions for which there is some evidence (but not conclusive proof) of an infectious basis include diabetes, atherosclerosis, acute leukemia, collagen vascular diseases, and inflammatory bowel disease. Detection of "uncultivatable" microorganisms by newer techniques, such as 16S RNA analysis, may uncover agents responsible for "noninfectious" diseases or suggest a role in conditions that are considered infectious but in which the pathogen or pathogens are controversial (e.g., bacterial vaginosis). In addition, we know that hepatitis C virus, human papillomavirus, and *Helicobacter pylori* cause human cancers. Furthermore, changes in our own microbiome may lead to disease. Alterations in the gut microbiome are associated with obesity. Another recent example comes from experiments with mice lacking TLR5. These mice develop hyperphagia and hallmark features of the metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and increased adiposity, associated with an altered gut microbiome. Further, transfer of this changed microbiota into germ-free wild-type mice induces most features of the metabolic syndrome in the recipients.

SUGGESTED READINGS

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Sogaard OS, Lohse N, Harboe ZB, et al. Improving the immunogenicity of pneumococcal conjugate vaccine in HIV-infected adults with a Toll-like receptor 9 agonist adjuvant: a randomized controlled trial. *Clin Infect Dis.* 2010;51:42-50. *Example of the use of Toll-like receptor agonists as adjuvants to enhance vaccine immunogenicity.*

Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol.* 2010;125:S24-S32. *Excellent review of recent advances, and how innate immunity interacts with adaptive immunity.*

Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science.* 2010;328:228-231. *The salient findings of these experiments are discussed in the text.*

287 PRINCIPLES OF ANTI-INFECTIVE THERAPY

GEORGE M. ELIOPOULOS

Among the pharmaceutical agents used in the treatment of human disease, antimicrobial agents are distinctive because they target invading microorganisms rather than abnormal human cellular functions. As a result, to select an appropriate antimicrobial regimen, it is necessary to consider both the activity of the agent against the known or suspected pathogen and the effects that agent might have on the individual under treatment. Although the term *anti-infective agent* can be used more broadly to include substances that ameliorate infection by altering the virulence of the pathogen or modulating the host's response to infection, for purposes of this chapter, *anti-infective agent* and *antimicrobial agent* are used interchangeably to refer to drugs that inhibit the growth of microbial pathogens. This chapter focuses primarily on agents directed against bacterial pathogens, although many parallels can be drawn to the use of antimicrobial agents for the treatment of fungal, viral, or parasitic infections.

On the time scale of human history, the modern antibiotic era is short. Since the introduction of penicillin for general clinical use in the mid-1940s, the numerous antimicrobial agents developed for human use have saved countless lives and have led to amazing advances in cancer chemotherapy, organ transplantation, and implant surgery that have improved and extended the lives of many others. Unfortunately, over time, resistance to available antibiotics has become widespread among many common bacterial pathogens, making the selection of appropriate antimicrobial regimens ever more

challenging and threatening to thrust an unfortunate few into a situation resembling the pre-antibiotic era.

SELECTING ANTIMICROBIAL THERAPY TARGETING THE PATHOGEN

Empirical Antimicrobial Therapy

In most instances, selection of the initial antimicrobial therapy proceeds empirically, before a causative organism is identified or tested for susceptibility to antimicrobial agents. The clinician's first decision is whether a patient's symptoms are likely to represent infection. Fever may result from neoplastic, rheumatologic, or other noninfectious processes and does not necessarily imply the presence of infection. Noninfectious causes of fever, such as deep vein thrombophlebitis, drug reaction, or vasculitis, may pose just as great a risk to the patient as infection and must not be overlooked.

Additional symptoms, signs, and laboratory or radiographic data usually help define whether infection is likely and, if so, localize the organ systems involved. This information allows an initial prediction about the organisms likely to be involved. For example, if the initial data cause one to suspect a diagnosis of community-acquired pneumonia in a previously healthy person who does not have any unusual exposures, *Streptococcus pneumoniae* and atypical bacteria such as *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* would be prominent on the list of potential pathogens to be targeted when selecting antimicrobial therapy. Examination of a Gram-stained slide of expectorated sputum may provide valuable information. The prominent appearance of gram-positive cocci in clusters, for example, would alert the clinician to the possible presence of *Staphylococcus aureus,* many isolates of which are now methicillin resistant.

Guidance regarding the probable pathogens for site-specific infections and the susceptibility of these organisms to antimicrobial agents is available from a number of sources. In some cases, the susceptibility of suspected pathogens can be predicted with a high degree of certainty. For example, *Streptococcus pyogenes* remains uniformly susceptible to penicillin G. In other instances, resistance has emerged to antimicrobials previously considered to be highly active against a species. Resistance rates for a given organism may vary widely by region, by health care institution, or even by patient care area within a hospital. For this reason, access to periodically updated, cumulative antibiotic susceptibility profile data specific to an institution can be very important. Typically presented in tabular form, these "antibiograms" show the percentage of recently isolated bacterial pathogens that proved "susceptible" to the antibiotics tested and can help guide the selection of appropriate empirical regimens at that practice site.

