In this issue of Mayo Clinic Proceedings, journal readers will discover the first of 15 articles that constitute the new Symposium on Antimicrobial Therapy. The articles will be published sequentially in the monthly issues of the journal, ending in mid-2012. This new symposium is published in part because of readers’ requests to once again address antimicrobial drugs, as was done in the Proceedings’ Symposium on Antimicrobial Agents, published between October 1998 and February 2000. The new 2011-2012 symposium arrives at an important time for infectious disease management worldwide.

The past 2 decades have seen an unprecedented wave of new and old infections thrust into the public’s attention. During that time, the number of emerging and reemerging infectious diseases has substantially increased. Emerging infections are infections that appear for the first time in a population, whereas reemerging infections are known infections that reappear after a decline in incidence or extend their geographic impact. Examples include pandemic influenza A (H1N1) virus, avian influenza virus, severe acute respiratory syndrome (SARS), west Nile virus infection, and ehrlichiosis. A feature of current emerging and reemerging infections is that disease first appearing at one geographic location traverses continents and affects millions of people within a very short period. First reported from Mexico in the spring of 2009, pandemic influenza A (H1N1) virus infection was noted in almost all countries in the world by March 2010, resulting in nearly 18,000 deaths. In only a few months, SARS spread from China to 26 countries and affected 8098 people, causing 774 deaths.

The human immunodeficiency virus (HIV) epidemic continues to affect communities worldwide; at the end of 2009, an estimated 33.3 million people were living with HIV. However, the most recent global figures indicate that the epidemic is beginning to slow down and perhaps reverse its course. Both HIV incidence and HIV-related deaths have decreased by nearly 20% worldwide. This decline is attributable in part to access to antiretroviral therapy; in 2009, more than 5 million people were receiving antiretroviral therapy.

Globally, tuberculosis (TB) continues to account for a substantial burden of disease, with 9.4 million (11%-13% HIV-positive) incident cases, 14 million prevalent cases, and 1.7 million deaths in 2009. The number of cases of multidrug-resistant TB in 2008 was estimated at 440,000. By July 2010, 58 countries and territories had reported at least 1 case of extensively drug-resistant TB. Intensive efforts to reduce the global burden of TB are under way. The cornerstone of these efforts is access to quality diagnosis and treatment. Although little progress has been made in the development of new anti-TB drugs, the scale-up of intensive efforts to improve TB care and control globally has resulted in up to 6 million lives being saved. The introduction of newer diagnostic modalities, including automated molecular tests that can be used in a resource-limited setting where the burden of TB is the highest, has generated great optimism and excitement.

Many infections have become increasingly difficult to treat because of the emergence of resistance to commonly used antibiotics. Bacteria develop resistance in response to selective pressure exerted by inappropriately used antibiotics. Mutations that confer resistance may be passed on to other bacteria of the same species as well as those of different species and genera. Hospital-acquired antibiotic-resistant infections are estimated to cause 100,000 deaths in the United States, with substantial direct and indirect economic costs to the country. These antibiotic-resistant infections are caused by a variety of organisms, including methicillin-resistant Staphylococcus aureus, penicillin-
resistant pneumococci, vancomycin-resistant enterococci, and resistant gram-negative bacteria (eg, \textit{Klebsiella pneumoniae}, \textit{Acinetobacter baumannii}, \textit{Pseudomonas aeruginosa}), and extended-spectrum β-lactamase–producing bacteria (eg, \textit{Escherichia coli}, \textit{Enterobacter} species).\textsuperscript{12} Some of the reasons for this epidemic of antibiotic resistance among bacteria include poor infection control practices, injudicious use of antibiotics in human medicine, and injudicious use of antibiotics in agriculture. The problem is further aggravated by the lack of a robust antibiotic drug–development pipeline.

Advances in cancer chemotherapy and transplantation, with the resultant increase in the number of people with compromised immunity, as well as an increase in the use of invasive procedures and wide-spectrum antibiotics, have contributed to an increase in the incidence of invasive fungal infections. Although some progress has been made in the development of new diagnostic assays and new antifungal drugs, they remain wholly inadequate, and optimal treatment strategies for many of these invasive fungal infections remain to be defined.\textsuperscript{13}

The \textit{Mayo Clinic Proceedings’} Editorial Board has selected 15 topics for the Symposium on Antimicrobial Therapy that we think will be of relevance and of practical value to general internists and other clinicians. In the first article, Leekha et al\textsuperscript{1} discuss general principles of antimicrobial therapy, dispensing pearls of infectious diseases practice that are difficult to find in any other single publication. Subsequent articles address a variety of infectious disease–related topics, ranging from pharmacology of antimicrobial agents to current concepts in the management of various infections, including bacterial, fungal, viral, mycobacterial, and parasitic infections. Topics addressed in this symposium also include laboratory testing to guide antimicrobial therapy, antibiotic prophylaxis, and current concepts in outpatient antibiotic therapy. All articles are authored by experts in the subject matter. As with previous symposia published by \textit{Mayo Clinic Proceedings}, once all the articles in this Symposium on Antimicrobial Therapy have appeared in the journal, they will be compiled into a book that we hope will serve as a valuable resource to the practicing clinician.

Zelalem Temesgen, MD
Division of Infectious Diseases
Mayo Clinic
Rochester, MN

General Principles of Antimicrobial Therapy

Surbhi Leekha, MBBS; Christine L. Terrell, MD; and Randall S. Edson, MD

On completion of this article, you should be able to: (1) determine the appropriate timing of initiation of antimicrobial therapy, (2) recognize different types of adverse effects of antimicrobial agents and modify antimicrobial therapy as appropriate, and (3) identify clinical scenarios in which use of antimicrobial agents is inappropriate.

Antimicrobial agents are some of the most widely, and often inappropriately, used therapeutic drugs worldwide. Important considerations when prescribing antimicrobial therapy include obtaining an accurate diagnosis of infection; understanding the difference between empiric and definitive therapy; identifying opportunities to switch to narrow-spectrum, cost-effective oral agents for the shortest duration necessary; understanding drug characteristics that are peculiar to antimicrobial agents (such as pharmacodynamics and efficacy at the site of infection); accounting for host characteristics that influence antimicrobial activity; and in turn, recognizing the adverse effects of antimicrobial agents on the host. It is also important to understand the importance of antimicrobial stewardship, to know when to consult infectious disease specialists for guidance, and to be able to identify situations when antimicrobial therapy is not needed. By following these general principles, all practicing physicians should be able to use antimicrobial agents in a responsible manner that benefits both the individual patient and the community.


The terms antimicrobial, antibiotic, and anti-infective encompass a wide variety of pharmaceutical agents that include antibacterial, antifungal, antiviral, and antiparasitic drugs. Of these, antibacterial agents are by far the most commonly used and thus are the focus of this article, although similar principles apply to the other agents as well. Evidence-based practice guidelines from the Infectious Diseases Society of America can help direct appropriate therapy for specific infectious disease syndromes as well as for infections caused by specific microorganisms.

These guidelines should be applied in the context of host characteristics, response to therapy, and cost of therapy. This article discusses many such factors that should guide appropriate use of antimicrobial therapy.

SELECTING AND INITIATING AN ANTIBIOTIC REGIMEN

OBTAINING AN ACCURATE INFECTIOUS DISEASE DIAGNOSIS
An infectious disease diagnosis is reached by determining the site of infection, defining the host (eg, immunocompromised, diabetic, or of advanced age), and establishing, when possible, a microbiological diagnosis. It is critical to isolate the specific pathogen in many serious, life-threatening infections, especially for situations that are likely to require prolonged therapy (eg, endocarditis, septic arthritis, disk space infection, and meningitis). Similarly, when a patient does not benefit from antimicrobial therapy chosen on the basis of clinical presentation, additional investigations are needed to determine the etiologic agent or exclude noninfectious diagnoses. To optimize an accurate microbiological diagnosis, clinicians should ensure that diagnostic specimens are properly obtained and promptly submitted to the microbiology laboratory, preferably before the institution of antimicrobial therapy. Infectious disease diagnoses also frequently rely on a detailed exposure history, as in the case of a patient with nonresolving pneumonia who has resided in or traveled to the southwestern United States where coccidioidomycosis is endemic. Although the microbiological diagnosis is ideally based on data such as bacterial or fungal culture or serologic testing, frequently the “most likely” microbiological etiology can be inferred from the clinical presentation. For example, cellulitis is most frequently assumed to be caused by streptococci or staphylococci, and antibacterial treatment can be administered in the absence of a positive culture. Similarly, community-acquired pneumonia that does not warrant hospitalization can also be treated empirically—with a macrolide or fluoroquinolone antibiotic—without performing specific diagnostic test-
ing. Finally, noninfectious conditions should be considered in the differential diagnosis for infections, especially when the diagnosis is not clear-cut.

**Timing of Initiation of Antimicrobial Therapy**

The timing of initial therapy should be guided by the urgency of the situation. In critically ill patients, such as those in septic shock, febrile neutropenic patients, and patients with bacterial meningitis, empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens. In more stable clinical circumstances, antimicrobial therapy should be deliberately withheld until appropriate specimens have been collected and submitted to the microbiology laboratory. Important examples of this principle are subacute bacterial endocarditis and vertebral osteomyelitis/diskitis. Patients with these infections are frequently ill for a period of several days to weeks before presentation, and administration of antibiotic therapy should be delayed until multiple sets of blood cultures (in the case of endocarditis) or disk space aspirate and/or bone biopsy specimens (for osteomyelitis/diskitis) have been obtained. Premature initiation of antimicrobial therapy in these circumstances can suppress bacterial growth and preclude the opportunity to establish a microbiological diagnosis, which is critical in the management of these patients, who require several weeks to months of directed antimicrobial therapy to achieve cure.

**Empiric vs Definitive Antimicrobial Therapy**

Because microbial results do not become available for 24 to 72 hours, initial therapy for infection is often empiric and guided by the clinical presentation. It has been shown that inadequate therapy for infections in critically ill, hospitalized patients is associated with poor outcomes, including greater morbidity and mortality as well as increased length of stay. Therefore, a common approach is to use broad-spectrum antimicrobial agents as initial empiric therapy (sometimes with a combination of antimicrobial agents; for further information on these combination regimens, see “Use of Antimicrobial Combinations”) with the intent to cover multiple possible pathogens commonly associated with the specific clinical syndrome. This is true for both community- and hospital-acquired infections. For example, in an otherwise healthy young adult with suspected bacterial meningitis who is seen in the emergency department, the most likely pathogens would be *Streptococcus pneumoniae* and *Neisseria meningitidis*, and thus a combination of a third-generation cephalosporin (ceftiraxone) plus vancomycin would be recommended as empiric therapy. Hospital-acquired infections are frequently related to the presence of invasive devices and procedures that result in loss of the normal barriers to infection, as is the case with intravascular catheter–associated bacteremia, ventilator-associated pneumonia, and catheter-associated urinary tract infections (UTIs). They are commonly caused by drug-resistant organisms, both gram-positive (eg, methicillin-resistant *Staphylococcus aureus* [MRSA]) and gram-negative (eg, *Pseudomonas aeruginosa*) bacteria, which are often endemic in hospitals because of the selection pressure from antimicrobial use. In selecting empiric antimicrobial therapy for such infections, clinicians should consider the following: (1) the site of infection and the organisms most likely to be colonizing that site (eg, intravascular catheter–associated bacteremia is frequently a result of colonization and infection caused by staphylococci present on the skin); (2) prior knowledge of bacteria known to colonize a given patient (eg, a screening nasal swab [currently conducted routinely by many hospitals before admitting patients to the intensive care unit] may indicate that the patient is colonized with MRSA); and (3) the local bacterial resistance patterns or antibiograms that are available for important pathogens at most hospitals.

Once microbiology results have helped to identify the etiologic pathogen and/or antimicrobial susceptibility data are available, every attempt should be made to narrow the antibiotic spectrum. This is a critically important component of antibiotic therapy because it can reduce cost and toxicity and prevent the emergence of antimicrobial resistance in the community. Antimicrobial agents with a narrower spectrum should be directed at the most likely pathogens for the duration of therapy for infections such as community-acquired pneumonia or cellulitis in the ambulatory setting because specific microbiological tests are not typically performed.

**Interpretation of Antimicrobial Susceptibility Testing Results**

When a pathogenic microorganism is identified in clinical cultures, the next step performed in most microbiology laboratories is antimicrobial susceptibility testing (AST). Antimicrobial susceptibility testing measures the ability of a specific organism to grow in the presence of a particular drug in vitro and is performed using guidelines established by the Clinical and Laboratory Standards Institute, a nonprofit global organization that develops laboratory process standards through extensive testing and clinical correlation. The goal of AST is to predict the clinical success or failure of the antibiotic being tested against a particular organism. Data are reported in the form of minimum inhibitory concentration (MIC), which is the lowest concentration of an antibiotic that inhibits visible growth of a microorganism, and are interpreted by the laboratory as “susceptible,” “resistant,” or “intermediate,” according to Clinical and Laboratory Standards Institute criteria. A report of “sus-
ceptible" indicates that the isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used for the particular site of infection. For this reason, MICs of different agents for a particular organism are not directly comparable. For example, MICs of 1 (susceptible) for ciprofloxacin and 2 (susceptible) for ceftriaxone against *Escherichia coli* do not imply that ciprofloxacin is twice as active as ceftriaxone. Instead, it indicates that concentrations achieved by giving recommended doses of both drugs are likely to be active against the organism. Although AST results are generally quite useful in narrowing the antibiotic regimen, AST has some limitations that should be kept in mind. First, it is important for both clinicians and laboratory personnel to be aware of the site of infection. For example, an isolate of *S. aureus* could be reported as susceptible to cefazolin in vitro; however, if this particular isolate was obtained from the cerebrospinal fluid (CSF), cefazolin would not be an optimal therapeutic choice because it does not achieve therapeutic concentrations in the CSF. Clinical laboratories may provide different AST interpretations for different sites of infection (eg, meningitis and nonmeningitis AST results for *S. pneumoniae*). In addition, some organisms carry enzymes that, when expressed in vivo, can inactivate antimicrobial agents to which the organism shows in vitro susceptibility. Although their presence is not immediately apparent from AST results, certain AST “patterns” can provide a clue to their existence. For example, extended-spectrum β-lactamases (ESBLs) in *Enterobacteriaceae* are enzymes that mediate resistance to almost all β-lactam agents except carbapenems (eg, meropenem or imipenem). Extended-spectrum β-lactamases can be difficult to detect because they have different levels of in vitro activity against various cephaplorins. In clinical practice, susceptibility to cephaplorins (cefoxitin, cefotetan) but resistance to a third-generation cephaplorin (eg, cefpodoxime, cefotaxime, ceftriaxone, ceftazidime) or aztreonam should alert one to the possibility of ESBL production. The production of ESBL should also be suspected when treatment with β-lactams fails despite apparent in vitro susceptibility. This should lead to additional testing, which usually involves growing the bacteria in the presence of a third-generation cephaplorin alone and in combination with clavulanic acid (a β-lactamase inhibitor); enhanced bacterial inhibition with the addition of clavulanic acid indicates ESBL. When detected by the laboratory, these bacteria should be considered resistant to all β-lactam agents except the carbapenem class.

In general, it is good practice to communicate directly with the microbiology laboratory when antimicrobial susceptibility patterns appear unusual. It is also useful to be aware of the limitations of AST at the local laboratory, particularly in smaller hospitals (eg, testing of relatively newer agents [such as daptomycin for gram-positive cocci] might not be routinely performed or reported but could be available on request).

**Bactericidal vs Bacteriostatic Therapy**

A commonly used distinction among antibacterial agents is that of bactericidal vs bacteriostatic agents. Bactericidal drugs, which cause death and disruption of the bacterial cell, include drugs that primarily act on the cell wall (eg, β-lactams), cell membrane (eg, daptomycin), or bacterial DNA (eg, fluoroquinolones). Bacteriostatic agents inhibit bacterial replication without killing the organism. Most bacteriostatic drugs, including sulphonamides, tetracyclines, and macrolides, act by inhibiting protein synthesis. The distinction is not absolute, and some agents that are bactericidal against certain organisms may only be bacteriostatic against others and vice versa. In most cases, this distinction is not significant in vivo; however, bactericidal agents are preferred in the case of serious infections such as endocarditis and meningitis to achieve rapid cure.

**Use of Antimicrobial Combinations**

Although single-agent antimicrobial therapy is generally preferred, a combination of 2 or more antimicrobial agents is recommended in a few scenarios.

**When Agents Exhibit Synergistic Activity Against a Microorganism.** Synergy between antimicrobial agents means that, when studied in vitro, the combined effect of the agents is greater than the sum of their independent activities when measured separately. For example, the combination of certain β-lactams and aminoglycosides exhibits synergistic activity against a variety of gram-positive and gram-negative bacteria and is used in the treatment of serious infections, for which rapid killing is essential (eg, treatment of endocarditis caused by *Enterococcus* species with a combination of penicillin and gentamicin). In this setting, the addition of gentamicin to penicillin has been shown to be bactericidal, whereas penicillin alone is only bacteriostatic and gentamicin alone has no significant activity. For certain streptococci, similar synergistic combinations that result in more rapid clearance of the infecting microorganism can also be used to shorten the course of antimicrobial therapy (eg, for endocarditis due to viridans group streptococci, a combination of penicillin or ceftriaxone with gentamicin for 2 weeks can be as effective as penicillin or ceftriaxone alone for 4 weeks).