There is mounting evidence that selection of an appropriate regimen (i.e., one that contains an antimicrobial that can be expected to inhibit the causative pathogen at the site of infection) and the prompt initiation of that empirical treatment result in improved clinical outcomes in those with serious infections. Published guidelines for the treatment of community-acquired pneumonia advise administration of the first dose of appropriate antimicrobial therapy while the patient is still in the emergency room.

Whenever possible, samples of purulent exudates, blood, or other body fluids suspected to be infected should be obtained for culture before starting antimicrobial therapy. Identification and susceptibility testing of the microorganisms detected can be used to direct subsequent definitive treatment. At times, however, this principle must be overridden. For example, when bacterial meningitis is suspected, antibiotic therapy (often with adjunctive corticosteroids) must not be delayed when a lumbar puncture cannot be performed promptly to obtain material for culture. In such instances, blood samples taken for culture before the administration of antibiotics often reveal the causative organism, or the pathogen may grow from spinal fluid even if lumbar puncture is delayed.

Definitive Antimicrobial Therapy

Identification of the causative microorganism and determination of its susceptibility to available drugs are the basis for optimizing definitive antimicrobial regimens. Often, the antibiotics used for empirical therapy are appropriate for definitive therapy and can be continued. At other times, the results allow one to switch to a narrower spectrum, better tolerated, or less expensive antimicrobial. In some instances, test results indicate the need to broaden the spectrum of an anti-infective regimen by adding or substituting agents active against pathogens inadequately targeted by the initial empirical regimen.

In almost all cases, it is desirable to test an infecting organism's susceptibility to antimicrobials that may be useful. To extend the example cited earlier, although it is not necessary to test the susceptibility of *S. pyogenes* to penicillin G, some isolates are resistant to macrolide antibiotics (e.g., erythromycin, azithromycin) and other drugs, so the testing of alternative agents might be useful for patients who are intolerant of β-lactam antibiotics. Even when the activity of certain antimicrobials can be predicted with great confidence, susceptibility testing is still useful. For example, surveillance studies examining hundreds of isolates have predicted that vancomycin or linezolid would inhibit virtually all *S. aureus* strains recovered from initial clinical specimens. Therefore, on statistical grounds, testing these agents would not seem warranted; however, rare isolates resistant to these agents have now been encountered, and it is advantageous to detect such isolates for both therapeutic and epidemiologic purposes. For most bacterial pathogens, resistance to commonly used agents is sufficiently frequent that testing of antimicrobials being considered for definitive therapy is essential. Organisms of the family Enterobacteriaceae that are resistant to multiple antibiotics are isolated often enough, even among outpatients, that susceptibility to agents previously considered broadly active, including third-generation cephalosporins, fluoroquinolones, and aminoglycosides, is no longer assured. Even more challenging problems of drug resistance are encountered among isolates of species such as *Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Stenotrophomonas maltophilia.*

Susceptibility Testing

Several methods are available for determining the susceptibility of a bacterial isolate to antimicrobial agents being considered for therapy. Tests used in clinical microbiology laboratories today are variations of three methods: serial dilution, disc diffusion, and gradient diffusion. The minimal inhibitory concentration (MIC) represents the lowest concentration of an antimicrobial tested that inhibits growth of the microorganism in test media.

In the dilution method, the antimicrobial is diluted in broth or agar to span a range of (usually) two-fold decreasing concentrations, and the medium is then inoculated with a standardized number of organisms. After incubation for a specified period (usually 16 to 24 hours) at 35 to 37° C, the series of dilution tubes or microtiter wells (for broth dilution) or agar plates (for agar dilution) is examined for growth. The MIC is determined by direct inspection as the lowest concentration that prevents turbidity of the broth or colony formation on agar. Modifications of this method allow the automation of many steps in the process, permitting more efficient test performance in clinical laboratories.

In the disc diffusion method, paper discs impregnated with a standardized amount of the antimicrobial are placed on an agar plate, the surface of which has been seeded with the bacterium to be tested. During incubation, the antimicrobial diffuses from the disc into the surrounding agar and inhibits growth of the seeded organism. After a specified period of incubation, the zone of growth inhibition around the disc is measured. By this method, the MIC is not determined directly. Instead, relying on accumulated data correlating inhibition zones with MICs, the measured zone is used to predict the susceptibility of the organism to the drug tested.

The gradient diffusion method is similar to the disc diffusion method, except that instead of using a round paper disc impregnated with a single concentration of the antimicrobial, this test uses a strip impregnated with the antimicrobial applied in a concentration gradient along its length. The strip is laid on the surface of an agar plate that has been inoculated with a suspension of the organism to be tested, and the plate is then incubated. By visually inspecting where the zone of growth inhibition on the agar surface intersects the strip (which is marked at intervals corresponding to MIC equivalents), it is possible to determine the MIC value directly.

To perform and interpret the results of susceptibility studies, it is necessary to identify the organism to be tested. This knowledge allows the selection of appropriate interpretive criteria to determine whether an organism is "susceptible," "intermediate," or "resistant" to an antimicrobial based on measurement of the MIC or the inhibition zone diameter. To illustrate this point, consider that an enterococcus is determined to be susceptible to penicillin if the MIC is less than or equal to 8 μg/mL, whereas for viridans streptococci, the corresponding breakpoint for susceptibility to penicillin is a MIC of 0.12 μg/mL. Thus, knowledge that the MIC of a gram-positive coccus growing in short chains is 2 μg/mL does not allow the determination of whether it is susceptible to penicillin unless the organism has been identified.

Additional tests are sometimes required to fully assess susceptibility to an antimicrobial. For oxacillin-susceptible *S. aureus,* a test for penicillinase production is performed to assess susceptibility to penicillin G. For erythromycin-resistant, clindamycin-susceptible *S. aureus,* the laboratory may perform

a supplementary D-zone test before reporting the clindamycin result. A positive D-zone test (i.e., blunting of the inhibition zone around a clindamycin disc in proximity to an erythromycin disc) predicts the presence of *erm* genes. Their product, a ribosomal methylase, can confer resistance to clindamycin if expressed; however, clindamycin is a poor inducer of this resistance trait (in contrast to erythromycin, which is a good inducer). Mutants with constitutive production of methylase can be selected during treatment, resulting in the emergence of clindamycin resistance and an increased risk of clinical failure when this drug is used to treat serious staphylococcal infections caused by strains with the *erm* gene.

In principle, tests for the presence of resistance genes, their products, or both can be used in place of phenotypic resistance testing. Such methods have the potential to provide answers more rapidly than can be obtained with the usual susceptibility tests of growth inhibition, which generally require several hours of incubation. However, at present, these tests have not been widely adopted, with the exception of testing for methicillin resistance by detection of the *mecA* gene or its product, penicillin-binding protein 2a.

Bactericidal Activity

In some circumstances, an antimicrobial regimen that kills pathogenic microorganisms would be preferable to an alternative regimen that only inhibits growth of the pathogen. Bactericidal activity is desirable in the treatment of endocarditis or meningitis; in these infections, bacteriostatic agents have generally performed poorly, possibly because of inadequate host responses to infection at these sites. Tests to measure the bactericidal activity of an antibiotic in vitro have been developed. Bactericidal activity is usually defined as a 99.9% reduction in the number of viable colony-forming units relative to the inoculum density at a specified incubation time, which is usually 20 to 24 hours.

Despite the theoretical benefit of determining the bactericidal activity of an antibiotic or drug regimen, these tests are rarely used clinically because of several factors, including (1) the labor-intensive nature of the tests, (2) the potential for discordant results owing to the various methods and criteria for determining bactericidal activity, and (3) imperfect correlation between bactericidal activity measured in vitro and clinical outcomes observed.

SELECTING ANTIMICROBIAL THERAPY APPROPRIATE TO THE INFECTION AND PATIENT

Nature of the Infection

Determination that a pathogenic microorganism is susceptible to an antibiotic in vitro does not ensure that treatment with that drug will result in a successful clinical outcome. The antimicrobial must reach the site of infection in adequate concentration, which is generally assumed to be some multiple of the MIC, and it must demonstrate activity in the infection milieu. For some infections and antimicrobials, these requirements cannot easily be met.

A number of antimicrobials fail to penetrate into cerebrospinal fluid sufficiently well to permit their use for the treatment of bacterial meningitis in adults. First-generation cephalosporins or aminoglycosides given intravenously do not enter the subarachnoid space well enough to allow their use as primary agents for treatment of this disease. Aminoglycosides have been administered by intrathecal or intraventricular instillation when needed for the treatment of gram-negative meningitis, but the availability of newer β-lactams with broad activity, high potency, and reasonable penetration represents a major advance.

In other situations, antimicrobials may penetrate to the site of infection, only to be inactivated by local factors. For example, daptomycin is inactivated by interaction with pulmonary surfactant, so this antibiotic is not indicated for the treatment of bronchopneumonia, even though it is highly active against *S. pneumoniae* isolates in vitro. Antibiotics can also be inactivated by cellular debris or macromolecules present within abscesses, and some exhibit reduced potency at the low pH and reduced oxygen tensions prevailing at these sites. Finally, high densities of microorganisms within abscesses may elaborate sufficiently high concentrations of β-lactamases to inactivate some relatively labile β-lactam antibiotics. All these factors provide a rationale for the drainage of large abscesses as an adjunct to antimicrobial therapy.

Bacterial infections associated with foreign bodies such as artificial joints, cardiac pacemakers, or prosthetic heart valves can be particularly difficult to eradicate without removing the foreign material. The reasons are not completely understood, but they relate, at least in part, to the presence of biofilm, which is composed of bacteria embedded within extracellular material that is adherent to the foreign body. Bacteria recovered from biofilms are metabolically different from and less susceptible to antimicrobial agents than planktonic cells (i.e., those freely suspended in liquid medium) of the same organism. Rifampin is often added to antimicrobial regimens for the treatment of infections involving prosthetic material. This inhibitor of RNA polymerase rapidly penetrates into biofilms and demonstrates relatively similar activity against both biofilm-associated and planktonic cells of a susceptible organism. However, because resistance to rifampin emerges rapidly, it is not used as a single agent in these circumstances; rifampin must be combined with a second active drug to minimize the risk that resistance will emerge. Despite such approaches, many infections involving implanted devices prove refractory to antimicrobial therapy alone and require removal of the foreign material for eradication.

Host Factors

After considering the nature of the infection and the antimicrobials determined in vitro to be active against a bacterial isolate (or likely to be active against probable pathogens when an isolate is not yet available), the ultimate choice of an antimicrobial regimen must take into account a number of additional patient-specific factors, some examples of which are examined in the following paragraphs.