**When Critically Ill Patients Require Empiric Therapy Before Microbiological Etiology and/or Antimicrobial Susceptibility Can Be Determined.** As already discussed, antibiotic combinations are used in empiric therapy for health care–associated infections that are frequently
caused by bacteria resistant to multiple antibiotics. Combination therapy is used in this setting to ensure that at least 1 of the administered antimicrobial agents will be active against the suspected organism(s). For example, when a patient who has been hospitalized for several weeks develops septic shock and blood cultures are reported to be growing gram-negative bacilli, it would be appropriate to provide initial therapy with 2 agents that have activity against gram-negative bacilli, particularly P aeruginosa, which is both a common nosocomial pathogen and frequently resistant to multiple agents—in this case, a combination of an antipseudomonal β-lactam with a fluoroquinolone or aminoglycoside could be used.

To Extend the Antimicrobial Spectrum Beyond That Achieved by Use of a Single Agent for Treatment of Polymicrobial Infections. When infections are thought to be caused by more than one organism, a combination regimen may be preferred because it would extend the antimicrobial spectrum beyond that achieved by a single agent. For example, most intra-abdominal infections are usually caused by multiple organisms with a variety of gram-positive cocci, gram-negative bacilli, and anaerobes. Antimicrobial combinations, such as a third-generation cephalosporin or a fluoroquinolone plus metronidazole, can be used as a potential treatment option in these cases and can sometimes be more cost-effective than a comparable single agent (eg, a carbapenem).

To Prevent Emergence of Resistance. The emergence of resistant mutants in a bacterial population is generally the result of selective pressure from antimicrobial therapy. Provided that the mechanisms of resistance to 2 antimicrobial agents are different, the chance of a mutant strain being resistant to both antimicrobial agents is much lower than the chance of it being resistant to either one. In other words, use of combination therapy would provide a better chance that at least one drug will be effective, thereby preventing the resistant mutant population from emerging as the dominant strain and causing therapeutic failure. This is why combination drug therapy is used as the standard for treatment of infections such as tuberculosis and the human immunodeficiency virus (HIV) when treatment duration is likely to be prolonged, resistance can emerge relatively easily, and therapeutic agents are limited.

Host Factors to Be Considered in Selection of Antimicrobial Agents

Although it is helpful for clinicians to gain familiarity with a few specific antimicrobial agents, a “one size fits all” approach is not appropriate in antimicrobial selection, and several host factors must be taken into account. Published guidelines on appropriate dose adjustments for individual antimicrobial agents are available from a variety of sources.12,13

Renal and Hepatic Function. Because the kidney and the liver are the primary organs responsible for elimination of drugs from the body, it is important to determine how well they are functioning during antimicrobial administration. In most cases, one is concerned with dose reduction to prevent accumulation and toxicity in patients with reduced renal or hepatic function. However, sometimes doses might need to be increased to avoid underdosing young healthy patients with rapid renal elimination or those with rapid hepatic metabolism due to enzyme induction by concomitant use of drugs such as rifampin or phenytoin.

Age. Patients at both extremes of age handle drugs differently, primarily due to differences in body size and kidney function. Most pediatric drug dosing is guided by weight. In geriatric patients, the serum creatinine level alone is not completely reflective of kidney function, and the creatinine clearance should be estimated by factoring in age and weight for these patients.

Genetic Variation. Genetic susceptibility to the adverse effects of antimicrobial agents, which has been demonstrated for several antimicrobial agents, is occasionally significant enough to warrant testing for such variability before administration of certain drugs. For example, the antiretroviral drug abacavir, which has become part of the standard combination treatment for HIV infection, is associated with a well-described and potentially fatal hypersensitivity reaction that can manifest with any combination of fever, rash, abdominal pain, and respiratory distress. The risk of experiencing this reaction has been shown to be significantly higher in patients with the human leukocyte antigen allele HLA-B*5701,14 and current HIV treatment guidelines recommend routine screening for the presence of this genetic susceptibility in patients before prescribing this drug. Another example is that of glucose-6-phosphate dehydrogenase (G6PD) deficiency, which can result in hemolysis in individuals when exposed to certain antimicrobial agents, such as dapsone, primaquine, and nitrofurantoin. These drugs should be avoided in those known to be deficient in G6PD, and it is advisable to test for this predisposition in patients who might have a higher risk of G6PD deficiency (eg, African Americans) before prescribing these agents. Many antimicrobial agents are handled by the hepatic cytochrome P450 system, and although variation in expression of these enzymes occurs, insufficient data are available to recommend routine clinical testing to guide antimicrobial dosing.

Pregnancy and Lactation. Special considerations for the use of antimicrobial agents in pregnancy relate to both the mother and the fetus. In the case of the mother, increases in plasma volume and renal blood flow, especially by the third trimester, can result in more rapid clearance and lower serum levels of pharmaceutical agents, includ-
ing antimicrobial agents. However, data to support the clinical relevance of this change are sparse, and higher antimicrobial doses are not routinely recommended in the third trimester of pregnancy. Some experts recommend an increased dose of several protease inhibitors for the management of HIV infection in pregnancy. In the case of the developing fetus, many antimicrobial agents can be either teratogenic or otherwise toxic to the fetus. Penicillins, cephalosporins, and macrolides have historically been the most commonly used antimicrobial agents considered safe in pregnancy, and a recent multicenter study of more than 13,000 women with pregnancies affected by birth defects found no association between adverse outcomes and these particular antimicrobial agents. In contrast, agents such as sulfonamides and nitrofurantoin, which were not previously considered harmful in early pregnancy, were found to be associated with several birth defects in this study. Other drugs, such as tetracyclines and chloramphenicol, have well-described fetal or neonatal adverse effects and should be avoided. In general, however, human studies on the safety of many antimicrobial agents in pregnancy and lactation are limited, and antimicrobial agents should be prescribed with caution.

**History of Allergy or Intolerance.** A history of antimicrobial allergy or intolerance should be routinely obtained in the evaluation and management of infection (for a fuller discussion, see “Adverse Effects”).

**History of Recent Antimicrobial Use.** Eliciting a history of exposure to antimicrobial agents in the recent past (approximately 3 months) can also help in selection of antimicrobial therapy. Because the causative microorganism for a current episode of infection emerged under the selective pressure of a recently used antimicrobial agent, it is likely to be resistant to that drug and/or drug class, and an alternative agent should be used.

**Oral vs Intravenous Therapy**

Patients hospitalized with infections are often treated with intravenous antimicrobial therapy because their admission is often prompted by the severity of their infection. However, patients with mild to moderate infections who require hospitalization for other reasons (eg, dehydration, pain control, cardiac arrhythmias) and have normal gastrointestinal function are candidates for treatment with well-absorbed oral antimicrobial agents (eg, treatment of pyelonephritis and community-acquired pneumonia with oral fluoroquinolones). Furthermore, patients initially treated with parenteral therapy can be safely switched to oral antibiotics when they become clinically stable. When using oral therapy for invasive infections (such as pneumonia, pyelonephritis, or abscesses), clinicians are advised to select an agent that has excellent absorption and bioavailability (ie, the percentage of the oral dose that is available unchanged in the serum). Examples of antibiotics with excellent bioavailability are fluoroquinolones, linezolid, trimethoprim-sulfamethoxazole, and metronidazole. For more serious infections, such as infective endocarditis and central nervous system infections (eg, meningitis), in which high serum or CSF drug concentrations are desired, a switch to oral therapy is less reliable and not generally recommended.

**Pharmacodynamic Characteristics**

Along with host factors, the pharmacodynamic properties of antimicrobial agents may also be important in establishing a dosing regimen. Specifically, this relates to the concept of time-dependent vs concentration-dependent killing. Drugs that exhibit time-dependent activity (β-lactams and vancomycin) have relatively slow bactericidal action; therefore, it is important that the serum concentration exceeds the MIC for the duration of the dosing interval, either via continuous infusion or frequent dosing. In contrast, drugs that exhibit concentration-dependent killing (aminoglycosides, fluoroquinolones, metronidazole, and daptomycin) have enhanced bactericidal activity as the serum concentration is increased. With these agents, the “peak” serum concentration, and not the frequency of the dosing interval, is more closely associated with efficacy. To illustrate the impact of this distinction on dosing options, we can take the example of a 70-year-old woman with a creatinine clearance estimated to be 30 mL/min who is being treated with ciprofloxacin for pyelonephritis caused by E coli. Antimicrobial dosing guidelines suggest that a dose of either 250 mg orally every 12 hours or 500 mg every 24 hours is an acceptable modification for her reduced kidney function. However, given that ciprofloxacin exhibits concentration-dependent killing, selection of the latter dosing schedule would be more appropriate. In contrast, if the same patient were being treated with intravenous ampicillin, for which the time above the MIC is more closely related to efficacy, a dose of 1 g every 4 hours would be preferable to 2 g every 8 hours.

**Efficacy at the Site of Infection**

In addition to possessing in vitro antimicrobial activity and achieving adequate serum levels, the efficacy of antimicrobial agents depends on their capacity to achieve a concentration equal to or greater than the MIC at the site of infection and modification of activity at certain sites. Antimicrobial concentrations attained at some sites (eg, ocular fluid, CSF, abscess cavity, prostate, and bone) are often much lower than serum levels. For example, first- and second-generation cephalosporins and macrolides do not cross the blood-brain barrier and are not recommended for cen-
tral nervous system infections. Fluoroquinolones achieve high concentrations in the prostate and are preferred oral agents for the treatment of prostatitis. Daptomycin, an excellent bactericidal agent against gram-positive bacteria, is not useful for treatment of pneumonia (eg, pneumococcal pneumonia) because it is inactivated by lung surfactant. Many antibiotics (eg, aminoglycosides) are less active in the low-oxygen, low-pH, and high-protein environment of abscesses, and drainage of abscesses to enhance antimicrobial efficacy is recommended when possible. Agents in the same class can differ from one another; for example, moxifloxacin does not achieve significant urinary concentrations because of its low renal excretion and is therefore not suitable for treatment of UTIs; in contrast, both levofloxacin and ciprofloxacin are excellent choices for UTIs caused by susceptible bacteria. The presence of foreign bodies at the site of infection also affects antimicrobial activity (see “Antimicrobial Therapy for Foreign Body–Associated Infections”).

**Selection of Antimicrobial Agents for Outpatient Parenteral Antimicrobial Therapy**

To decrease cost, and with the help of advances both in antimicrobial agents and in technology to assist antimicrobial administration, prolonged treatment of serious infections with intravenous or parenteral antimicrobial agents has increasingly shifted away from the hospital to the outpatient setting, and guidelines to assist with delivery of high-quality outpatient parenteral antimicrobial therapy (OPAT) have been developed. Therapy can be provided via one of several types of indwelling central venous access catheters (a peripherally inserted central catheter is most frequently used) and can be delivered at an infusion center, by a home-visiting nurse, by self-administration, or in a nursing home. In addition to the general principles for selection of antimicrobial agents that have already been discussed, OPAT requires some further considerations. First, other things being equal, an agent that requires less frequent administration is preferred. For example, for the treatment of osteomyelitis or other serious infections caused by methicillin- or oxacillin-sensitive *Staphylococcus aureus*, cefazolin is frequently used in favor of nafcillin or oxacillin because it allows administration every 8 hours. Its use makes treatment outside the hospital setting much more feasible than the administration every 4 hours required for the other drugs. Agents with once- or twice-daily dosing have gained popularity for OPAT and include ceftriaxone, ertapenem, vancomycin, and daptomycin. An alternative for most β-lactams, which require frequent dosing, is use of a continuous infusion pump; however, such a device can frequently be cost-prohibitive. Second, the agent must possess chemical stability and should last for about 24 hours after mixing to allow enough time for delivery and administration. As an important illustration of the principle, the use of intravenous ampicillin for OPAT via self-administration or continuous infusion is often precluded because of a short (approximately 8-hour) stability period at room temperature. Ampicillin or penicillin (in combination with an aminoglycoside) is the drug of choice for endocarditis caused by penicillin-sensitive enterococci; therefore, OPAT for this type of infection usually necessitates either nursing home stay or investment in a continuous infusion device (for penicillin only). Third, agents with minimal toxicity or predictable toxicity amenable to monitoring are preferred as OPAT is generally used in the context of longer-term antimicrobial therapy. Finally, when possible, provided adherence can be expected, consideration should be given to using oral agents (as discussed in “Oral vs Intravenous Therapy”) in the outpatient setting.

**Use of Therapeutic Drug Monitoring**

Monitoring serum concentrations for drugs is most useful for medications that have a fairly narrow therapeutic index, which is the ratio of the toxic to the therapeutic dose. Fortunately, most antimicrobial agents have a wide therapeutic index, allowing standard doses to be used, with predictable modifications on the basis of age, weight, and renal and hepatic function. However, certain antimicrobial agents require monitoring of serum levels because the therapeutic window is narrow. This could be due primarily to toxicity at high levels (eg, aminoglycosides) or therapeutic failure at low drug levels (eg, vancomycin) but is usually a combination of both (eg, voriconazole). In some cases, the use of serum drug level monitoring is supported by its beneficial effect on clinical outcomes (eg, voriconazole in the treatment of invasive fungal infections).

**Considerations for Continuing Antibiotic Therapy**

**Duration of Antimicrobial Therapy**

The duration of therapy for many infections has long been based on anecdotal data and expert opinion. In view of the deleterious effects of prolonged courses of antimicrobial agents, including the potential for adverse reactions, problems with adherence, selection of antibiotic-resistant organisms, and high cost, a number of studies have tried to define the optimal duration of therapy, with an emphasis on shorter courses of therapy. For example, evidence supports limiting treatment of uncomplicated UTI in women to 3 days, community-acquired pneumonia to 5 days, and ventilator-associated pneumonia to 8 days. However, when administering abbreviated treatment courses, it is important for clinicians to ensure that their patients fit...
the profile of the study population and carefully monitor high-risk patients for improvement. For example, in the study of short-course treatment for ventilator-associated pneumonia,27 the 8-day course was not sufficient for the treatment of infections due to P aeruginosa or in immunocompromised patients. In other situations, a longer duration of therapy is clearly warranted (eg, 4-6 weeks for endocarditis, osteomyelitis, and intra-abdominal abscesses, and weeks to months for invasive fungal infections) to achieve cure and prevent relapse. In many such infections, treatment duration has to be carefully individualized on the basis of clinical and radiologic response and may require the guidance of an expert in infectious diseases.

**Assessment of Response to Treatment**

Response to treatment of an infection can be assessed using both clinical and microbiological parameters. Clinical parameters of improvement include symptoms and signs (eg, a decrease in fever, tachycardia, or confusion), laboratory values (eg, decreasing leukocyte count), and radiologic findings (eg, decrease in the size of an abscess). Although radiologic criteria are commonly used in assessing response to infectious disease therapy, radiologic improvement can frequently lag behind clinical improvement, and routine radiographic follow-up of all infections is not always necessary. For example, in a study of clinical and radiographic follow-up of patients with community-acquired pneumonia,28 clinical cure was observed in 93% of patients after 10 days of follow-up, whereas radiographic resolution was noted in only 31% of patients. In fact, several weeks or even months may be required before chest radiography or computed tomography shows complete resolution of an infiltrate.

Bacteremia is the most common scenario in which microbiological response is closely assessed because clearance of the bloodstream is as important as clinical improvement. Persistent bacteremia can often be the only clue to the presence of an inadequately treated source or to the existence or development of endovascular infection (such as endocarditis or an intravascular device infection).

Persistent bacteremia can also be associated with the emergence of antimicrobial resistance and should always be investigated.29

**Adverse Effects**

Although the term antimicrobial allergy is frequently used synonymously with adverse reaction or adverse effect, allergic reactions constitute only one subset of adverse reactions to antimicrobial agents (see the Table for a useful classification of antimicrobial adverse effects).

Allergic or hypersensitivity reactions can be either immediate (IgE-mediated) or delayed and usually manifest as a rash; anaphylaxis is the most severe manifestation of IgE-mediated allergy. In a recent national study of the prevalence of adverse drug effects, antibiotics were implicated in 19% of all emergency department visits for drug-related adverse events, and 79% of all antibiotic-associated adverse events were classified as allergic reactions.30 Although a history of serious allergic reaction should be carefully documented to avoid inadvertent administration of the same drug or another drug in the same class, self-report of antibiotic allergies can be quite unreliable—it has been shown that only 10% to 20% of patients reporting a history of penicillin allergy were truly allergic when assessed by skin testing.31 Historical details should be elicited to help distinguish allergic from nonallergic reactions and IgE-mediated from delayed reactions because failure to do so can result in unnecessary avoidance of the most effective, narrow-spectrum, and cost-effective antimicrobial agent (eg, use of vancomycin in place of a β-lactam). Although no single test or clinical finding leads to a diagnosis of antibiotic allergy, a negative skin test should be obtained in most cases; (eg, use of vancomycin in place of a β-lactam).

Risk factors for anaphylaxis include a history of serious allergy (such as anaphylaxis) and help optimize antibiotic use.32-34 Both clinicians and patients should understand that a negative skin test does not mean that a patient is not at risk for developing a non–IgE-mediated delayed allergic reaction, but that in many circumstances the benefit of receiving a more appropriate antibiotic would outweigh the risk of a less significant allergic reaction. If an ongoing reaction is attributed to an antimicrobial drug allergy, this usually requires discontinuation of the offending agent. Related drugs (eg, cephalosporins in patients with a history of penicillin allergy) can be used under careful observation, provided that the reaction is not severe or the skin test is negative. In some cases, if the offending agent is the only or highly preferred agent, desensitization may be necessary. Desensitization involves administration of the drug in progressively increasing doses given by mouth; protocols are available for certain agents, such as β-lactams and sulfonamides, and should be guided by experts in allergic diseases.
Nonallergic drug toxicity is usually, but not always, associated with higher doses and/or prolonged use and is particularly noted in patients with poor kidney or liver function that results in impaired clearance. Examples include nephrotoxicity with aminoglycosides, neurotoxicity of penicillins, and peripheral neuropathy with prolonged use of metronidazole; these potential adverse effects need to be discussed with patients before initiation of therapy. For patients receiving prolonged systemic antimicrobial therapy, periodic clinical and laboratory monitoring is also recommended, particularly for those drugs that cause predictable toxicity with increasing duration of use (eg, monitoring complete blood cell count, including white blood cell differential, with β-lactams, trimethoprim-sulfamethoxazole, and linezolid; creatinine kinase level with daptomycin; and creatinine level with aminoglycoside and β-lactams). In addition, drug doses should be adjusted in response to changes in creatinine level to avoid toxicity and attain optimal serum concentrations.

Many antimicrobial agents interact with other drugs to increase or decrease their serum levels and effects. This is frequently the case with antimicrobial agents that are metabolized by and/or affect the cytochrome P450 enzyme system (eg, rifampin is a powerful inducer, whereas macrolides and azole antifungal agents are inhibitors of cytochrome P450 enzymes). Clinicians should always remain alert to the possibility of such interactions of antimicrobial agents with other drugs, and it is advisable to review a patient’s medication list when prescribing antimicrobial agents. Certain drug combinations can also cause additive toxicity, as exemplified by the concomitant use of amphotericin and gentamicin, which can significantly increase the risk of nephrotoxicity.

SPECIAL SITUATIONS IN INFECTIOUS DISEASE THERAPY

ANTIMICROBIAL THERAPY FOR FOREIGN BODY–ASSOCIATED INFECTIONS

Prosthetic implants and devices are increasingly being used in modern medical treatment. An unfortunate consequence of this increased use is the emergence of infections associated with the placement of such devices, involving both temporary (eg, urinary catheter, central venous catheter) and permanent (eg, prosthetic joint, artificial heart valve) implants. One of the important characteristics of device-related infection is the formation of biofilms, which have been described as “a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface.”36 Bacteria growing in biofilms have been shown to be relatively protected from the effects of antimicrobial therapy, probably as a result of alteration of their metabolic state.36 Primary care physicians should be aware of this because prolonged antibiotic treatment for these infections can be ineffective, associated with adverse effects, and result in the emergence of resistant strains of organisms.37 Certain agents (eg, rifampin38 and fluoroquinolones39) have better activity against staphylococci in biofilms and are recommended in the management of infections of prosthetic valves10 and joints40 caused by these organisms. However, because of the difficulty of eradicating infections with antimicrobial therapy alone, removal of the implant is often necessary for cure. As an alternative, for patients unable to tolerate implant removal, long-term suppressive antimicrobial therapy is sometimes used, with variable success. It is advisable to involve an infectious diseases expert in the management of infections associated with implanted foreign bodies.

USE OF ANTIMICROBIAL AGENTS AS PROPHYLACTIC OR SUPPRESSIVE THERAPY

In an ideal scenario for use of an antimicrobial agent as prophylactic treatment, the infection would occur predictably in a certain setting and would be well known to be associated with a specific organism or organisms, and an effective antimicrobial agent would be available with no or limited long-term toxicity and with little likelihood of leading to the emergence of resistance. Not surprisingly, such scenarios are relatively rare. However, antimicrobial prophylaxis is appropriate in some instances, a discussion of which follows.

Presurgical Antimicrobial Prophylaxis. Antimicrobial prophylaxis is used to reduce the incidence of postoperative surgical site infections. Patients undergoing procedures associated with high infection rates, those involving implantation of prosthetic material, and those in which the consequences of infection are serious should receive perioperative antibiotics. The antibiotic(s) should cover the most likely organisms and be present in the tissues when the initial incision is made, and adequate serum concentrations should be maintained during the procedure. A single dose of a cephalosporin (such as cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures; this practice targets the most likely organisms (ie, skin flora), while avoiding unnecessary broad-spectrum antimicrobial therapy. Duration of prophylaxis for surgical site infection should not exceed 24 hours in most cases.41

Antimicrobial Prophylaxis in Immunocompromised Patients. Immunocompromised patients, particularly those with HIV infection/AIDS, those who are undergoing chemotherapy for cancer, or those who are receiving immuno-suppressive therapy after organ transplant, are at increased risk of infection. These infections are caused by predictable
organisms at an increased frequency and/or associated with high mortality (eg, invasive aspergillosis associated with prolonged neutropenia, Pneumocystis pneumonia in the setting of impaired cell-mediated immunity [eg, AIDS, organ transplant]). In these specific settings, evidence supports the use of prolonged antimicrobial prophylaxis until immune markers are restored (eg, trimethoprim-sulfamethoxazole to prevent Pneumocystis pneumonia).45

Antimicrobial Prophylaxis to Prevent Transmission of Communicable Pathogens to Susceptible Contacts. Antimicrobial agents can be prescribed prophylactically to prevent transmission of pathogens to susceptible contacts; for example, antiviral agents can be used to limit the spread of influenza in nursing home residents, ciprofloxacin can be given to close contacts of a patient with meningitis caused by N meningitidis, and macrolides can be prescribed to reduce transmission of pertussis.

Antimicrobial Prophylaxis Before Dental and Other Invasive Procedures in Patients Susceptible to Bacterial Endocarditis. It should be noted that guidelines recommending antimicrobial prophylaxis in this setting have recently been updated and limit such use to only a few very high-risk scenarios—prosthetic valves, prior endocarditis, or congenital heart disease before surgical correction.43

Traumatic Injuries With a High Probability of Infectious Complications. Certain types of injuries pose a particularly high risk of infection because of disruption of normal barriers and/or delivery of a high inoculum of pathogenic organisms (eg, antibiotic prophylaxis has been shown to be of some benefit and is recommended for certain types of animal bites44 and after penetrating brain injury). An example of inappropriate antimicrobial “prophylaxis” is prolonged antimicrobial use in those with open but not infected wounds, including surgical wounds. No consensus has yet been reached on the use of antimicrobial prophylaxis in some other settings, such as before invasive procedures in patients with prosthetic joints.

Nonantimicrobial Therapy for Infections
Antimicrobial therapy is usually, but not always, the most important therapy for infectious diseases. The best-recognized example of nonantimicrobial therapy in the treatment of infections is the use of operative drainage or débridement. This procedure is useful when the organism burden is very high or in the management of abscesses, for which the penetration and activity of antimicrobial agents are often inadequate. Other therapies used in the treatment of infectious diseases involve modulating the host inflammatory response to infection. Systemic corticosteroids, thought to act by decreasing the deleterious effects of the host inflammatory response, have been found beneficial when used in conjunction with antimicrobial therapy for the treatment of bacterial meningitis,46 tuberculous meningitis,47 and Pneumocystis pneumonia in patients with AIDS.48 Temporary discontinuation or dose reduction of immunosuppressive agents is often required for successful treatment of infections, such as cytomegalovirus disease in organ transplant recipients or patients with rheumatologic disorders. Similarly, granulocyte colony-stimulating factor is sometimes administered to patients with prolonged neutropenia who develop invasive infections with filamentous fungi. Intravenous immunoglobulin therapy, which acts to neutralize toxin produced by the bacteria, can be used in addition to surgical débridement and antimicrobial therapy in the treatment of necrotizing fasciitis caused by group A streptococci.49 Probiotics (such as Lactobacillus and Saccharomyces species) are occasionally used in the management of colitis caused by Clostridium difficile, with the hope of restoring the normal flora that has been altered by antimicrobial administration.40 Some of these interventions lack a strong evidence base but are often recommended by experts on the basis of clinical experience.

JUDICIOUS USE OF ANTIMICROBIAL AGENTS

Cost Considerations in Antibiotic Selection and Antimicrobial Stewardship
The “cost” of an antimicrobial agent is dependent on many factors in addition to the purchase price of a particular agent and may include administration costs, prolonged hospitalization as a consequence of adverse effects, the cost of serum concentration monitoring, and clinical efficacy. One strategy that can significantly reduce cost is the switch from intravenous to oral therapy. Oral therapy is generally less expensive, potentially associated with fewer adverse effects, and can result in considerable cost savings by facilitating earlier dismissal and a shortened hospital stay.51 Even if the purchase price of an oral agent is greater than its parenteral equivalent, the reduction in hospital stay can result in significant cost savings. This has been demonstrated for oral linezolid when compared with intravenous vancomycin for the treatment of complicated skin and soft tissue infections caused by MRSA.52,53

Cost considerations in the selection and continuation of appropriate antimicrobial therapy in acute care hospitals are part of a broader activity that is referred to as antimicrobial stewardship. Antimicrobial stewardship programs are aimed at “optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.”54 These programs are usually coordinated by a team of infectious disease physician(s) and pharmacist(s) and are often computer-based. Some
components recommended for these programs include the following: prospective audit and feedback of antimicrobial prescriptions to clinicians, formulary restriction, education, use of clinical order sets and guidelines, de-escalation of therapy, and intravenous to oral antimicrobial conversion when appropriate. Clinicians should make it a priority to become aware of such programs in their institutions.

**PREVENTING EMERGENCE OF ANTIBIOTIC RESISTANCE**

The widespread—and often inappropriate—use of antimicrobial agents is the single most important cause of the emergence of drug resistance, both in the community and hospital settings. Prior antibiotic exposure has been shown to be the most frequent risk factor for the development of community-acquired respiratory infections caused by drug-resistant *S. pneumoniae*. This is not surprising because acute upper respiratory illnesses account for the highest proportion of ambulatory antibiotic prescriptions, with most being dispensed in situations in part, responsible for the epidemic of a fluoroquinolone-resistant strain of *E. coli*, the most common cause of nosocomial infectious diarrhea. More recently, an increase in levofloxacin use as initial therapy for UTI as a result of policy change at a single institution was found to have led to a rapid increase in fluoroquinolone resistance among outpatient urinary *E. coli* isolates at that institution. For this reason, those involved in antimicrobial stewardship should avoid the excessive prescribing of a single class of antibiotic.

**COMMON MISUSES OF ANTIBIOTICS**

In some settings, the use of antibiotics is clearly inappropriate. A discussion follows of some of the typical scenarios in which they are contraindicated.

**Prolonged Empiric Antimicrobial Treatment Without Clear Evidence of Infection.** One of the most common mistakes in antimicrobial use is continuing to add or switch antibiotics when a patient does not appear to be responding to therapy, even though there is no clear evidence of an infectious disease. Many noninfectious, inflammatory, or neoplastic syndromes can present with symptoms and signs that mimic infectious diseases. Examples include adult-onset Still disease and other connective tissue disorders that can present with high fever; drug-induced fever; the fever associated with pulmonary embolism; lymphoma; and Wegener granulomatosis, which can present with fever, cavitary pulmonary nodules, and recurrent sinusitis.

**Treatment of a Positive Clinical Culture in the Absence of Disease.** Colonization with potentially pathogenic organisms without any associated manifestation of disease occurs frequently in certain populations (eg, colonization of the urinary tract in women of advanced age or in the presence of an indwelling urinary catheter, colonization of endotracheal tubes in mechanically ventilated patients, and colonization of chronic wounds). Appropriate management in these situations involves obtaining cultures from these sites only when indicated and avoiding treatment of a “positive” culture result when symptoms and signs of active infection are absent (eg, asymptomatic bacteriuria).

**Failure to Narrow Antimicrobial Therapy When a Causative Organism Is Identified.** As already discussed, initial therapy is often empiric and relies on broad-spectrum agents until culture or other tests help determine the microbiological etiology. Once culture and susceptibility data are available, an antibiotic with the narrowest possible spectrum should be selected for continuation of therapy. Often, however, this does not occur, particularly if the patient has improved while receiving empiric therapy, and the physician is uncomfortable about changing therapy in the face of clinical improvement.

**Prolonged Prophylactic Therapy.** As already discussed, infection can be prevented in certain situations by the prophylactic use of antimicrobial agents (eg, presurgical prophylaxis). However, in most cases, guidelines support the use of a single, preoperative dose of an antimicrobial agent. Prolonged “prophylaxis” simply sets the stage for the emergence of antimicrobial resistance. For example, the common practice of prolonging antimicrobial therapy until the removal of surgical drains is not evidence based.

**Excessive Use of Certain Antimicrobial Agents.** The frequent use of certain agents (or classes of antimicrobial agents) in a hospital or other health care setting can result in selection of organisms that are resistant to that particular antibiotic. For example, the increased use of fluoroquinolones during the past decade is thought to be, in part, responsible for the epidemic of a fluoroquinolone-resistant strain of *C. difficile*, the most common cause of nosocomial infectious diarrhea. More recently, an increase in levofloxacin use as initial therapy for UTI as a result of policy change at a single institution was found to have led to a rapid increase in fluoroquinolone resistance among outpatient urinary *E. coli* isolates at that institution. For this reason, those involved in antimicrobial stewardship should avoid the excessive prescribing of a single class of antibiotic.
CONCLUSION

Appropriate use of antimicrobial agents involves obtaining an accurate diagnosis, determining the need for and timing of antimicrobial therapy, understanding how dosing affects the antimicrobial activities of different agents, tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible. In addition, nonantimicrobial interventions, such as abscess drainage, are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management.

REFERENCES


The Symposium on Antimicrobial Therapy will continue in the March issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are now a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
SYMPOSIUM ON ANTIMICROBIAL THERAPY


Souha S. Kani, MD, and Zeina A. Kanafani, MD

On completion of this article, readers should be able to (1) recognize the burden of multidrug-resistant gram-negative organisms in causing health care–associated infections and their effect on patient outcome, (2) recognize the various mechanisms leading to resistance, and (3) identify the current approach and the choice of empirical and directed therapy in the management of infections with these multidrug-resistant pathogens.

The development of antimicrobial resistance among gram-negative pathogens has been progressive and relentless. Pathogens of particular concern include extended-spectrum β-lactamase–producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Pseudomonas aeruginosa. Classic agents used to treat these pathogens have become outdated. Of the few new drugs available, many have already become targets for bacterial mechanisms of resistance. This review describes the current approach to infections due to these resistant organisms and elaborates on the available treatment options.


Antimicrobial resistance has been shaping the field of infectious diseases since the discovery of penicillin. Many of the advances in antimicrobial drug development have resulted from efforts to combat ever-evolving mechanisms of resistance that render existing agents obsolete, thus prompting the search for new molecules that promise to be more effective and more resilient. Yet, the hope for a magic all-encompassing antimicrobial agent has long passed, and new antimicrobial agents in the drug development pipeline is a small fraction of what it used to be.

Nowhere is the concept of antimicrobial resistance better portrayed than with the gram-negative bacilli, which have proven to be tough adversaries for clinicians and researchers alike. Of the 6 famous ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter species, Pseudomonas aeruginosa, and Enterobacter species) recognized as the most important emerging threats of this century, 4 are gram-negative bacilli (K pneumoniae, Acinetobacter species, P aeruginosa, and Enterobacter species). This review will address 3 major types of multidrug-resistant (MDR) gram-negative pathogens: extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, carbapenemase-producing Enterobacteriaceae, and MDR P aeruginosa. The resistance mechanisms exhibited by these organisms and the epidemiology of the infections they cause will be discussed. Existing and emerging therapeutic approaches to each type of organism will then be surveyed.

MECHANISMS OF RESISTANCE

Production of β-lactamase is the most commonly encountered mechanism of resistance of bacterial pathogens to β-lactam antibiotics. Many enzymes have been described, encoded either by chromosomal genes or by genes located on movable elements such as plasmids and transposons. Classification schemes for β-lactamases are based on molecular structure (Ambler classification) or functional similarities (Bush-Jacoby-Medeiros classification) (Table 1). Extended-spectrum β-lactamase enzymes initially arose through point mutations in the genes encoding the classic TEM and SHV β-lactamases, thereby generating an array of enzymes with an expanded spectrum of activity.

The potent hydrolytic activity of CTX-M enzymes against cefotaxime was later recognized. Unlike TEM, SHV, and CTX-M ESBL enzymes that are predominantly expressed by Enterobacteriaceae, the oxacillin-hydrolyzing enzymes have been mostly isolated from P aeruginosa, and some have evolved to exhibit the ESBL phenotype. In contrast to the plasmid-mediated ESBL enzymes, AmpC β-lactamases are predominantly chromosomally encoded. Their expression is mostly noted in Enterobacter species, Citrobacter species, and P aeruginosa. Although chromosomal AmpC

From the Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

Dr Kani has received honoraria as a speaker on antimicrobial resistance for the Pfizer-sponsored Antimicrobial Practices and Executions for eXcellence Program.