Allergies

It is imperative to obtain a history of previous allergic reactions to antimicrobial agents. Some reactions are by nature so severe and potentially life-threatening that one must avoid using the same agent or drugs within the same class for which cross-reactivity is likely to occur. Examples of such reactions include an immediate hypersensitivity reaction to penicillin (e.g., hives, lip swelling, laryngeal edema, circulatory collapse) or a mucocutaneous bullous eruption from a sulfonamide (e.g., Stevens-Johnson syndrome).

In cases in which the allergic reaction was mild, such as a faint, self-limited rash in a patient receiving penicillin, the clinician may elect to use a related antimicrobial, such as a cephalosporin, when the probability of cross-sensitivity and the risk for a severe adverse outcome if a reaction were to occur are both assessed to be low. In these instances, careful monitoring of the patient for adverse reactions is essential. Rarely, for patients with significant allergies to potentially life-saving antimicrobial agents for which no alternative exists, desensitization of the patient to the antimicrobial is attempted so that the agent can be used. For example, desensitization protocols are available for penicillin and for trimethoprim-sulfamethoxazole. Because of the risks involved, these procedures may need to be performed in intensive care unit settings.

Pregnancy

A number of antimicrobial agents have the potential to cause fetal harm if administered to a pregnant woman. For example, tetracyclines can cause tooth discoloration and hypoplasia of dental enamel and are thus avoided in pregnant women and young children. Streptomycin given during pregnancy can cross the placenta, and evidence of eighth nerve toxicity has been reported. A few other antimicrobials are labeled by the Food and Drug Administration (FDA) as pregnancy category D (evidence of human risk) or are contraindicated because of fetal harm (category X). Many more antimicrobials, however, are assigned to category C; for these drugs, the potential risk to the fetus is based on animal studies. When designing antimicrobial regimens, the possibility of pregnancy should be considered in any woman of childbearing age so that the risks of candidate agents can be individually reviewed and the safest possible therapy selected.

It should also be noted that many antibiotics used to treat lactating women can be found in breast milk. Thus, it may be necessary to suspend breastfeeding during treatment if exposure of the infant to the drug must be avoided.

Pregnant women may be particularly susceptible to certain antimicrobial-associated toxicities. Death resulting from hepatic failure has been described in pregnant women receiving large doses of tetracycline. Potentially life-threatening hepatic steatosis has been observed in patients treated with a combination of the antiretroviral agents didanosine plus stavudine; pregnant women may be especially vulnerable to this toxic effect.

Age

For reasons discussed earlier, tetracycline antibiotics are avoided in children during tooth development to prevent discoloration and enamel hypoplasia

of the permanent teeth. Because fluoroquinolone antimicrobials produce erosion of cartilage and arthropathy in juvenile animals, they are avoided in children when alternative agents are available. Recently, limited pediatric indications were added for ciprofloxacin (for complicated urinary tract infection and pyelonephritis and, along with levofloxacin, for treatment after inhalational exposure to anthrax). Musculoskeletal complaints appear to be more frequent in children treated with ciprofloxacin than with nonfluoroquinolone antimicrobials.

Pediatric dosing regimens differ from those appropriate for adults. Some agents, such as linezolid, are eliminated much more rapidly in young children (excluding preterm neonates) than in older children and adults, so higher doses are required. In premature infants and neonates, renal function has not yet reached full capacity, and drug elimination may be delayed. Similarly, hepatic clearance activity is not fully developed in the very young, which has led to cardiovascular collapse and fatalities from chloramphenicol treatment. Absorption of oral antimicrobials may also differ with age if their absorption is dependent on gastric pH. The gastric pH of young children is higher than that of adults, and achlorhydria resulting in higher gastric pH is more common in adults older than 60 years than in younger adults. Thus, in young children and older adults, the absorption of oral drugs that are unstable in acid, such as penicillin G, may be higher than that in younger adults. In contrast, antimicrobials such as ketoconazole require gastric acid for absorption and may be less bioavailable in persons with reduced gastric acid production.

A curious association between the appearance of a rash and the patient's age and sex was noted during development of the fluoroquinolone antimicrobial gemifloxacin. In clinical studies, rash was more common in young women than in men and older women, suggesting there may be hormonal influences on the risk of developing a rash.

Renal and Hepatic Function

Renal excretion and hepatobiliary excretion are the major routes of elimination for antimicrobial agents. Relatively few antibacterial agents can be administered without dosage adjustments in patients with renal dysfunction. Included among these drugs are nafcillin, ceftriaxone, doxycycline, azithromycin, and linezolid. Although linezolid exposure is not significantly altered, microbiologically inactive metabolites of the compound do accumulate in end-stage renal disease; what, if any, effect this has is unknown.

A number of antimicrobial agents require major dosage adjustments in the presence of renal dysfunction. The dosing interval for ceftazidime, usually administered every 8 hours in patients with normal renal function, is extended to once every 48 hours in persons with creatinine clearance below 10 mL/minute. Vancomycin is also administered at substantially increased dosing intervals or at smaller doses as renal function declines. Because of the increased efficiency of newer hemodialysis membranes in removing vancomycin, dosages are usually based on measured serum drug concentrations, and dosing may be required after each dialysis session.