Address correspondence to Souha S. Kani, MD, Division of Infectious Diseases, American University of Beirut Medical Center, Cairo Street, PO Box 11-0236, Riad El Solh, Beirut 1107 2020, Lebanon. (sk11@aub.edu.lb). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

© 2011 Mayo Foundation for Medical Education and Research
enzymes are usually poorly expressed in *Escherichia coli* and *Klebsiella* species, plasmid-mediated AmpC enzymes can confer β-lactam resistance similar to *Enterobacter* isolates. Other less commonly encountered ESBL enzymes include PER-1, VEB-1, and BES-1.6

Carbapenemases are the β-lactamases with the widest spectrum of activity. In addition to hydrolyzing carbapenems, carbapenemases are active against most other members of the β-lactam family with few exceptions. The major drive behind the emergence of carbapenemases has been the widespread use of carbapenems both in the empirical and directed treatment of serious infections, which placed selection pressure on bacterial pathogens. On the basis of their molecular structure, carbapenemases belong to the A, B, or D classes of β-lactamase enzymes7 (Table 1). The plasmid-borne *K pneumoniae* carbapenemases (KPCs) are currently among the most prevalent and widely distributed carbapenemases. They are particularly difficult to detect by microbiology laboratories because many isolates have minimum inhibitory concentrations (MICs) against imipenem or meropenem that, albeit high, remain in the susceptible range.8,9 It has been observed through in vitro studies that ertapenem may be the most appropriate substrate for detection of KPC production.8 Other clinically important carbapenemases include the metallo-β-lactamases and the oxacillin-hydrolyzing carbapenemases. Besides β-lactamase production, *P aeruginosa* isolates can exhibit additional resistance mechanisms, such as aminoglycoside-modifying enzymes, efflux pumps, porin loss, and various target site modifications.10

<table>
<thead>
<tr>
<th>Ambler class</th>
<th>Bush-Jacoby- Medeiros group</th>
<th>Active site</th>
<th>Enzyme type</th>
<th>Inhibition by clavulanate</th>
<th>Host organisms</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2b, 2bc, 2br, 2c, 2e, 2f</td>
<td>Serine</td>
<td>Broad-spectrum β-lactamases (TEM, SHV) ESBL (TEM, SHV, CTX-M)</td>
<td>Yes, except 2br</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Ampicillin, cephalothin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbapenemases (KPC, GES, SME)</td>
<td></td>
<td></td>
<td>Penicillins, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ESBL (TEM, SHV, CTX-M)</td>
<td></td>
<td></td>
<td>All β-lactams</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ESBL (OXA)</td>
<td></td>
<td></td>
<td>All β-lactams</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Zinc-binding thiol group</td>
<td>Carbapenemases (VIM, IMP)</td>
<td>No</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Cephapenems, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbapenemases (VIM, IMP)</td>
<td>No</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Cephapenems, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbapenemases (VIM, IMP)</td>
<td>Yes</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Oxacillin, ampicillin, cephalothin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbapenemases (VIM, IMP)</td>
<td>Yes</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Penicillins, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>Serine</td>
<td>AmpC cephamycinases (AmpC)</td>
<td>No</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Cephapenems, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmpC cephamycinases (AmpC)</td>
<td>No</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Cephapenems, 3rd-generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmpC cephamycinases (AmpC)</td>
<td>Yes</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>Oxacillin, ampicillin, cephalothin</td>
</tr>
<tr>
<td>D</td>
<td>2d</td>
<td>Serine</td>
<td>Broad-spectrum β-lactamases (OXA) ESBL (OXA)</td>
<td>Yes</td>
<td>Enterobacteriaceae and nonfermenters</td>
<td>All β-lactams</td>
</tr>
</tbody>
</table>

**Table 2. Classification of Carbapenemases**

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Examples</th>
<th>Substrates</th>
<th>Inhibition by clavulanate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B1</td>
<td>BcII, IMP-1, CcrA, VIM-2, SPM-1</td>
<td>All β-lactams</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>B1</td>
<td>BcII, IMP-1, CcrA, VIM-2, SPM-1</td>
<td>All β-lactams</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>CphA, Sfh-1, L1, FEZ-1, Gob-1, CAU-1</td>
<td>No hydrolysis of aztreonam; variable hydrolysis of carbapenems</td>
<td>No</td>
</tr>
<tr>
<td>D</td>
<td>OXA-23, OXA-24, OXA-48, OXA-50, OXA-51, OXA-55, OXA-58, OXA-60, OXA-62</td>
<td>No hydrolysis of aztreonam; variable hydrolysis of extended-spectrum cephalosporins and carbapenems</td>
<td>Variable</td>
<td></td>
</tr>
</tbody>
</table>

KPC = *Klebsiella pneumoniae* carbapenemase.
Citation: "ANTIMICROBIAL THERAPY AGAINST RESISTANT GRAM-NEGATIVE ORGANISMS" "EPIDEMIOLOGY"

The medical literature abounds with studies illustrating the global increase in the burden of antimicrobial resistance among gram-negative pathogens. However, wide regional differences exist, accentuating the need to take into account the local epidemiology (at the level of the country, the region, the hospital, and at times the individual hospital unit) when making decisions about empirical therapy for serious infections.

The Study for Monitoring Antimicrobial Resistance Trends collected 6156 gram-negative isolates from patients with intra-abdominal infections in 28 countries during 2004. The overall rate of ESBL production was 17% among K pneumoniae and 10% among E coli isolates, with the highest rates being in isolates from Latin America, the Middle East, Africa, and Asia and the lowest being in Europe and the United States. These results were confirmed by the Tigecycline Evaluation and Surveillance Trial global surveillance database in 2007. Most notable in the epidemiology of ESBL-producing organisms is the recent worldwide dissemination of CTX-M–type β-lactamases, particularly the CTX-M-15 enzyme. In a recent multinational study, CTX-M enzymes were the most frequently identified ESBLs, accounting for 65% of all β-lactamases.

Although chromosomally mediated carbapenemases have long been recognized in gram-negative bacilli, they were mostly species-specific with a limited potential for spread except in a clonal manner. Recent trends, however, have refocused attention on plasmid-mediated carbapenemases such as KPCs. Since the first report from North Carolina in the late 1990s, a multitude of studies have described the relatively rapid emergence of KPC enzymes. In addition to certain regions of the United States, hospital outbreaks due to KPC-bearing gram-negative pathogens have been reported from Europe, Asia, and South America. Other carbapenemases that have been associated with recent outbreaks include IMP and VIM metallo-β-lactamases. In addition, 2009 witnessed the emergence of the New Delhi metallo-β-lactamase in Enterobacteriaceae, which led to the hospitalization of many patients in India and Pakistan.

THERAPEUTIC APPROACHES

A summary of therapeutic approaches and challenges for 3 of the emerging gram-negative organisms of most concern follows (see also Table 3), including an inventory of existing antibiotic options for each organism.

**Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae**

The propensity of ESBL-producing organisms to be concomitantly resistant to other classes of antibiotics greatly limits the choice of antibiotics that can be used for treatment. The genes encoding for ESBL enzymes are located on large plasmids that can harbor resistance genes to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole.

Infections with ESBL-producing pathogens are usually suspected in patients who have recently received broad-spectrum antibiotics, particularly third-generation cephalosporins and quinolones. Other risk factors include age older than 60 years, comorbid conditions, recent hospital and intensive care unit admission, and invasive devices.

---

### Table 3. Suggested Approach to the Management of Patients With Serious Infections Due to Multidrug-Resistant Gram-Negative Pathogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>First-line therapy</th>
<th>Second-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical therapy</td>
<td>Carbapenem</td>
<td>Tigecycline (not in urinary tract infections)</td>
</tr>
<tr>
<td>Monomicrobial infection</td>
<td>with or without an antipseudomonal agent</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Mixed gram-positive and gram-negative infection</td>
<td>Anti-MRSA agent plus a carbapenem</td>
<td>Tigecycline (not in urinary tract infections)</td>
</tr>
<tr>
<td>Directed therapy</td>
<td>Carbapenem</td>
<td>Tussexine (not in urinary tract infections)</td>
</tr>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>Piperacillin-tazobactam (low inoculum)</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>Carbapenemase-producing Enterobacteriaceae</td>
<td>Tigecycline</td>
<td>Tigecycline (parenteral formulation)</td>
</tr>
<tr>
<td>Multidrug resistant Enterobacteriaceae</td>
<td>Colistin</td>
<td>Fosfomycin (parenteral formulation)</td>
</tr>
<tr>
<td>Multidrug resistant Pseudomonas aeruginosa</td>
<td>Antipseudomonal agent (among carbapenems, use doripenem or meropenem)</td>
<td>Combination therapy</td>
</tr>
</tbody>
</table>

---

*ESBL = extended-spectrum β-lactamase; MRSA = methicillin-resistant Staphylococcus aureus.*

*b Local susceptibility patterns should be taken into consideration before deciding on empirical therapy.

*c Based on available culture and susceptibility results.*
Antibiotic Options. Carbenapemems. Carbenapemems are considered first-line agents in treating infections caused by ESBL-producing organisms (imipenem at 500 mg intravenously [IV] every 6 hours up to 1 g IV every 8 hours in serious infections or meropenem at 1 g IV every 8 hours). However, no data from randomized controlled trials support their use for this purpose. Most of the evidence instead originates from case series and retrospective studies, which compile the responses and outcomes of patients with bacteremia receiving carbapenem therapy. In a multinational study of 85 patients with ESBL-producing K pneumoniae bacteremia, carbapenem use was an independent predictor of lower mortality rate compared with the use of other antibiotic agents that exhibited in vitro activity. This therapeutic advantage of carbapenems has been attributed to the high inoculum effect as well as high MICs of other agents that are close to the susceptibility breakpoints. More recent data have shown that ertapenem at 1 g/d may be used successfully for ESBL-associated bacteremia. When dosed at 500 mg IV every 8 hours, doripenem, the newest addition to the carbapenem class, exhibits an activity against ESBL-producing pathogens that is similar to that of imipenem and meropenem.

Tigecycline. Tigecycline, the first member of the glycyclcline class of antibiotics, is approved by the US Food and Drug Administration for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia when appropriately dosed (100-mg loading dose IV followed by 50 mg IV every 12 hours). Tigecycline is active in vitro against Enterobacteriaceae, including ESBL-producing isolates. Clinical data, although promising, are still limited. Despite its excellent activity, one of the factors hindering the wider use of tigecycline for ESBL-associated infections is the fact that a large proportion of these infections are in the urinary tract, where tigecycline has a limited penetration. Although some case reports have reported a favorable outcome, tigecycline is not a suitable choice for the treatment of urinary tract infections. In addition, because of its rapid tissue distribution after intravenous infusion, concerns have been raised about using tigecycline for the treatment of primary bloodstream infections. In a recently published comparative study of tigecycline vs imipenem-cilastatin in patients with hospital-acquired pneumonia, tigecycline fared worse in the subset of patients with ventilator-associated pneumonia. It is our opinion that dose escalation needs to be considered if tigecycline is used for ventilator-associated pneumonia with MDR organisms other than Pseudomonas species.

β-Lactam/β-Lactamase Inhibitor Combinations. Classic β-lactam inhibitors, such as sulbactam, clavulanate, and tazobactam, have variable inhibitory activity against ESBL enzymes (Table 1). Tazobactam, which appears to be the most potent of the 3, is active against some of the TEM, SHV, and CTX-M enzymes. In a Spanish study from 11 centers, the cure rate of patients with cystitis treated with amoxicillin-clavulanate was 93% with susceptible ESBL-producing isolates and 56% with isolates of intermediate susceptibility and resistance, suggesting that amoxicillin-clavulanate may be successful in the treatment of simple cystitis. Clinical data supporting the use of piperacillin-tazobactam are mounting. Because it achieves high concentrations in the urinary tract, piperacillin-tazobactam may be used successfully in the treatment of urinary tract infections and in other infections in which a low bacterial inoculum is expected. In a series of patients with infections due to ESBL-producing organisms, piperacillin-tazobactam was used successfully against susceptible isolates originating from the urinary tract as well as other sites. Although it was initially thought that piperacillin-tazobactam should be avoided in serious infections such as bacteremias, this notion is being challenged by emerging evidence showing that the use of piperacillin-tazobactam against susceptible isolates often results in a favorable outcome.

Cephalosporins. Studies suggest that the use of cephalosporins, including cephapneys and cefepime, is associated with a worse outcome compared with the use of carbapenems, despite apparent in vitro susceptibility. Cephalosporins are therefore not recommended in patients with suspected or confirmed infections with ESBL-producing organisms.

Aminoglycosides, Fluoroquinolones, and Trimethoprim-Sulfamethoxazole. The high rates of concurrent resistance to these agents and the potential for emergence of resistance on treatment often preclude their use for empirical coverage. Some studies have observed a suboptimal response to quinolones vs carbapenems in ESBL-producing isolates with retained susceptibility to quinolones. Aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole should be used with caution in serious infections even after documentation of in vitro activity. Clinical response should be closely monitored, and switching to carbapenems should be considered in patients who do not improve.

Colistin. Colistin has been successfully used to treat ESBL-associated infections in a few case reports. In the absence of formally adopted Clinical and Laboratory Standards Institute breakpoints for susceptibility of colistin against Enterobacteriaceae, susceptibility testing by E-test and disk diffusion methods has been proposed recently. Colistin use is discussed in more detail in the “Multidrug-Resistant P aeruginosa” section.

Fosfomycin. Fosfomycin inhibits bacterial cell wall synthesis, thereby exhibiting bactericidal activity against
gram-positive and gram-negative pathogens.42 Fosfomycin is approved by the US Food and Drug Administration for the treatment of uncomplicated urinary tract infections at a single oral dose of 3 g. The emergence of resistance among gram-negative bacilli has sparked new interest in using fosfomycin to treat infections caused by MDR isolates. In vitro studies have shown that fosfomycin remains active against ESBL-producing E coli and K pneumoniae isolates.43 The drug appears to be useful in the oral treatment of ESBL-associated infections of the urinary tract, and initial clinical studies are promising.44 An intravenous formulation of fosfomycin, currently available in some European countries, could be useful in treating systemic infections.45

**Other Agents.** Also active in vitro against ESBL-producing organisms are the β-lactams temocillin46 and pivmecillinam,47 the carbapenems biapenem,48 faropenem,49 and tompopenem,50 and the urinary tract agent nitrofurantoin.51 More data are needed to support their use in the clinical setting.

**CARBAPENEM-RESISTANT ENTEROBACTERIACEAE**

Recognizing carbapenemase expression is the key to the appropriate management of infections caused by carbapenem-resistant Enterobacteriaceae. Unusually elevated MICs to carbapenems should arouse suspicion for a carbapenem-resistant isolate and preclude the use of carbapenems even if the MICs do not exceed the breakpoints for resistance. As with ESBL-producing organisms, carbapenemase-producing strains are likely to exhibit simultaneous resistance to aminoglycosides and fluorquinolones.52

**Antibiotic Options. Tigecycline.** Isolates may show in vitro susceptibility to tigecycline,53 but clinical experience with carbapenem-resistant strains is limited. A recent review by Hirsch and Tam54 gathered data from 15 publications on the treatment of 55 patients with KPC-related infections. A favorable outcome was achieved in 5 of 7 patients treated with tigecycline. Despite tigecycline being one of the first-line agents for use in the setting of carbapenemase-producing isolates, it is worth noting that clinical failures have been reported in the literature, as exemplified by a brief report by Anthony et al,55 in which some patients with MDR gram-negative pathogens, including ESBL- and KPC-producing isolates, had a negative clinical and/or microbiological outcome with tigecycline. In addition, as discussed previously, primary bloodstream infections and urinary tract infections present a challenge for the use of tigecycline.

**Colistin.** Although colistin retained activity against carbapenemase-producing Enterobacteriaceae in initial studies,56 more recent data suggest that resistance to colistin is emerging, and outbreaks of colistin-resistant strains have been reported.57 In the review by Hirsch and Tam,54 monotherapy with polymyxins (n =7) was associated with poor response rates, whereas combination therapy (n= 11) gave more promising results.

**Fosfomycin.** The activity of fosfomycin was evaluated against 68 KPC-producing K pneumoniae isolates, 23 of which were nonsusceptible to tigecycline and/or colistin.58 The susceptibility rates were 93% for the overall group, 87% for the group nonsusceptible to tigecycline and/or colistin, and 83% (5 of 6 isolates) for the extremely drug-resistant subgroup that was nonsusceptible to tigecycline and/or colistin. Clinical correlation of this in vitro study is needed.

**Rifampin.** In vitro studies suggest that rifampin has a synergistic activity when used as part of a combination therapy regimen against carbapenemase-producing E coli and K pneumoniae.59 More clinical data are needed.

**Agents Under Development.** Agents under development include new β-lactamase inhibitors with activity against carbapenemases, such as MK-7655,60 NXL104,61 and 6-alkyl-lidenepenam sulfones,62 and several bis-indole compounds,63 the mode of action of which is currently unidentified.

**MULTIDRUG-RESISTANT P AERUGINOSA**

For the purpose of this review, we define MDR P aeruginosa as strains that are resistant to 2 or more classes of antibiotics. In recent years, the treatment of infections caused by P aeruginosa has become a challenging task for clinicians. The emergence of antimicrobial resistance has played a pivotal role in determining the approach to patients with Pseudomonas species infections. Central to this approach is the recognition that delayed therapy correlates with increased mortality even when a patient is considered clinically stable at the time of initial evaluation.64 Because the treatment of serious P aeruginosa infections is frequently empirical until the organism is isolated and susceptibility testing performed, high resistance rates raise the likelihood of administering inappropriate initial therapy, hence contributing to the observed high mortality rates.

**Antibiotic Options.** When used in the appropriate dosage, the following agents have shown reliable activity against Pseudomonas isolates.

**Antipseudomonal Penicillins.** Ticarcillin should be dosed at 3 g IV every 4 hours and piperacillin at 4 g IV every 4 hours.

**β-Lactam/β-Lactamase Inhibitor Combinations.** Ticarcillin-clavulanate should be dosed at 3 g of ticarcillin and 0.1 g of clavulanic acid IV every 4 hours, and piperacillin-tazobactam should be dosed at 4 g of piperacillin and 0.5 g of tazobactam IV every 6 hours or 3 g of piperacillin and 0.375 g of tazobactam IV every 4 hours.

**Cephalosporins.** Ceftazidime should be dosed at 2 g IV every 8 hours and cefepime at 2 g IV every 8 hours. Because of their good activity and narrow spectrum com-
pared with carbapenems, cephalosporns are still considered treatments of choice if the isolate is susceptible.

**Monobactams.** Aztreonam should be dosed at 2 g IV every 8 hours. *P. aeruginosa* isolates that produce metallo-

β-lactamases may be susceptible to aztreonam, which demonstrates resistance to hydrolysis by class B β-lactamases. In contrast, imipenem has been associated with a higher risk of isolation of quinolone-resistant *Pseudomonas* isolates. In vitro studies have shown that MICs were lowest with doripenem, followed by meropenem, then imipenem. However, doripenem, like other carbapenems, has minimal activity against metallo-β-lactamase–producing *P. aeruginosa* strains. In contrast, imipenem has been associated with a higher risk of selecting for resistant *Pseudomonas* isolates compared with other carbapenems. Whether these in vitro differences among carbapenems translate into clinical outcome differences has not yet been determined. Carbenems are usually used in the empirical treatment of suspected *Pseudomonas* species infections or when a polymicrobial infection is considered a possibility. In view of their broad spectrum of activity and the inherent risk of selecting for MDR organisms including *P. aeruginosa* and *Acinetobacter* species, antibiotic therapy should be de-escalated when possible based on culture results.

**Fluoroquinolones.** Ciprofloxacin should be dosed at 400 mg IV every 8 hours or 750 mg orally every 12 hours, and levofloxacin should be dosed at 750 mg orally or IV daily. Although both ciprofloxacin and levofloxacin are active against *P. aeruginosa*, levofloxacin use might be associated with a higher risk of isolation of quinolone-resistant *P. aeruginosa* than ciprofloxacin.

**Colistin.** Colistin base should be dosed daily at 2.5 to 5.0 mg/kg intramuscularly or IV in 2 to 4 divided doses. The increasing rates of MDR *Pseudomonas* isolates have prompted clinicians to turn to agents such as the polymyxins that had for a while fallen out of use due to their adverse effect profile. Studies have shown that, despite the risk for nephrotoxicity in patients receiving colistin, this drug may be useful as salvage therapy when therapeutic choices are seriously limited.

More recently, compiled data seem to indicate that colistin use is associated with a lower than expected incidence of nephrotoxicity. This may be due to better fluid management and critical care services. Nonetheless, renal function should be well monitored during therapy and dose adjustment should be performed in patients with reduced creatinine clearance as follows: serum creatinine of 1.3 to 1.5 mg/dL, 2.5 to 3.8 mg/kg IV daily; serum creatinine of 1.6 to 2.5 mg/dL, 2.5 mg/kg IV daily; and serum creatinine of 2.6 to 4.0 mg/dL, 1.5 mg/kg IV daily.

It should be noted, however, that the ideal dose of colistin has not been evaluated in randomized clinical trials. In a recent retrospective analysis of 258 episodes of MDR gram-negative infections, 68 of which were caused by *P. aeruginosa*, higher daily doses of colistin were independently associated with better survival regardless of the pathogen. The average daily dose of colistin that was used was 480±200 mg IV. The nephrotoxicity rate in this series was 10% and was independent of the dose used.

**Other Antimicrobial Agents.** Other antimicrobial agents possess activity against *P. aeruginosa* but are generally not recommended as monotherapy because of their high propensity to induce resistance. Hence, they are mostly used in combination with other antipseudomonal agents, such as aminoglycosides (amikacin at 5.0-7.5 mg/kg of ideal body weight IV every 8 hours, gentamicin and tobramycin at 1.0-2.5 mg/kg of ideal body weight IV every 8-12 hours) and rifampin (at 600 mg orally or IV once daily, particularly in cases of *P. aeruginosa* bacteremia refractory to standard treatment).

**Combination Therapy.** The use of combination therapy in *Pseudomonas* species infections has been a controversial issue among specialists in infectious diseases. Whereas counterarguments include the additional costs and increased risk of adverse effects inherent in the concurrent use of multiple agents, proponents of combination therapy cite the potential for synergistic efficacy as well as the potential benefit of reducing the risk of emergence of resistance. Another rationale is to ensure an initial broad spectrum of activity when the risk of MDR isolates is high by using drugs with different mechanisms of action and/or resistance.

The results of clinical studies on the value of combination therapy in the treatment of *P. aeruginosa* have been conflicting. Although older studies showed that combination therapy was more effective at reducing mortality rates in patients with *Pseudomonas* bacteremia than monotherapy, these results could not be corroborated by other authors. At least 2 meta-analyses have been published without resolving the question of whether the benefits of combination therapy outweigh the risks. The first meta-analysis evaluated 64 randomized trials comparing β-lactam monotherapy with combination therapy (a β-lactam and an aminoglycoside) in more than 7500 immunocompetent patients with severe infections, 426 of whom were infected with *P. aeruginosa*. Combination therapy offered no survival advantage but was associated with a higher risk of nephrotoxicity than was monotherapy. A second meta-analysis evaluated 17 studies, only 2 of which were randomized trials, in patients with gram-negative bacteremia. Mortal-
ity rates were significantly reduced in the *P. aeruginosa* subgroup but not in the overall population.

Data from in vitro studies and clinical trials regarding the prevention of resistance emergence during treatment of *P. aeruginosa* infections with combination therapy are scarce and inconclusive. For example, one study suggested that the addition of levofloxacin to imipenem might hamper the emergence of resistance. In another study, addition of an aminoglycoside to various β-lactam antibiotics did not alter the risk of selection for resistant isolates.

The most used drug combination for *Pseudomonas* species infections is an aminoglycoside with a β-lactam. In a more recent study, the checkerboard technique was used to test for synergistic activity of various combinations of anti-pseudomonal agents (ceftazidime-tobramycin, piperacillin-tazobactam-tobramycin, imipenem-tobramycin, imipenem-isepamycin, imipenem-ciprofloxacin, and ciprofloxacin-tobramycin). Ceftazidime-tobramycin and piperacillin-tazobactam-tobramycin combinations were associated with the highest ratios of synergy. Antagonism was not observed in any of the combinations. In addition, on the basis of in vitro findings, the following drug combinations have been found to provide enhanced activity against highly resistant *P. aeruginosa*: a fluoroquinolone with either ceftazidime or cefepime, ticarcillin with tobramycin and rifampin, polymyxin B with rifampin, ceftazidime with colistin, clarithromycin with tobramycin, and colistin with rifampin.

These novel combinations are not meant for routine use and should be restricted to the treatment of MDR isolates because they include agents that, when used alone, may be inactive or unreliable for the treatment of *Pseudomonas* species infections. Clinical data to support the use of these regimens are not yet available. In addition to the checkerboard technique, the E-test is another useful tool for determining MICs and testing antimicrobial combinations that can provide clinicians with potential treatment options. A novel parameter, the susceptible breakpoint index, allows ranking of the antimicrobial combinations by order of expected activity.

Empirical therapy with 2 antipseudomonal agents may be considered when the perceived risk of antimicrobial resistance is substantial or in the setting of neutropenic fever, severe sepsis or septic shock, or serious infections such as pneumonia, endocarditis, and meningitis. Once susceptibility results become available, treatment with 1 active agent is acceptable.

**Inhaled Antibiotics.** Intermittent aerosolization of antibiotics into the respiratory tract has been used in patients with *P. aeruginosa* pneumonia, particularly in the setting of cystic fibrosis. This mode of delivery is used to attain high drug levels locally in the respiratory tract without increasing systemic adverse effects. Several agents have been used as inhaled therapy, including tobramycin, colistin, and β-lactams.

Tobramycin is the inhaled antibiotic that has been the most widely used in the treatment of *P. aeruginosa* pneumonia. The supporting evidence comes from studies that showed increased bacterial eradication with inhaled tobramycin. However, clinical outcomes were not always consistent in different patient populations. For example, in one study, inhaled tobramycin was associated with improved pulmonary function and with weight gain in adolescent patients with cystic fibrosis during a 2-year period of long-term, intermittent use. In contrast, the overall clinical outcome in intubated adult patients with gram-negative pneumonia did not change with inhaled tobramycin administration despite confirmed bacterial eradication.

Inhaled colistin has also been used successfully in the management of MDR *P. aeruginosa* pneumonia that does not improve with IV administered therapy. In one study from Singapore, nebulized colistin was used alone in the treatment of 21 patients with pneumonia due to MDR *Acinetobacter baumannii* and *P. aeruginosa*. Overall clinical and microbiological response rates were 57% and 86%, respectively, and nephrotoxicity was not observed.

Despite these results, more data on clinical efficacy are needed, specifically regarding patient outcomes. At this point, the routine use of inhaled antibiotics is not recommended for *P. aeruginosa* pneumonia.

**Agents Under Development.** A number of antimicrobial agents with antipseudomonal activity are currently in various phases of development. However, clinical data regarding efficacy are still lacking.

**Drugs in Phase 2 Trials.** The following drugs are currently in phase 2 trials: sitafloxacin (a quinolone with better activity against gyrA or parC mutants than ciprofloxacin), KB001 (a high-affinity antibody fragment that reduces the toxicity and pathogenicity of *P. aeruginosa*), CXA-101 (a novel cephalosporin with potent activity against MDR strains), and ceftazidime/NXL104 (a cephalosporin/β-lactamase inhibitor combination meant to restore the in vitro activity of ceftazidime against class A, C, and some class D β-lactamase–producing strains).

**Drugs in Phase 1 Trials.** BLI-489/piperacillin (another β-lactamase inhibitor combination) and CB-182,804 (a lipopeptide with apparent bactericidal activity against MDR strains) are currently in phase 1 trials (more information on CB-182,804 available at http://www.cubist.com/products/gram-negative.php).

**Experimental Agents.** These agents have not undergone any clinical trials and include new β-lactams, new β-lactamase inhibitors, peptides, efflux inhibitors, and virulence modulators.
**Extended-Infusion Strategy for β-Lactams**

Because the killing activity of β-lactams is time-dependent, a positive correlation exists between their efficacy and the amount of time the drug concentration exceeds the MIC value during the dosing interval. To optimize dosing strategies to achieve better bacterial killing, studies have evaluated the role of administering β-lactams in extended infusions with encouraging results. Lodise et al. compared the outcome of patients with *P. aeruginosa* infections treated with piperacillin-tazobactam in 2 dosage regimens (3.375 g IV for 30 minutes every 4-6 hours vs 3.375 g IV for 4 hours every 8 hours). Patients with Acute Physiology And Chronic Health Evaluation (APACHE) II scores of 17 or greater who received extended-infusion therapy had lower mortality rates (12.2% vs. 31.6%; *P*=0.04) and shorter hospital stays compared with those who received intermittent-infusion therapy (21 days vs 38 days; *P*=0.02). More recently, 3 immunocompromised patients with MDR *P. aeruginosa* infections were treated successfully with continuous infusions of β-lactam antibiotics (cefazidime in 2 patients and aztreonam in the third patient).

Carbapenems have also been evaluated in extended-infusion regimens. Using a Monte Carlo simulation, lengthening meropenem infusions from 30 minutes to 3 hours was found to be advantageous with isolates of *P. aeruginosa* and *Acinetobacter* species with intermediate resistance. This benefit was not observed with Enterobacteriaceae, which usually exhibit low MICs, and with resistant isolates having very high MICs. Subsequently, doripenem was used in clinical trials in extended infusions and at lower doses compared with other carbapenems with equivalent efficacy results (doripenem infused at 500 mg during a 4-hour period every 8 hours vs imipenem infused at 500 mg during a 30-minute period every 6 hours or at 1 g during a 60-minute period every 8 hours and meropenem infused at 1 g as a 3- to 5-minute bolus every 8 hours). When used at higher doses in a murine model (1 g every 8 hours), an extended infusion of doripenem during a 4-hour period achieved a static antibacterial effect on KPC-producing isolates.

Extended-infusion strategy therefore appears to be a valuable approach in certain settings and deserves further study. The effect of this dosing regimen on the potential for selection of resistant mutants is yet to be determined.

**CONCLUSION**

The treatment of infections caused by MDR pathogens is complicated. Treatment options are currently limited, and it will be some time before more investigational agents become available for clinical use, if ever. Meanwhile, prevention strategies should go hand in hand with antimicrobial treatment. The importance of antimicrobial stewardship and infection control policies cannot be discounted in the fight against the worldwide emergence and spread of MDR pathogens.

**REFERENCES**

ANTIMICROBIAL THERAPY AGAINST RESISTANT GRAM-NEGATIVE ORGANISMS


The Symposium on Antimicrobial Therapy will continue in the April issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are now a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
Current Concepts in the Management of Tuberculosis

IRENE G. SIA, MD, MSc, and MARK L. WIELAND, MD, MPH

Tuberculosis (TB) poses a serious threat to public health throughout the world but disproportionately afflicts low-income nations. Persons in close contact with a patient with active pulmonary TB and those from endemic regions of the world are at highest risk of primary infection, whereas patients with compromised immune systems are at highest risk of reactivation of latent TB infection (LTBI). Tuberculosis can affect any organ system. Clinical manifestations vary accordingly but often include fever, night sweats, and weight loss. Positive results on either a tuberculin skin test or an interferon-γ release assay in the absence of active TB establish a diagnosis of LTBI. A combination of epidemiological, clinical, radiographic, microbiological, and histopathologic features is used to establish the diagnosis of active TB. Patients with suspected active pulmonary TB should submit 3 sputum specimens for acid-fast bacilli smears and culture, with nucleic acid amplification testing performed on at least 1 specimen. For patients with LTBI, treatment with isoniazid for 9 months is preferred. Patients with active TB should be treated with multiple agents to achieve bacterial clearance, to reduce the risk of transmission, and to prevent the emergence of drug resistance. Directly observed therapy is recommended for the treatment of active TB. Health care professionals should collaborate, when possible, with local and state public health departments to care for patients with TB. Patients with drug-resistant TB or coinfection with human immunodeficiency virus should be treated in collaboration with TB specialists. Public health measures to prevent the spread of TB include appropriate respiratory isolation of patients with active pulmonary TB, contact investigation, and reduction of the LTBI burden.


AFB = acid-fast bacilli; BCG = bacille Calmette-Guérin; CFP-10 = culture filtrate protein 10; DOT = directly observed therapy; EMB = ethambutol; ESAT-6 = early-secreted antigenic target 6; HIV = human immunodeficiency virus; IFN-γ = interferon-γ; IGRA = IFN-γ release assay; INH = isoniazid; LTBI = latent TB; MDR-TB = multidrug-resistant TB; NAA = nucleic acid amplification; PZA = pyrazinamide; RIF = rifampin; TB = tuberculosis; TBI = TB infection; TST = tuberculin skin test; XDR-TB = extensively drug-resistant TB

Effective medical therapy for tuberculosis (TB) has existed for more than half a century, yet TB remains among the most pressing public health issues of our day. Tuberculosis is, in part, a disease of poverty.1 The fact that it remains the eighth leading cause of death in the world speaks to the challenges facing practitioners and public health officials as they try to control a disease that is so entwined in the cultural and economic fabric of society. Challenges to effective solutions include lack of access to diagnosis and treatment, the frequent coexistence of epidemics of TB and human immunodeficiency virus (HIV), and the increasing prevalence of multidrug-resistant TB (MDR-TB).2 Although a chasm in disease burden exists between resource-rich and poor regions, an increasingly mobile and connected global community has ensured that TB remains highly relevant to practitioners throughout the world. This review highlights key principles in the management of TB. For purposes of definition, TB infection (TBI) occurs when a susceptible person inhales droplets containing Mycobacterium tuberculosis nuclei that travel through the respiratory tract to the alveoli. In most patients, an immune response limits propagation of TBI, resulting in an asymptomatic, noninfectious, localized infection that may remain in the body for many years. These patients have positive immunologic test results for M tuberculosis and carry a diagnosis of latent TB (LTBI). A constellation of clinical, radiographic, microbiological, and histopathologic hallmarks are used to diagnose active TB disease.3

EPIDEMIOLOGY

An estimated one-third of the world’s population is infected with TB.4 Tuberculosis accounted for 1.3 million deaths in 2007, and the prevalence of active disease is estimated at 13.7 million (206 per 100,000 persons).5 Incidence rates of active TB are highest (≥100 cases per 100,000 persons) in sub-Saharan Africa, India and Central Asia, parts of Eastern Europe, Southeast Asia, and Micronesia. Intermediate incidence rates (26-100 per 100,000 persons) are observed in Central and South America, China, and northern Africa. Low rates (<25 per 100,000 persons) occur in the United States, Canada, Australia, Western Europe, and Japan.5,6

While absolute numbers have been on the rise, the prevalence of TB in relationship to population has trended downward during the past 15 years, and global public

From the Division of Infectious Diseases (I.G.S.) and Division of Primary Care Internal Medicine (M.L.W.), Mayo Clinic, Rochester, MN.

Address correspondence to Irene G. Sia, MD, MSc, Division of Infectious Diseases, 200 First St SW, Rochester, MN 55905 (sia.irene@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

© 2011 Mayo Foundation for Medical Education and Research

For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
cases of active TB increased by 50% between 1999 and 2004, which was especially dramatic in London, where transmission is higher. 

Patients with negative smears but positive cultures may still progress to active disease. Those with greater susceptibility to TB are more likely to contract primary disease or reactivate LTBI. 