In some instances, clearance of the antimicrobial agent is not affected by renal dysfunction, but excipients may accumulate, with the potential for toxic effects. For example, clearance of the antifungal agent voriconazole is not dependent on renal function. However, its intravenous preparation contains the solubilizing agent sulfobutyl ether β-cyclodextrin, which does accumulate in the presence of renal insufficiency. The intravenous preparation should not be used in those with renal dysfunction, but the oral formulation, which does not contain β-cyclodextrin, can be administered. A number of other antimicrobials may accumulate in the presence of severe liver disease, with the possibility of an increased risk for adverse events. Antimicrobials requiring dose adjustments for various levels of hepatic insufficiency include metronidazole, chloramphenicol, tigecycline, caspofungin, and voriconazole. For ceftriaxone, dosage adjustments or careful monitoring may be required in patients with both hepatic and renal dysfunction. Several of the newer antimicrobials, such as daptomycin, linezolid, and micafungin, have not been studied sufficiently to determine whether dosing modifications are required in patients with severe liver disease.

Drug-Drug Interactions

One of the most important considerations in the selection of an appropriate antimicrobial regimen is to determine whether the drug or drugs will interact with other medications the patient is taking. Some drug-drug interactions can have severe or even fatal consequences. There are too many potential interactions to list comprehensively, but some examples are provided in this section. Fortunately, resources are now available that allow the clinician to check for potential drug-drug interactions when an antimicrobial agent is ordered.

A large number of antimicrobials are eliminated via cytochrome P-450 pathways. As a result, they may interfere with the elimination of other drugs cleared by these pathways, leading to their accumulation to potentially dangerous levels. Several macrolide antibacterials, some fluoroquinolones, and human immunodeficiency virus (HIV) protease inhibitors are among the most likely antimicrobials to inhibit the clearance of other drugs. For example, use of the protease inhibitor nelfinavir is contraindicated with several drugs, including the antiarrhythmics amiodarone and quinidine, ergot derivatives, the neuroleptic drug pimozide, and certain sedative-hypnotic agents. Macrolides may result in increased levels of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which can lead to rhabdomyolysis. Although quinupristin-dalfopristin is not eliminated by the cytochrome P-450 system, this drug inhibits the elimination of various agents cleared by this pathway, including cyclosporine, midazolam, nifedipine, and others.

In contrast, administration of rifampin induces the cytochrome P-450 system and may enhance the clearance of other drugs, some of which have narrow therapeutic windows. This may result in a number of important effects, including reduced effectiveness of oral contraceptives and increased warfarin requirements to maintain desired levels of anticoagulation. It is very important to consider these potential interactions not only when starting rifampin therapy but also when *stopping* treatment. When rifampin is stopped, unless the previously increased dose of warfarin is adjusted downward accordingly, excessive anticoagulation and possibly serious bleeding can occur.

A number of other drug interactions have been described. Linezolid has weak monoamine oxidase inhibitor activity. As such, it has the potential to enhance the hypertensive effect of adrenergic agonists and has been associated with the development of serotonin syndrome in patients taking selective serotonin re-uptake inhibitors (SSRIs). Patients with this syndrome can exhibit a number of signs and symptoms, including fever, tachycardia, tremulousness, agitation, confusion, and clonus, occasionally with fatal results. Serotonin syndrome (Chapter 442) has been described in patients taking linezolid together with drugs other than SSRIs; in principle, it could occur when linezolid is combined with any of a large number of agents that increase serotonin concentrations in the central nervous system.

Other Host Factors

Several additional host factors may influence the choice of a suitable antimicrobial regimen. Some antimicrobials have the potential to induce hemolysis in persons with glucose-6-phosphate dehydrogenase deficiency (Chapter 164). Among the drugs that should be avoided in these individuals are primaquine, nitrofurantoin, and various sulfonamides.

Coexisting diseases should also be taken into account. Use of fluoroquinolones has been associated with abnormalities in glucose homeostasis. Hyperkalemia has been observed in patients with renal insufficiency during treatment with trimethoprim-sulfamethoxazole because trimethoprim blocks the renal excretion of potassium in the distal tubule.

In some cases, the patient's occupation might play a role in the selection of a treatment regimen. Antibiotics that can cause transient (minocycline) or permanent (streptomycin) dizziness or unsteadiness may create hazardous situations in those whose occupations require excellent balance. Antimicrobial agents with the potential to cause photosensitivity, such as tetracyclines, fluoroquinolones, trimethoprim, and sulfonamides, may be problematic in persons with significant sun exposure during outdoor employment or other activities.

ANTIMICROBIAL COMBINATIONS

It is very common for hospitalized patients to receive more than one antimicrobial agent simultaneously. The rationale for using antimicrobials in combination is not always clearly defined, and there are a number of potential disadvantages to combination therapy. The basis for using combination therapy is considered in this section.

Reasons to Use Combination Antimicrobial Therapy

The clinical indications for using combination antimicrobial therapy can be divided into five categories. Two of these categories (empirical therapy and polymicrobial infections) relate to maximizing the likelihood that at least one agent in the combination will be active against known or suspected pathogens. The other three reasons (minimizing toxicity, preventing the emergence of resistance, and obtaining synergistic inhibition or killing) attempt to exploit the unique advantages of combinations versus any component drug alone.