Host factors dramatically influence which of those exposed to TB are most likely to contract primary disease or progress to active disease. Those with greater susceptibility include persons with immune systems that have been compromised through either diseases, such as HIV infection and hematologic and reticuloendothelial malignancies, or through immunosuppressive medications, such as corticosteroids, tumor necrosis factor inhibitors, calcineurin inhibitors, and cytotoxic chemotherapeutic agents. Furthermore, patients with chronic diseases, such as diabetes, chronic kidney disease, and silicosis, are at elevated risk. Finally, age younger than 4 years, long-term malnutrition, and substance abuse are independent risk factors for disease.

**TRANSMISSION**

Tuberculosis is transmitted through droplet aerosolization by an individual with active pulmonary disease. The highest risk of transmission occurs among patients with cavitary or positive acid-fast bacilli (AFB) smears; however, patients with negative smears but positive cultures may still transmit the disease.

Host factors dramatically influence which of those exposed to TB are most likely to contract primary disease or progress to active disease. Those with greater susceptibility include persons with immune systems that have been compromised through either diseases, such as HIV infection and hematologic and reticuloendothelial malignancies, or through immunosuppressive medications, such as corticosteroids, tumor necrosis factor inhibitors, calcineurin inhibitors, and cytotoxic chemotherapeutic agents. Furthermore, patients with chronic diseases, such as diabetes, chronic kidney disease, and silicosis, are at elevated risk. Finally, age younger than 4 years, long-term malnutrition, and substance abuse are independent risk factors for disease.

**CLINICAL MANIFESTATIONS**

**PULMONARY TB**

**Primary Pulmonary TB.** Symptoms occurring around the time of inoculation are referred to as primary pulmonary TB. Symptoms are generally mild and include low-grade fever. Two-thirds of persons with primary pulmonary TB remain asymptomatic. Physical examination findings are generally unremarkable, and the most common radiographic finding is hilar adenopathy. Less common radiographic findings include pulmonary infiltrates in the mid and lower lung field.

**Reactivation TB.** Approximately 90% of TB cases among adults can be attributed to reactivation TB. Symptoms present insidiously, most commonly with fever, cough, weight loss, fatigue, and night sweats. Less common symptoms include chest pain, dyspnea, and hemoptysis. Physical examination findings are nonspecific and may include rales or signs of pleural effusion (eg, dullness to percussion). Chest radiography demonstrates infiltrates in the apical-posterior segment of the upper lobes, and up to 20% of these infiltrates are associated with cavities characterized by air-fluid levels. Although not specific for TB, apical computed tomographic findings may show a “tree in bud” morphology manifested by centrilobular lesions, nodules, and branching linear densities. Among the roughly 15% of patients who present without upper lung field infiltrates, a variety of radiographic findings have been described, including lower lung infiltrates (especially superior segments), nodules, effusions, and hilar adenopathy. Finally, up to 5% of patients with active pulmonary disease may have normal findings on chest radiography. This is particularly worth noting among patients coinfected with HIV, who are more likely to have atypical (eg, less predisposition for upper lobes) or normal findings on chest radiography.

**Endobronchial TB.** Endobronchial TB develops as the direct extension of TB from a pulmonary parenchymal source or sputum inoculation into the bronchial tree. Symptoms may include barking cough with sputum production, and examination may reveal rhonchi and wheeze; the wheezing may lead to misdiagnosis of asthma. Diagnosis and response to therapy may be assessed through bronchoscopy.

**EXTRAPULMONARY TB**

Extrapulmonary TB accounts for roughly 15% of TB cases among immunocompetent hosts and for 50% to
TABLE 1. Diagnosis of Common Extrapulmonary TB Manifestations

<table>
<thead>
<tr>
<th>Site</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous lymphadenitis</td>
<td>Excisional biopsy with culture</td>
</tr>
<tr>
<td>CNS TB</td>
<td>Characteristic CSF exam (see text for details)</td>
</tr>
<tr>
<td>Pleural TB</td>
<td>Pleural biopsy with pathology and culture</td>
</tr>
<tr>
<td>Tuberculous peritonitis</td>
<td>Pericardiocentesis with culture</td>
</tr>
<tr>
<td>Skeletal TB</td>
<td>Needle biopsy and culture</td>
</tr>
<tr>
<td>Genitourinary TB</td>
<td>Biopsy and culture of masses</td>
</tr>
<tr>
<td>Miliary (disseminated) TB</td>
<td>Culture of involved sites</td>
</tr>
</tbody>
</table>

AFB = acid-fast bacilli; CNS = central nervous system; CSF = cerebrospinal fluid; TB = tuberculosis.

70% of cases that occur in the context of coinfection with HIV. In low-incidence countries, immigrants from endemic countries are much more likely to present with extrapulmonary TB. As a rule, TB can present in any organ system; therefore, vigilance and examination for extrapulmonary disease are important for all persons being evaluated for TBI. A summary of the most common presentations of extrapulmonary TB follows (see also Table 1).

**Tuberculous Lymphadenitis.** Up to 40% of extrapulmonary TB cases are attributable to tuberculous lymphadenitis. It presents most commonly in the cervical lymph nodes, followed by the mediastinal and axillary nodes. A typical presenting symptom is long-term, unilateral, nontender lymphadenopathy; systemic symptoms are often absent. On examination, the node is typically matted and adherent to surrounding structures. If tuberculous lymphadenitis is clinically suspected, fine-needle aspiration should be pursued, followed by lymph node biopsy if the aspiration is nondiagnostic.

**Pleural TB.** Accounting for roughly 4% of all TB cases, pleural TB is the second leading cause of extrapulmonary TB. In addition to constitutional symptoms, patients may present with nonproductive cough and pleuritic chest pain. Chest radiography typically shows a unilateral effusion, and pleural fluid analysis shows lymphocyte-predominant exudative features with low glucose levels and low pH. Pleural fluid culture is positive in only roughly 30% of cases, whereas the combination of histology and culture from a closed pleural biopsy specimen yields a diagnosis in most cases.

**Central Nervous System TB.** A devastating manifestation of the disease, central nervous system TB occurs in approximately 1% of all TB cases. Tuberculous meningitis is clinically heralded by a 2- to 3-week prodrome of malaise, headache, low-grade fever, and personality changes. This prodrome is followed first by a meningeal phase that mimics bacterial meningitis (fever, nuchal rigidity, altered mental status) and then by a paralytic phase characterized by rapid progression to stupor, coma, seizures, paralysis, and death. Diagnosis requires a high index of suspicion, and cerebrospinal fluid analysis demonstrates elevated protein levels (100-150 mg/dL; to convert to g/L, multiply by 10), low glucose levels (<45 mg/dL; to convert to mmol/L, multiply by 0.0555), mononuclear pleocytosis, and an elevated cell count (100-150 cells/μL). A less common manifestation of the disease is central nervous system tuberculoma, which is characterized by single or multiple conglomerate caseous foci within the brain that cause focal neurologic symptoms and signs of elevated intracranial pressure. Finally, spinal tuberculosis arachnoiditis represents a focal inflammatory disease producing gradual encasement of the cord with associated neurologic deficits.

**Tuberculous Peritonitis.** The most common manifestation of TB in the gastrointestinal tract is tuberculous peritonitis. Cirrhosis and portal hypertension are associated with an increased proclivity for tuberculous peritonitis. Patients present with insidious onset of ascites (73%), abdominal pain (65%), weight loss (61%), and low-grade fever (59%). Clinically, tuberculous peritonitis may be mistaken for ovarian carcinoma or peritoneal carcinomatosis. Unexplained lymphocytic ascites should prompt definitive diagnostic testing for peritoneal TB. Culture of tubercles obtained through peritoneal biopsy remains the criterion standard for diagnosis.

**Tuberculous Pericarditis.** In the developing world, tuberculosis pericarditis is likely the most common cause of pericardial effusion and constrictive pericarditis; however, in high-income nations, it is rare. Patients present with pericardial effusion, constrictive pericarditis, or a mixed effusive and constrictive condition. Symptoms are those of effusion or constriction from any cause (dyspnea, cough, orthopnea, edema) in the context of systemic symptoms (night sweats, low-grade fevers, weight loss).

**Skeletal TB.** Skeletal TB occurs in 1% to 5% of patients with TB and presents most commonly in the thoracic vertebrae. Patients present with localized pain over the afflicted site; systemic symptoms are often absent. Diagnosis is confirmed through culture of specimens obtained through needle aspiration or biopsy.

**Miliary TB.** The lymphatic and hematogenous spread of TB is referred to as miliary TB. Patient presentation is variable, and systemic symptoms (fever, weight loss, night sweats) are common. When miliary TB occurs in the context of primary infection, patients may
DIAGNOSIS

The diagnosis of LTBI is established by a positive result on either a tuberculin skin test (TST) or an interferon-γ (IFN-γ) release assay (IGRA), in the absence of active TB. Active TB is diagnosed on the basis of a combination of epidemiological (eg, exposure, travel to or residence in a high prevalence area, previous TB), clinical (eg, cough lasting longer than 2-3 weeks, fever, night sweats, weight loss), radiographic (eg, infiltrates, fibrosis, cavitation), microbiological (eg, positive sputum smear or culture), and histopathologic (eg, caseating granuloma) features. Patients in whom clinical suspicion for TB infections is strong on the basis of clinical criteria should undergo chest radiography. Patients with chest radiographic findings suggestive of pulmonary TB should submit 3 sputum specimens, preferably obtained on different days, for AFB smears and culture. At least 1 early morning sputum specimen should be submitted. Patients unable to produce sputum spontaneously should undergo sputum induction, which requires inhalation of an aerosol of sterile hypertonic saline (3%-15%) in negative-pressure isolation rooms. Bronchoscopy with bronchoalveolar lavage may be necessary in patients unable to produce adequate expectorated or induced sputum samples. Nucleic acid amplification (NAA) testing should be performed on at least 1 respiratory specimen. Confirmation of the diagnosis of TB requires laboratory identification of M tuberculosis by AFB smear microscopy with NAA test and/or culture (Figure).
Interpretation of skin-test results is the same for bacille Calmette-Guérin (BCG) vaccinated and non-BCG vaccinated persons. The estimated interval between *M. tuberculosis* infection and skin test reactivity (ie, skin test conversion) is 2 to 12 weeks. Therefore, those in close contact with patients who have active pulmonary TB with initial negative test results should have the test repeated 8 to 12 weeks after exposure. Skin test conversion may also be due to new delayed-type hypersensitivity after infection with nontuberculous mycobacteria or BCG vaccination. The phenomenon of reversion (ie, decrease in the size of the tuberculin reaction) may present problems in skin test interpretation when serial TSTs are performed. Therefore, TST should not be performed if a positive TST result has been documented previously or if the patient has been treated for TB. False-positive skin tests can result from BCG vaccination or infection with nontuberculous mycobacteria. False-negative test results may occur because of the following technical and biological limitations: presence of active TB; presence of other bacterial, fungal, and viral (eg, HIV) infections; live virus vaccination; immunosuppressive therapy; long-standing renal failure; malnutrition; lymphoid diseases; and age.

The TST may have a booster effect on immunologic memory in patients with a history of TB, previous BCG vaccination, and exposure to nontuberculous mycobacteria. This results in a positive TST 1 to 4 weeks after initial negative findings on TST. Evaluation for the booster phenomenon with a second TST 1 to 4 weeks after the first test (the 2-step method) should be considered for persons from countries with a high incidence of TB, for those with a history of BCG vaccination, and (as a baseline assessment) for those who need periodic retesting, such as health care workers. Test interpretation is based on the induration observed with the second test.

About 10% of immunocompetent persons with LTBI will develop TB disease over their lifetime, with the greatest risk for progression (5%) being in the first 2 years after infection with *M. tuberculosis*. Approximately 50% of TB cases will occur within 2 years after initial infection. Targeted tuberculin testing identifies persons at high risk of developing TB who would benefit from treatment for LTBI. These include persons at risk of becoming infected with *M. tuberculosis* and those with clinical conditions associated with increased risk of progression of TB infection to active TB (Table 2). A joint statement from the American Thoracic Society and the Centers for Disease Control and Prevention provides guidelines on testing and treatment of LTBI in the United States.

**TABLE 2. Interpretation of TST Results for Populations at Risk of TB**

<table>
<thead>
<tr>
<th>At-risk populations</th>
<th>Positive TST reaction size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy people at low risk of TB</td>
<td></td>
</tr>
<tr>
<td>Patients with HIV infection</td>
<td></td>
</tr>
<tr>
<td>Patients receiving immunosuppressive therapy</td>
<td></td>
</tr>
<tr>
<td>Abnormal findings on chest radiography consistent with previous TB infection</td>
<td></td>
</tr>
<tr>
<td>Persons who have come in close contact with an actively contagious patient</td>
<td></td>
</tr>
<tr>
<td>Patients with certain chronic conditions</td>
<td></td>
</tr>
<tr>
<td>Patients with certain malignancies</td>
<td></td>
</tr>
<tr>
<td>Foreign-born persons from high-incidence regions (&gt;25/100,000)</td>
<td></td>
</tr>
<tr>
<td>Employees and residents of high-risk facilities</td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td></td>
</tr>
</tbody>
</table>

**Tuberculin Skin Test**

The TST, also known as the Mantoux test, requires the intradermal injection of 0.1 mL of 5 tuberculin units of purified protein derivative into the volar surface of the forearm. The TST measures cell-mediated immunity manifesting as a delayed-type hypersensitivity to tuberculin purified protein derivative, which contains a mixture of antigens shared by several species of mycobacteria. The test result is recorded as the diameter of transverse induration in millimeters 48 to 72 hours after administration. Interpretation of the TST result varies depending on the prevalence of and the risk for progression to TB in different groups. Induration between 5 and 15 mm is considered positive and may be indicative of LTBI (Table 2). The size of induration has predictive value in that persons with TB have larger indurations; however, it does not correlate with risk for progression to active TB. An increase of 10 mm or more in the skin test reaction within 2 years in persons with negative previous results (conversion) is indicative of recent *M. tuberculosis* infection. The TST cannot discriminate between active TB and LTBI.

Interpretation of skin-test results is the same for bacille Calmette-Guérin (BCG) vaccinated and non-BCG vaccinated persons. The estimated interval between *M. tuberculosis* infection and skin test reactivity (ie, skin test conversion) is 2 to 12 weeks. Therefore, those in close contact with patients who have active pulmonary TB with initial negative test results should have the test repeated 8 to 12 weeks after exposure. Skin test conversion may also be due to new delayed-type hypersensitivity after infection with nontuberculous mycobacteria or BCG vaccination. The phenomenon of reversion (ie, decrease in the size of the tuberculin reaction) may present problems in skin test interpretation when serial TSTs are performed. Therefore, TST should not be performed if a positive TST result has been documented previously or if the patient has been treated for TB. False-positive skin tests can result from BCG vaccination or infection with nontuberculous mycobacteria. False-negative test results may occur because of the following technical and biological limitations: presence of active TB; presence of other bacterial, fungal, and viral (eg, HIV) infections; live virus vaccination; immunosuppressive therapy; long-standing renal failure; malnutrition; lymphoid diseases; and age.

The TST may have a booster effect on immunologic memory in patients with a history of TB, previous BCG vaccination, and exposure to nontuberculous mycobacteria. This results in a positive TST 1 to 4 weeks after initial negative findings on TST. Evaluation for the booster phenomenon with a second TST 1 to 4 weeks after the first test (the 2-step method) should be considered for persons from countries with a high incidence of TB, for those with a history of BCG vaccination, and (as a baseline assessment) for those who need periodic retesting, such as health care workers. Test interpretation is based on the induration observed with the second test.

About 10% of immunocompetent persons with LTBI will develop TB disease over their lifetime, with the greatest risk for progression (5%) being in the first 2 years after infection with *M. tuberculosis*. Approximately 50% of TB cases will occur within 2 years after initial infection. Targeted tuberculin testing identifies persons at high risk of developing TB who would benefit from treatment for LTBI. These include persons at risk of becoming infected with *M. tuberculosis* and those with clinical conditions associated with increased risk of progression of TB infection to active TB (Table 2). A joint statement from the American Thoracic Society and the Centers for Disease Control and Prevention provides guidelines on testing and treatment of LTBI in the United States.
antigens, including ESAT-6, CFP-10, and TB7.7(p4). The T-SPOT.TB test (Oxford Immunotec Limited, Abingdon, United Kingdom) is an enzyme-linked immunospot assay that uses peripheral blood mononuclear cells incubated with mixtures of peptides containing ESAT-6 and CFP-10 to measure the number of cells secreting IFN-γ (IFN-γ-spot–forming cells). Results of IGRA are reported both qualitatively (positive, negative, indeterminate, or borderline) and quantitatively (IU/mL or IFN-γ-spot–forming cells). Reversion of IGRA test results from positive to negative has been observed, particularly in those with negative results on the initial TST. Conversion of IGRA (ie, a change in test results from negative to positive within 2 years) has not been associated with an increased risk of subsequent progression to TB disease.

The IGRA can be used in the same setting as TST but has the advantage of being able to differentiate M tuberculosis infection from previous BCG vaccination and most nontuberculous mycobacterial infections; it may also be able to discriminate true-negative responses from anergy. However, currently available IGRA, like TST, cannot distinguish active TB from latent infection. Because ESAT-6 and CFP-10 proteins are present in Mycobacterium marinum, Mycobacterium kansasii, and Mycobacterium szulgai, false-positive IGRA results are possible. As with negative TST findings, negative findings on IGRA may not exclude TB infection in immunosuppressed persons. An IGRA is the preferred method of testing for groups of people who have low rates of returning to have their TST test results read and for those who have received BCG vaccine. The TST is preferred for testing children younger than 5 years. For other groups being tested for LTBI, either TST or IGRA may be used. A summary of tests for TB is presented in Table 3.

### CHEST RADIOGRAPHY

Chest radiography is indicated for all persons being evaluated for LTBI or active TB. Pulmonary TB as a result of endogenous reactivation of latent infection classically presents with infiltrates in the apical and posterior segments of the right upper lobe, the apical-posterior segment of the left upper lobe, and the superior segment of the lower lobe. Cavitation, fibrosis, and/or enlargement of the hilar and mediastinal lymph nodes may be present. In some cases, pulmonary TB may present as lobar or segmental infiltrates, lung mass, scattered fibronodular lesions (“milairy”), or pleural effusions.

### SMEAR MICROSCOPY

Smear microscopy for the detection of AFB is the most rapid and inexpensive method for TB diagnosis. Two commonly
used methods for AFB staining are the carbolfuchsin methods (eg, Ziehl-Neelsen and Kinyoun methods) and the fluorochrome procedure using auramine O or auramine-rhodamine dyes. The fluorochrome method with fluorescence microscopy is preferred because it is far more sensitive than the carbolfuchsin methods. The finding of AFB on respiratory specimens associated with the appropriate epidemiological, clinical, and radiographic findings is highly suggestive of TB.

**Nucleic Acid Amplification Test**

The NAA test is useful for the rapid detection of *M tuberculosis* in respiratory specimens. The Enhanced Amplified MTD (Mycobacterium Tuberculosis Direct) test (Gen-Probe, San Diego, CA) detects *M tuberculosis* ribosomal RNA directly from AFB smear–positive and AFB smear–negative respiratory specimens from patients with suspected TB. The Amplicor MTB (Mycobacterium Tuberculosis) test (Roche Diagnostic Systems, Branchburg, NJ) detects *M tuberculosis* DNA in AFB smear–positive respiratory specimens.

Interpretation of NAA test results should be correlated with AFB smear results. Positive findings on the NAA test and a positive sputum AFB smear are strongly indicative of TB. When NAA and sputum microscopy test results are discordant, physicians should exercise their clinical judgment in deciding whether to start anti-TB treatment while culture results are awaited. When the clinical suspicion for TB is high, a positive NAA test result in smear-negative cases can be valuable for the early detection of TB in approximately 50% to 80% of cases. Findings on the NAA test often remain positive after cultures become negative during therapy and can remain positive even after completion of therapy; therefore, it should not be used for assessing infectivity or response to treatment.

**Culture**

Culture remains the criterion standard for laboratory confirmation of TB. Three types of culture media are available for the microbiological detection of *M tuberculosis*: egg-based (Löwenstein-Jensen), agar-based (Middlebrook 7H10 or 7H11), and liquid (Middlebrook 7H12 and other commercial broth systems). Mycobacterial growth tends to be slightly better on the egg-based medium but more rapid on the agar medium. Growth in liquid media is faster than growth on solid media and allows detection in 1 to 3 weeks. The development of automated liquid culture systems for mycobacterial growth detection, such as BACTEC 460TB and BACTEC MGIT960 (Becton Dickinson Microbiology Systems, Sparks, MD), VersiTREK Myco (Trek Diagnostic Systems, Westlake, OH), and BacT/Alert 3D (bioMérieux, Durham, NC), which are faster and more sensitive than solid media, has clearly facilitated TB diagnosis in the past decade.

**New Technology**

Several recently developed tests for TB, including molecular drug resistance, have the potential for providing rapid diagnosis and targeted treatment. These fully automated tests provide rapid drug-resistance testing for RIF and INH; however, they require sophisticated technology and are currently available only at reference laboratories.

**Other Considerations**

At the start of LTBI therapy, baseline measurements of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin are recommended for patients who have a history of liver disease (eg, hepatitis B or C, alcoholic hepatitis, or cirrhosis), use alcohol regularly, have risk factors for chronic liver disease, are infected with HIV, are pregnant, or have given birth within the past 3 months. All patients diagnosed as having LTBI should be offered voluntary HIV counseling and testing.

All patients with active TB should receive counseling and be tested for HIV infection. Serologic tests for hepatitis B and C should be performed for patients with risk factors such as injection drug use, foreign birth, and HIV infection. Susceptibility testing for INH, RIF, ethambutol (EMB), and pyrazinamide (PZA) should be performed on any initial culture that is positive. Susceptibility testing to the second-line drugs should be performed on specimens from patients who have had previous therapy, are known to have resistance to first-line drugs, are contacts of patients with drug-resistant TB, or have persistently positive cultures 3 months or more after starting treatment. Baseline measurements of platelet count and serum aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, and serum creatinine levels are recommended for all patients starting TB treatment.

**Treatment**

**Latent TB Infection**

Treatment for LTBI is recommended for persons deemed to be at relatively high risk of developing active TB (Table 2) and should be initiated only after active TB has been excluded by clinical and radiographic evaluations. Failure to rule out TB may result in inadequate treatment and development of drug resistance. For most patients, treatment with INH for 9 months is preferred (Table 4). Pyridoxine supplementation (25 mg/d) to INH is recommended for patients at an increased risk of neuropathy, including those with preexisting peripheral neuropathy, nutritional deficiency, diabetes mellitus, HIV infection, renal failure, alcoholism, or thyroid disease and those who are pregnant or breast-feeding. Intermittent treatment (ie, a twice-weekly regimen) should only be performed as directly
observed therapy (DOT). Due to the high rates of hospitalization and death from liver injury, the combination of RIF and PZA is no longer recommended for the treatment of LTBI.94

**Active TB**

Patients with active TB should be treated with multiple agents to achieve bacterial clearance, to reduce the risk of transmission, and to prevent the emergence of drug resistance. Directly observed therapy, which involves direct observation of patients ingesting anti-TB medications, is the preferred management strategy for all patients being treated for TB. For treatment to be successful, patient-centered case management and close collaboration between health care professionals and local public health programs are imperative.

Medications for treating TB are classified as first- and second-line drugs (Table 5). First-line drugs are INH, RIF, EMB, and PZA. The rifamycin derivatives rifapentine and rifabutin are also considered among the first-line drugs. Second-line drugs include the aminoglycosides streptomycin, kanamycin, and amikacin; the polypeptide capreomycin; p-aminosalicylic acid; cycloserine; the thioamides ethionamide and prothionamide; and several fluoroquinolones (eg, moxifloxacin, levofloxacin and gatifloxacin). The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America have issued a joint statement on treatment of TB in the United States.68 An overview of these recommendations follow.

Four treatment regimens are recommended for patients with drug-susceptible disease. Although these regimens are broadly applicable, treatment must be individualized on the basis of each patient’s clinical situation. Each of the 4 TB treatment regimens has an initial phase of 2 months followed by a continuation phase of 4 or 7 months (Table 6). Treatment in the initial phase is usually empirical because susceptibility data may not be available. To guard against drug resistance and to ensure maximal effectiveness, the initial phase of treatment should include 4 drugs (INH, RIF, PZA, and EMB). If the isolate is susceptible to INH and RIF, EMB can be discontinued. Depending on the regimen chosen, medication in the initial phase may be given daily throughout treatment, daily for 2 weeks then twice weekly thereafter, or 3 times weekly throughout. Susceptibility data should direct treatment in the continuation phase, which lasts for 4 months in most patients. The continuation phase of treatment should be extended to 7 months for the following 3 groups of patients: those with cavitary pulmonary TB whose sputum culture remains positive after 2 months of treatment; those in whom the initial phase of treatment did not include PZA (eg, those who have severe liver disease or are pregnant); and those being treated with once-weekly INH and rifapentine whose sputum culture remains positive after 2 months of treatment. Extending the continuation phase of treatment in these situations reduces the rate of relapse. During the continuation phase, medications may be given daily or 2 to 3 times a week with DOT.

The minimum duration of treatment for culture-positive TB is 6 months. If PZA is not included in the initial phase, treatment should be given for 9 months. Smear-negative, culture-negative pulmonary TB may be treated successfully with 4 months of a combination INH-RIF regimen. Completion of anti-TB treatment is determined by both the total number of doses taken and the duration of therapy.

**Follow-up Evaluation**

Patients receiving treatment for TB infection or disease should be counseled about adverse effects and should have clinical evaluations at least once monthly to assess adherence and evaluate for possible adverse effects of anti-TB medications (Table 5). Patients receiving INH for LTBI therapy should be given no more than a 1-month drug supply and should be monitored monthly for drug-induced hepatotoxicity or other adverse effects.93 Laboratory monitoring during treatment for LTBI is indicated only for patients with abnormal baseline liver function test results and other risks of liver disease and for evaluation of possible adverse effects during treatment.76

Patients being treated for pulmonary TB should have sputum microscopy and culture performed at least once a month until 2 consecutive negative specimens are obtained. Sputum culture after 2 months of treatment is particularly important because a positive result is associated with increased risk of relapse96-99 and requires 7 months of continuation therapy. Platelet counts and measurements of hepatic and renal function are necessary for those with baseline abnormalities or those at increased risk of toxicity (eg, hepatitis B or C infection, alcohol abuse).98 When EMB is to be used, visual acuity and red-green color discrimination should be monitored.

---

**TABLE 4. Treatment Regimens for Latent Tuberculosis Infection**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult dose (maximum)</th>
<th>Interval and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg (300 mg)</td>
<td>Daily for 9 mo</td>
</tr>
<tr>
<td>Alternative regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>15 mg/kg (900 mg)</td>
<td>Twice weekly for 9 mo</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg (300 mg)</td>
<td>Daily for 6 mo</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>15 mg/kg (900 mg)</td>
<td>Twice weekly for 6 mo</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg (600 mg)</td>
<td>Daily for 4 mo</td>
</tr>
</tbody>
</table>

Data from MMWR Recomm Rep.75
TABLE 5. **Doses and Adverse Effects of Antituberculosis Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult dose (daily maximum)</th>
<th>Important adverse effects</th>
<th>Use in pregnancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg (300 mg)</td>
<td>Hepatitis (risk increases with age), peripheral neuropathy, rash</td>
<td>Safe for fetus; increased hepatotoxicity postpartum</td>
<td>Should be supplemented with pyridoxine in pregnant patients or in patients at risk of neuropathy</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg (600 mg)</td>
<td>GI upset, hepatotoxicity, pruritus, orange discoloration of bodily fluids</td>
<td>Safe</td>
<td>Induces hepatic microsomal enzymes, resulting in decreased effectiveness of some drugs; use with caution in women taking oral contraceptives and advise on use of the supplement barrier method; has important interactions with antiretroviral agents</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>10 mg/kg (600 mg)</td>
<td>GI symptoms, hepatotoxicity, pruritus, orange discoloration of bodily fluids</td>
<td>Insufficient information</td>
<td>Can be used in a once-weekly regimen; not recommended in patients infected with HIV; induces hepatic microsomal enzymes, resulting in increased metabolism of coadministered drugs</td>
</tr>
<tr>
<td>Rifabutin(^b)</td>
<td>5 mg/kg (300 mg)</td>
<td>Neutropenia, uveitis, polyarthralgia, rash, hepatotoxicity, and orange discoloration of bodily fluids</td>
<td>Limited data; use with caution</td>
<td>Interacts with protease inhibitors and nonnucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>40-55 kg: 14.5-20.0 mg/kg (800 mg)</td>
<td>Optic neuritis and peripheral neuropathy</td>
<td>Safe</td>
<td>Can affect visual acuity and color vision and so these should be monitored</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>40-55 kg: 18.2-25.0 mg/kg (1000 mg)</td>
<td>Hepatotoxicity, GI symptoms, polyarthralgia, asymptomatic hyperuricemia, gout, rash, dermatitis</td>
<td>Limited data; probably safe</td>
<td>Routine measurement of uric acid not recommended</td>
</tr>
<tr>
<td>76-90 kg: 17.8-21.1 mg/kg (1600 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76-90 kg: 22.2-26.3 mg/kg (2000 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10-15 mg/kg (1.0 g in 2 doses)</td>
<td>Dose-related psychosis, seizures, depression, and headache</td>
<td>Crosses placenta; may be used if necessary</td>
<td>Use with pyridoxine for prevention and treatment of adverse neurotoxic effects; measure serum concentration and perform periodic renal, hepatic, and hematologic tests</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15-20 mg/kg (1.0 g/d in 1 or 2 divided doses)</td>
<td>GI effects, including metallic taste; neurotoxicity, including peripheral and optic neuritis; endocrine effects, including hypothyroidism, gynecomastia, alopecia, and impotence; and hepatotoxicity</td>
<td>Contraindicated</td>
<td>Perform liver function tests, measure thyroid-stimulating hormone monthly</td>
</tr>
<tr>
<td>Levofloxacin(^b)</td>
<td>500-1000 mg</td>
<td>GI upset, dizziness, tremulousness, insomnia, rash, photosensitivity, QT prolongation</td>
<td>Avoid</td>
<td>Should not be administered within 2 h of antacids and other medications containing divalent cations</td>
</tr>
<tr>
<td>Moxifloxacin/gatifloxin(^b)</td>
<td>400 mg</td>
<td>GI upset, dizziness, tremulousness, insomnia, rash, photosensitivity, QT prolongation</td>
<td>Avoid</td>
<td>Should not be administered within 2 h of antacids and other medications containing divalent cations</td>
</tr>
<tr>
<td>p-Amino-salicylic acid</td>
<td>8-12 g in 2 or 3 doses</td>
<td>Hepatitis, often severe GI intolerance, malabsorption syndrome, hypothyroidism, and coagulopathy</td>
<td>Has been used safely</td>
<td>Perform liver function and thyroid function tests</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg/d (1 g); in those &gt;59 y, 10 mg/kg (750 mg)</td>
<td>Otoxicity, neurotoxicity (weakness, circumoral paresthesia), nephrotoxicity</td>
<td>Contraindicated</td>
<td>Perform audiography, vestibular testing, and Romberg testing; measure serum creatinine levels; monitor serum drug concentration</td>
</tr>
<tr>
<td>Amikacin/kanamycin(^b)</td>
<td>15 mg/kg/d (1 g); in those &gt;59 y, 10 mg/kg (750 mg)</td>
<td>Otoxicity, nephrotoxicity</td>
<td>Contraindicated</td>
<td>Perform audiography, vestibular testing, and Romberg testing; measure serum creatinine levels; monitor serum drug concentration</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15 mg/kg/d (1 g); in those &gt;59 y, 10 mg/kg (750 mg)</td>
<td>Otoxicity, nephrotoxicity</td>
<td>Avoid</td>
<td>Perform audiography, Romberg testing, and vestibular testing; measure serum creatinine, potassium, and magnesium levels; monitor serum drug concentration</td>
</tr>
</tbody>
</table>

\(^a\) GI = gastrointestinal; HIV = human immunodeficiency virus.
\(^b\) Not approved by the Food and Drug Administration for treatment of tuberculosis.
Follow-up chest radiography after 2 months and at the completion of treatment is optional. Expert consultation should be sought for the management of patients who develop substantial adverse effects and require alternative treatment regimens.100-103

**TREATMENT IN SPECIAL SITUATIONS**

**INFECTION WITH HIV**

In general, the treatment of LTBI and TB in HIV-infected adults is the same as in adults not infected with HIV, with a few exceptions. Treatment for TB can be complicated by the interaction between rifamycins, antiretroviral agents, and other anti-infective drugs prescribed for opportunistic infections. In persons receiving antiretroviral therapy, RIF should be avoided or used with caution. Rifabutin, which has fewer problematic drug interactions, may be substituted for RIF. During the continuation phase of treatment, the INH-rifapentine regimen should never be used because of the high relapse rate.

Concurrent initiation of anti-TB and antiretroviral therapy may cause increased adverse effects and paradoxical reactions in patients not already receiving treatment. The term *immune reconstitution inflammatory syndrome* is used to describe this paradoxical reaction, which presents as worsening clinical (eg, high fever, weight loss, increased lymphadenopathy) and radiographic (eg, increased pulmonary infiltrates) manifestations of TB resulting from the immune reconstitution achieved by antiretroviral therapy.104-107 The mechanism for these paradoxical reactions is unclear but appears to be immune mediated: lower CD4 counts in patients with HIV infection seem to be associated with a higher risk of developing immune reconstitution inflammatory syndrome.104,108 For these reasons, antiretroviral therapy should be delayed for 2 to 8 weeks after starting anti-TB therapy.109 Treatment of HIV-related TB is complex and is best managed by those with expertise in both HIV infection and TB.

**EXTRAPULMONARY TB**

The same basic principles for the treatment of pulmonary TB apply to extrapulmonary TB. For TB at any site, a treatment course of 6 to 9 months with regimens that include INH and RIF is recommended; the single exception is meningitis, for which 9 to 12 months of treatment is recommended. The addition of corticosteroids to anti-TB treatment is recommended for patients with TB of the pericardium and central nervous system, including the meninges.

**PREGNANCY AND BREAST-FEEDING**

For the treatment of TB in pregnant women, the initial regimen should be INH, RIF, and EMB for at least 9 months.