Provide Broad Coverage during Empirical Therapy

A common reason for using more than one antimicrobial in hospitalized patients is to provide broad coverage against potential pathogens and to maximize the likelihood of delivering an active antimicrobial agent as quickly as possible to seriously ill patients. When the pathogen is unknown, the antimicrobial regimen often includes an agent broadly active against gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA), such as vancomycin, as well as an agent active against aerobic or facultative gram-negative bacteria. Selection of the latter is strongly influenced by local patterns of antimicrobial resistance specific to the institution and might include an extended-spectrum cephalosporin, an aminoglycoside, a fluoroquinolone, a β-lactam–β-lactamase inhibitor drug, or a carbapenem. The latter two choices also provide activity against gram-negative anaerobes. Alternatively, one could add an agent such as metronidazole to provide anaerobic activity. Because of the high frequency of antibiotic resistance in *Pseudomonas aeruginosa* isolates, in settings in which that pathogen is encountered frequently, empirical use of two agents with antipseudomonal activity may be justified to maximize the likelihood that at least one of the agents will inhibit the organism.

Combination therapy is widely used in the initial treatment of hospitalized patients with community-acquired pneumonia. Commonly used regimens include a third-generation cephalosporin such as ceftriaxone with a macrolide or fluoroquinolone. The cephalosporin provides antimicrobial activity against *S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and several other "typical" bacterial pathogens associated with community-acquired pneumonia, with the notable exception of MRSA. The macrolide azithromycin is commonly used, or a fluoroquinolone that inhibits "atypical" bacteria that cause pneumonia, including *M. pneumoniae, C. pneumoniae,* and *Legionella* species. Although fluoroquinolones approved for respiratory tract infections are likely to cover most or all of the organisms targeted by the cephalosporin, isolates of *S. pneumoniae* resistant to fluoroquinolones do exist, so guidelines recommend combination therapy in patients with severe pneumonia requiring hospitalization.

Treat Documented Polymicrobial Infections

For many infections from which two or more pathogens are recovered, it is possible to provide adequate coverage with a single, broadly active antimicrobial agent. Switching to a single agent reduces the patient's exposure to potential antibiotic toxicities, is usually more convenient for nursing staff, and may be less expensive. For some patients, susceptibility profiles or allergies to broad-spectrum agents justify the use of antibiotic combinations for the treatment of polymicrobial infections.

Attempt to Reduce Toxicity

It is theoretically possible to use two or more drugs of different classes with additive antimicrobial activities and independent toxicities, each at relatively low doses, to achieve sufficient potency while avoiding toxicity. However, there are no situations in which the approach of using submaximal doses of multiple agents is predictably effective in accomplishing this goal. This does not exclude the possibility that, in isolated instances, a successful response might be attained when drugs with marginal activities are combined.

Prevent the Emergence of Drug Resistance

The treatment of tuberculosis provides the paradigm for using combinations of drugs in an attempt to prevent the emergence of resistance to any one agent. The basis for this approach is that if resistance to two different agents occurs by independent mechanisms, the probability of resistance developing to both drugs is the product of the probability of resistance developing to each drug, which is likely to be very low, so resistance should not emerge. Similar reasoning has justified the use of combination regimens when rifampin is required for the treatment of nonmycobacterial infections. Rifampin is not used alone (with rare exceptions, such as brief courses for the eradication of meningococcal carriage) because resistance to this agent emerges quickly. As mentioned earlier, rifampin is particularly useful in the treatment of infections related to foreign devices because of its activity against biofilm-associated bacteria. In such cases, it is combined with another active antimicrobial, such as vancomycin for coagulase-negative staphylococcal prosthetic valve endocarditis (usually with a brief course of gentamicin as well, to reduce the bacterial inoculum further at the beginning of therapy) or a fluoroquinolone for orthopedic device–related infections.

It has been difficult to show unequivocally that combination therapy protects against the emergence of resistance to antimicrobial drugs in other situations, including infections caused by *P. aeruginosa* or *Enterobacter* species. There are two plausible explanations of why combinations do not prevent resistance predictably. First, there may be differential penetration of the two antimicrobials at an infected site or differences in activity at the site of infection. Thus, a more readily penetrating agent may be left relatively unprotected in a privileged site of infection. Second, for many commonly encountered bacteria, resistance mechanisms against unrelated antimicrobial classes may not be truly independent. Some bacterial efflux pumps recognize chemically unrelated substrates, so upregulation of pump activity may confer resistance to several classes of antimicrobials. In other instances, there may be coordinated upregulation of efflux mechanisms and downregulation of outer membrane protein channels (porins), again potentially conferring resistance simultaneously to two or more antimicrobial classes.

Attain Synergism

Decades ago, the surprising benefits of using penicillin and streptomycin together for the treatment of enterococcal endocarditis were discovered empirically. Penicillin alone usually inhibits but does not kill enterococci, and failure rates were high when penicillin G was used alone to treat enterococcal endocarditis. Streptomycin has no significant activity against enterococci at clinically relevant concentrations. However, the combination results in bactericidal synergism in vitro and high cure rates in patients with enterococcal endocarditis. Detailed studies of this phenomenon demonstrated that in the presence of a cell wall–active antibiotic, uptake of the aminoglycoside into the bacterial cell increases substantially. Unfortunately, increasing rates of high-level resistance to streptomycin (MIC > 2000 μg/mL), gentamicin (MIC > 500 μg/mL), or both have nullified the benefit of such combinations against a substantial number of enterococcal isolates today. An example of bactericidal synergism between vancomycin and gentamicin against an *Enterococcus* isolate is illustrated in Figure 287-1A.

Combinations of cell wall–active agents plus aminoglycosides have been shown to achieve synergistic killing against a broad range of gram-positive and gram-negative bacteria when tested in vitro. Modest clinical benefits were shown when short courses of gentamicin were added to nafcillin for the

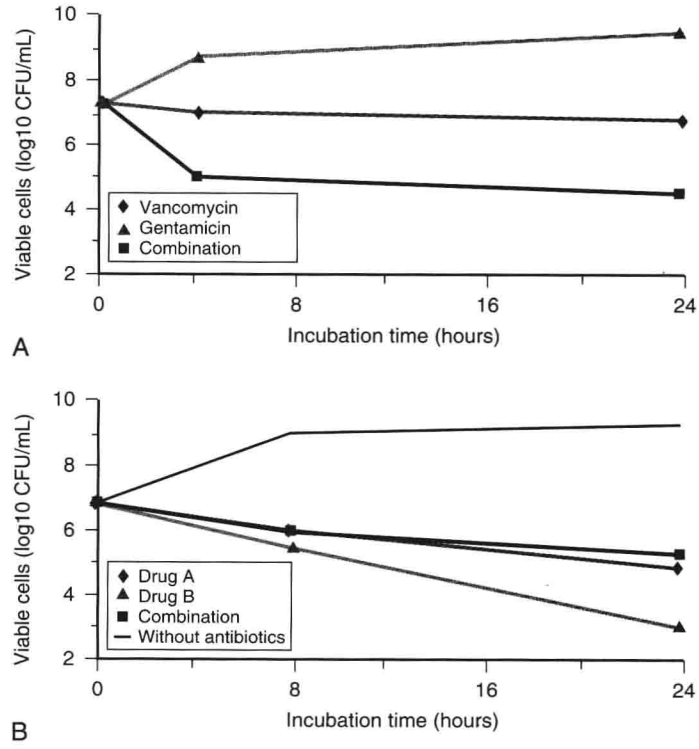

FIGURE 287-1. Bactericidal synergism and antagonism. A, Bactericidal synergism between vancomycin and gentamicin against an isolate of *Enterococcus* species. Killing by the combination of drugs is substantially greater than that by each agent alone. **B,** Antagonism of the bactericidal activity of drug B by the more slowly bactericidal drug A. Killing by the combination of drugs is less than that by drug B alone. Growth in the absence of antibiotics is also shown. CFU = colony-forming unit.

treatment of *S. aureus* endocarditis, but at the cost of added nephrotoxicity. Against strains of viridans streptococci that are relatively insensitive to penicillin, the addition of an aminoglycoside for the first 2 weeks of a 4-week course of penicillin G is believed to result in a higher likelihood of cure.

Although it was once considered important in the treatment of gram-negative bacterial infections, especially in immunocompromised (e.g., neutropenic) patients, the clinical value of a synergistic combination of a cell wall–active agent and an aminoglycoside has been difficult to prove in recent experience. To a large extent, the introduction of agents with very potent activity against gram-negative bacteria has diminished the perceived value of synergistic combinations. Nevertheless, there is some evidence that administering two or more active drugs for empirical therapy may achieve a better outcome than is possible with a single active agent for *P. aeruginosa* infections, especially in neutropenic patients. The major value of combination therapy in this setting is to ensure that at least one active agent is administered promptly (Chapter 289). The combination of sulfamethoxazole and trimethoprim, agents that block sequential steps in folic acid synthesis, can also achieve bactericidal (or bacteriostatic) synergism against a number of important gram-positive and gram-negative pathogens. Quinupristin and dalfopristin are streptogramin antibiotics that display inhibitory activity against gram-positive organisms. Combining these two agents, as is done in the commercial formulation, results in bactericidal synergism against organisms susceptible to both.

β-Lactam–β-lactamase inhibitor antimicrobials represent another example of synergistic combinations. Four drugs in this category are currently marketed in the United States: amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam. The β-lactamase inhibitors themselves, clavulanic acid, sulbactam, and tazobactam, are devoid of significant antimicrobial activity, with rare exceptions. However, by inhibiting common β-lactamases that are sensitive to these agents, the inhibitors restore the activity of the hydrolyzable companion penicillins against many target pathogens elaborating these enzymes.

Antagonism

Antibiotic combinations can sometimes result in microbiologic antagonism, such that the combination may have *reduced* activity when compared with the most active single agent of the treatment regimen. Time-kill curves illustrating in vitro antagonism are shown in Figure 287-1B. In this example, the more slowly bactericidal drug A antagonizes the killing effect of the intrinsically more bactericidal drug B. Antagonistic interactions against *S. aureus* between less bactericidal (linezolid) and more bactericidal (vancomycin) antimicrobials have also been demonstrated in vivo in experimental endocarditis. In vitro antagonism can be demonstrated when certain β-lactams are tested in combination against gram-negative bacteria with inducible β-lactamases. Here, exposure to one β-lactam can de-repress the synthesis of inducible β-lactamases, which then degrade the second antibiotic.

It is uncommon to encounter clinically apparent antagonism between antibiotics in the patient care setting, in part because offending combinations are not likely to be used in routine clinical care today. However, if unusual antimicrobial combinations are used, in desperation, against isolates exhibiting multiple drug resistance, it is possible that clinically relevant antagonism will be encountered more often in the future. Antagonism of bactericidal activities may also be difficult to detect in clinical practice because most common infections (with the exception of endocarditis and meningitis) do not unequivocally benefit from bactericidal therapy. As long as one agent maintains inhibitory activity, it is unlikely that failure resulting from antagonism will be observed.

CONSIDERATIONS IN ANTIMICROBIAL ADMINISTRATION

Route of Administration

In almost all instances, antimicrobial therapy for infections of mild to moderate severity that are treated in the outpatient setting can be undertaken with oral agents. There are notable exceptions, such as the use of intramuscular injections of benzathine penicillin for the treatment of syphilis or ceftriaxone for the treatment of otitis media or gonorrhea caused by strains resistant to oral agents.

Drugs such as levofloxacin and linezolid demonstrate virtually complete bioavailability when administered by the oral route in persons with normally functioning gastrointestinal tracts, and they can be used as an alternative to intravenous therapy in many patients with more serious infections. Even for these well-absorbed antimicrobials, however, treatment of seriously ill patients in the hospital is often initiated with intravenous formulations because of the uncertainty of gastrointestinal tract function under conditions of hemodynamic instability.

Antimicrobial therapy can be administered by other routes, including topical administration for the treatment of infected skin lesions (e.g., mupirocin ointment) and intravaginal administration for candidiasis (e.g., azole creams) or for bacterial vaginosis (e.g., metronidazole gel). Topical administration *onto* the eye is used to treat conjunctivitis or as adjunctive therapy for deeper infections; administration *into* the globe itself is a component of regimens for the treatment of endophthalmitis. Infections associated with peritoneal dialysis are frequently treated by intraperitoneal instillation of antimicrobials admixed with the dialysis solution. Rarely, direct administration into the thecal space or into the cerebral ventricles is necessary for the treatment of meningitis when the required antimicrobials do not achieve adequate concentrations in cerebrospinal fluid after systemic administration. Vancomycin is almost always given orally, but it is occasionally administered directly into the intestine for the intraluminal treatment of *Clostridium difficile*–associated diarrhea.

The availability of protocols for the outpatient use of long venous catheters, whether inserted centrally or peripherally, has made it possible to administer antimicrobial agents that are not well absorbed orally. Thus, many patients who require long-term antibiotic treatment for infections such as endocarditis, osteomyelitis, neuroborreliosis, and other conditions can be treated as outpatients after an initial period of hospitalization for a full assessment of the infection, initiation of therapy, and stabilization of the medical condition. In addition to monitoring for adverse effects from the antibiotic itself, patients treated via indwelling intravenous devices require close observation for complications related to the catheter, such as thrombophlebitis, entry site infections, or line-related blood stream infections.

Pharmacodynamic Considerations

In recent years, the scientific basis for selecting a dosing regimen has extended well beyond empirical dosing strategies based primarily on the pharmacokinetic characteristics of antimicrobial agents. Pharmacodynamics relate the time course of antibiotic concentrations after dosing, the observed antimicrobial effects against likely pathogens, and the potential adverse effects of the agent.

Studies of the pharmacokinetic and pharmacodynamic properties of antimicrobial agents allow the prediction of their activities with various dosing regimens. For β-lactam antibiotics, the time during which the concentration of free drug (i.e., the non-protein-bound fraction) exceeds the MIC of the pathogen best relates to antimicrobial effectiveness in animal models. This provides the rationale for the frequent dosing schedules of β-lactams with short half-lives, such as penicillin G and the antistaphylococcal penicillins.

In contrast, the aminoglycosides and fluoroquinolones demonstrate concentration-dependent killing of bacteria. For these drugs, animal models show that the ratio of either peak concentration to MIC or the area under the 24-hour drug concentration curve to MIC better predicts effectiveness. With these agents, less frequent, higher dosing would be optimal. For the aminoglycosides, less frequent dosing may also allow more time for washout of the drug from the kidney, thus potentially minimizing the risk for nephrotoxicity; however, the advantages of this approach are not striking.

For daptomycin, the adoption of once-daily dosing largely mitigated the muscle toxicity that had been seen with more frequent dosing and allowed the use of this agent for serious gram-positive infections.

MONITORING ANTIMICROBIAL CONCENTRATIONS

From a practical point of view, there are few situations in which assays to determine concentrations of antimicrobials in blood or body fluids are readily available. Commercial assays for the measurement of serum aminoglycoside concentrations are available and, because of these agents' great potential for toxicity, are used frequently. Commercial assays to measure vancomycin concentrations are also widely available. It may be prudent to monitor serum concentrations of vancomycin in patients with unstable renal function, those undergoing hemodialysis, patients at the extremes of body composition, or those with particularly serious infections in which high concentrations may be desirable. In some young adults, clearance of vancomycin may be so great that unexpectedly low concentrations result with the usual dosing regimens.