---

**TABLE 6. Treatment Regimens for Drug-Susceptible Pulmonary Tuberculosis**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and doses (duration)</th>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and doses (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isoniazid</td>
<td>7 d/wk for 56 doses (8 wk)</td>
<td>1a</td>
<td>Isoniazid</td>
<td>7 d/wk for 126 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>5 d/wk for 40 doses (8 wk)</td>
<td>2b</td>
<td>Isoniazid</td>
<td>Twice weekly for 36 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td></td>
<td>1c</td>
<td>Isoniazid</td>
<td>Twice weekly for 36 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td>2a</td>
<td>Isoniazid</td>
<td>Twice weekly for 36 doses (18 wk)</td>
</tr>
<tr>
<td>2</td>
<td>Isoniazid</td>
<td>7 d/wk for 14 doses (2 wk),</td>
<td>3a</td>
<td>Isoniazid</td>
<td>Twice weekly for 54 doses (18 wk)</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>then twice weekly for 12 doses (6 wk); or</td>
<td>3</td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>then twice weekly for 12 doses (6 wk)</td>
<td></td>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td>4</td>
<td>Isoniazid</td>
<td>Twice weekly for 62 doses (31 wk)</td>
</tr>
<tr>
<td>3</td>
<td>Isoniazid</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>4a</td>
<td>Isoniazid</td>
<td>7 d/wk for 217 doses (31 wk); or</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td></td>
<td></td>
<td>Rifampin</td>
<td>5 d/wk for 155 doses (31 wk)</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td></td>
<td>4b</td>
<td>Isoniazid</td>
<td>Twice weekly for 62 doses (31 wk)</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td></td>
<td>Rifampin</td>
<td></td>
</tr>
</tbody>
</table>

* Ethambutol need not be included when the organism is known to be fully susceptible.

Data from *MMWR Recomm Rep.*

---

Follow-up chest radiography after 2 months and at the completion of treatment is optional. Expert consultation should be sought for the management of patients who develop substantial adverse effects and require alternative treatment regimens.100-103

**TREATMENT IN SPECIAL SITUATIONS**

**INFECTION WITH HIV**

In general, the treatment of LTBI and TB in HIV-infected adults is the same as in adults not infected with HIV, with a few exceptions. Treatment for TB can be complicated by the interaction between rifamycins, antiretroviral agents, and other anti-infective drugs prescribed for opportunistic infections. In persons receiving antiretroviral therapy, RIF should be avoided or used with caution. Rifabutin, which has fewer problematic drug interactions, may be substituted for RIF. During the continuation phase of treatment, the INH-rifapentine regimen should never be used because of the high relapse rate.

Concurrent initiation of anti-TB and antiretroviral therapy may cause increased adverse effects and paradoxical reactions in patients not already receiving treatment. The term *immune reconstitution inflammatory syndrome* is used to describe this paradoxical reaction, which presents as worsening clinical (eg, high fever, weight loss, increased lymphadenopathy) and radiographic (eg, increased pulmonary infiltrates) manifestations of TB resulting from the immune reconstitution achieved by antiretroviral therapy.104-107 The mechanism for these paradoxical reactions is unclear but appears to be immune mediated: lower CD4 counts in patients with HIV infection seem to be associated with a higher risk of developing immune reconstitution inflammatory syndrome.104,108 For these reasons, antiretroviral therapy should be delayed for 2 to 8 weeks after starting anti-TB therapy.109 Treatment of HIV-related TB is complex and is best managed by those with expertise in both HIV infection and TB.

**EXTRAPULMONARY TB**

The same basic principles for the treatment of pulmonary TB apply to extrapulmonary TB. For TB at any site, a treatment course of 6 to 9 months with regimens that include INH and RIF is recommended; the single exception is meningitis, for which 9 to 12 months of treatment is recommended. The addition of corticosteroids to anti-TB treatment is recommended for patients with TB of the pericardium and central nervous system, including the meninges.

**PREGNANCY AND BREAST-FEEDING**

For the treatment of TB in pregnant women, the initial regimen should be INH, RIF, and EMB for at least 9 months.
Although teratogenicity data for PZA are limited, it is probably safe to use in pregnancy. Breast-feeding should not be discouraged for women receiving anti-TB treatment. Pyridoxine supplementation (25 mg/d) is recommended for all pregnant and breast-feeding women taking INH.

**DRUG-RESISTANT TB**

Treatment of drug-resistant TB (resistance of the organism to 1 first-line drug) has become even more complex, difficult, and expensive with the emergence of MDR-TB and XDR-TB. Patients with drug-resistant TB may acquire further drug resistance and are at high risk of treatment failure. These patients should receive prompt expert consultation. General guidelines for treating patients with drug-resistant TB include using multiple (4-6) drugs, including an injectable agent to which the organism is susceptible. Treatment includes second-line drugs that have many adverse effects and are more expensive and less effective than first-line drugs. Careful supervision under DOT is mandatory to ensure adherence to therapy. Treatment is extended to 24 months after culture conversion, with posttreatment follow-up for 24 months. Case series reveal a possible role for surgical therapy in select cases of MDR-TB and XDR-TB.

**CONTROL AND ELIMINATION**

Active TB is frequently treated in the outpatient setting. Patients with active TB should be managed in conjunction with local public health offices and TB control agencies to coordinate visits and maximize adherence. When active TB is suspected, patients should wear a simple surgical mask when they are out of the house or near other people.

Initial treatment in the hospital may be appropriate for patients who are acutely ill, those with substantial comorbid illness, or infectious patients who are nonadherent to therapy. These patients should be admitted to a negative-pressure isolation room with at least 6 air exchanges per hour. Health care professionals should wear a fit-tested N95 mask; those who have not been fit-tested or are unable to use an N95 mask should use a powered air-purifying respirator. Simple surgical masks are more effective than N95 masks at preventing extrusion of respiratory droplets; therefore, patients with TB should wear a simple surgical mask when they are not in their isolation room. Patients may be removed from isolation when clinical improvement is seen on effective therapy and when 3 consecutive sputum samples on separate days are AFB smear-negative. If patients with active pulmonary TB are medically stable for discharge but are not yet AFB smear-negative, they may be discharged only if a definitive plan for outpatient therapy has been coordinated with the local TB control agency, if no children younger than 4 years or no immunocompromised persons live with them, and if they agree to leave their home only for medical appointments. The preferred mechanism of therapy for both inpatients and outpatients is DOT.

Treatment of patients with active TB is the top public health priority for TB control, followed by contact investigation of all persons who came into close contact with these patients before initiation of therapy. Such contact investigation should be carried out on all patients with confirmed active pulmonary TB and on selected patients with suspected pulmonary TB before testing is complete. Patients with extrapulmonary TB are generally not infectious; therefore, contact investigation is not indicated.

The third priority for TB elimination and control is to reduce the population-based burden of LTBI through targeted testing and treatment. This strategy is particularly important in low-incidence nations, where most TB cases arise from reactivation of LTBI. In high-incidence, resource-poor settings, this strategy is rarely feasible. Testing for LTBI is indicated to detect patients at risk of new infection or at risk of reactivation of LTBI due to underlying medical conditions. Persons at risk of new infection include contacts of patients with active pulmonary TB, employees at facilities with a high risk of exposure (eg, prisons, health care facilities, homeless shelters), and those who have recently immigrated (ie, within the past 5 years) from regions of the world where TB is endemic. Persons at highest risk of reactivation include those taking immunosuppressive medications (ie, chemotherapy, tumor necrosis factor α inhibitors) and those with HIV infection, hematologic malignancy, silicosis, dialysis-dependent renal failure, or changes on chest radiography consistent with previous TB.

**CONCLUSION**

Tuberculosis remains a devastating disease throughout the world. Efforts to eradicate it have been thwarted by poverty, lack of health care access, drug resistance, immunosuppressed populations (eg, HIV-infected persons), and global migration. Effective management requires prompt recognition using a combination of clinical, radiographic, microbiological, and histopathologic hallmarks and initiation of appropriate multidrug therapy. In addition to effective treatment of patients with active TB, public health management strategies include contact investigation and testing of persons who came into close contact with patients with active TB before initiation of therapy and reduction of the population-based burden of LTBI through targeted testing and treatment.
REFERENCES

CURRENT CONCEPTS IN THE MANAGEMENT OF TUBERCULOSIS


The Symposium on Antimicrobial Therapy will continue in the May issue.

*This activity was designated for 1 AMA PRA Category 1 Credit(s).™*
Antiparasitic Therapy

SHANTHI KAPPAGODA, MD, SM; UPINDER SINGH, MD; AND BRIAN G. BLACKBURN, MD

Parasitic diseases affect more than 2 billion people globally and cause substantial morbidity and mortality, particularly among the world’s poorest people. This overview focuses on the treatment of the major protozoan and helminth infections in humans. Recent developments in antiparasitic therapy include the expansion of artesminin-based therapies for malaria, new drugs for soil-transmitted helminths and intestinal protozoa, expansion of the indications for antiparasitic drug treatment in patients with Chagas disease, and the use of combination therapy for leishmaniasis and human African trypanosomiasis.


AL = artemether-lumefantrine; CBC = complete blood cell count; CL = cutaneous leishmaniasis; CNS = central nervous system; DEC = diethylcarbamazine; G6PD = glucose-6-phosphate dehydrogenase; HAT = human African trypanosomiasis; HIV = human immunodeficiency virus; LF = lymphatic filariasis; ML = mucocutaneous leishmaniasis; NCC = neurocysticercosis; STH = soil-transmitted helminth; TMP-SMX = trimethoprim-sulfamethoxazole; VL = visceral leishmaniasis; VLM = visceral larva migrans

Parasitic diseases cause substantial morbidity and mortality worldwide, taking the heaviest toll among the world’s poorest people. This article reviews the treatment of the major protozoan and helminth infections in humans.

PROTOZOA AND THE DISEASES THEY CAUSE

Protozoa are single-celled eukaryotes that cause a diverse array of human diseases. They are generally categorized as systemic or intestinal and usually do not cause eosinophilia.

SYSTEMIC PROTOZOA

Malaria. Human malaria is caused by the mosquito-borne parasites Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi, which parasitize red blood cells and cause hemolytic anemia. Malaria kills nearly 1 million people and causes almost 300 million symptomatic illnesses annually. It is found in sub-Saharan Africa, Asia, Oceania, and Latin America. Uncomplicated malaria can manifest as fever, anemia, thrombocytopenia, myalgias, cough, and diarrhea. Severe malaria is defined in part by respiratory distress, renal failure, altered mental status or seizures, intolerance of oral medications, metabolic acidosis or hypoglycemia, and parasitemia greater than 5%. The mortality rate of severe malaria is high.

Treatment of Uncomplicated P. falciparum Malaria. The preferred treatment for uncomplicated Plasmodium malaria acquired in areas with chloroquine resistance is atovaquone-proguanil, artemether-lumefantrine (AL), or oral quinine plus doxycycline.1 Atovaquone-proguanil is a well-tolerated, oral fixed-dose combination. Atovaquone inhibits parasite mitochondrial electron transport. Proguanil inhibits the dihydrofolate reductase step in purine synthesis and lowers the concentration of atovaquone necessary to kill Plasmodium species. Adverse effects include nausea, vomiting, abdominal pain, and hepatitis.

Artemether-lumefantrine is an oral fixed-dose combination recently approved in the United States. Artemether is a semisynthetic derivative of artemisinin, a sesquiterpene lactone. Lumefantrine, a fluorene derivative, may interfere with heme metabolism. Artemether-lumefantrine is rapidly effective against all erythrocytic stages of malaria. Adverse effects include nausea, vomiting, dizziness, headache, and possibly QT prolongation.2 It should be taken with fatty foods to increase absorption.

Oral quinine plus doxycycline (or plus tetracycline or clindamycin) is effective for uncomplicated malaria. Quinine is an aryl-amino alcohol, which may cause toxic heme accumulation in the parasite. It can cause cinchonism (nau-
sea, vomiting, tinnitus, high-frequency hearing loss, and dizziness). Both tetracyclines and clindamycin inhibit expression of the *Plasmodium* apicoplast genome. Adverse effects include nausea, vomiting, abdominal pain, candidiasis, and photosensitivity for doxycycline and nausea, vomiting, abdominal pain, and diarrhea for clindamycin.

Mefloquine, an aryl-amino quinoline, has the same mechanism of action as quinine. Due to resistance, it is not recommended for patients infected in much of Southeast Asia. It can cause neuropsychiatric disturbances and QT prolongation at treatment doses and is a second-line agent.

Chloroquine is recommended for uncomplicated *P. falciparum* malaria acquired in areas without chloroquine resistance. It is a 4-aminoquinoline and may act by disrupting heme metabolism. Adverse effects include nausea, vomiting, diarrhea, headache, and blurred vision. Pruritis also occurs, mostly in African patients. Hydroxychloroquine is an acceptable alternative.1

**Treatment of Severe Malaria.** Severe malaria (usually caused by *P. falciparum*) should be treated with parenteral medications, such as intravenous artesunate, quinine, or quindine. Artesunate is preferred because it works faster, is more effective, and is better tolerated than quinine. In the United States, artesunate is available from the Centers for Disease Control and Prevention for severe malaria in patients who meet certain criteria. Artesunate is combined with atovaquone-proguanil, doxycycline, clindamycin, or mefloquine to prevent recurrent parasitemia. Artesunate is well tolerated, with adverse effects similar to artemether. At high doses, it may cause neutropenia.

Quinidine gluconate, which has the same mechanism of action as quinine, is available for severe malaria in the United States. Patients should be monitored with telemetry and have blood glucose and drug levels followed up closely. Adverse effects include infusion-related hypotension, QT prolongation, torsades de pointes, and hypoglycemia. Although less cardiotoxic than quinidine, parenteral quinine is not available in the United States. It can cause infusion-related hypotension, hypoglycemia, and cinchonism. Both quinine and quindine should be combined with doxycycline, tetracycline, or clindamycin, and patients can transition to oral therapy after improvement.

**Treatment of Uncomplicated Non-*falciparum* Malaria.** Chloroquine plus primaquine is effective for uncomplicated *P. vivax* and *P. ovale* malaria in most of the world. Patients infected in areas with chloroquine-resistant *P. vivax* and *P. ovale* (particularly Papua New Guinea and Indonesia) should be treated with atovaquone-proguanil, mefloquine, or quinine plus doxycycline. Patients infected with *P. vivax* or *P. ovale* should receive primaquine (an 8-aminoquinolone) for 14 days to prevent relapse. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients, G6PD levels should be measured before use. Other adverse effects include nausea and vomiting. *P. malariae* or *P. knowlesi* infections can usually be treated with chloroquine.1,7

**Resistance.** Chloroquine resistance is widespread. Due to resistance, mefloquine is not recommended for malaria acquired in much of Southeast Asia. Parts of South America and equatorial Africa also have high mefloquine treatment failure rates. Atovaquone-proguanil–resistant *P. falciparum* is rare. The World Health Organization recommends that artemisinins be used exclusively in combination regimens, but strains of *P. falciparum* with decreased sensitivity to artemisinins have emerged along the border between Cambodia and Thailand, in part because of long-standing monotherapy practices. Of 22 African countries, 2 (Ghana and Burkina Faso) had failures in more than 10% of *P. falciparum* cases treated with AL in one study. Treatment failure rates with AL of more than 20% have occurred only in Cambodia. Chloroquine-resistant *P. vivax* occurs primarily in Southeast Asia and Oceania, but cases have been reported in South America, Ethiopia, and the Solomon Islands. *P. vivax* treatment failure rates of more than 10% with AL have occurred in Papua New Guinea. The Worldwide Antimalarial Resistance Network has developed an online database of malaria resistance.10

Treatment regimens for all types of malaria are summarized in Table 1.

**New Developments.** Arterolane, a synthetic trioxolane derived from artemisinins, is undergoing phase 3 clinical trials in combination with piperaquine for *P. falciparum* malaria.11 In 2 recent clinical trials, both once-daily pyronaridine-artesunate and azithromycin plus artesunate were noninferior to AL for *P. falciparum* malaria.12,13

**African Trypanosomiasis.** Human African trypanosomiasis (HAT, or sleeping sickness) is caused by 2 subspecies of *Trypanosoma brucei* that are endemic only to Africa and transmitted by tsetse flies. In the United States, only 1 or 2 cases occur annually (among returning travelers). *T. brucei rhodesiense* causes a rapidly progressive disease in Eastern and Southern Africa, whereas *T. brucei gambiense* causes a more indolent disease in West and Central Africa. Initially, patients develop fever, lymphadenopathy, hepatosplenomegaly, and rash. Later, a chronic meningoencephalitis occurs with headaches, listlessness, disordered sleep, and neuromuscular dysfunction. Drugs for HAT are toxic; however, left untreated, the disease is fatal.

**T. gambiense.** Pentamidine and suramin are available for early-stage *T. gambiense* disease. Neither drug crosses the blood-brain barrier, and for late-stage (central nervous system [CNS]) disease, eflornithine and melsaroprol are used (Table 1).
## TABLE 1. Treatment Regimens for Protozoal Infections in Adults

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic protozoa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria—uncomplicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or species unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine-resistant</td>
<td>Atovaquone-proguanil</td>
<td>Nausea, vomiting,</td>
<td>Should be taken with food</td>
</tr>
<tr>
<td>area (everywhere</td>
<td>250 mg/100 mg, 4 adult tablets</td>
<td>vomiting, Headache, dizziness,</td>
<td>Should be taken with fatty foods</td>
</tr>
<tr>
<td>except Central America</td>
<td>orally every day for 3 d</td>
<td>vomiting</td>
<td></td>
</tr>
<tr>
<td>west of Panama Canal,</td>
<td>20 mg/120 mg, 4 tablets oral starting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haiti, Dominican Republic,</td>
<td>dose, followed by 4 tablets orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and parts of the Middle</td>
<td>orally twice a day for 2 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Artemether-lumefantrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Quinine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>625 mg salt orally 3 times a day for</td>
<td>Cinchonism, hypoglycemia</td>
<td></td>
</tr>
<tr>
<td><em>plus</em> Doxycycline</td>
<td>7 d for patients infected in Southeast Asia or for 3 d in other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Tetracycline</td>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Clindamycin</td>
<td>6-7 mg/kg orally 3 times a day for</td>
<td>Nausea, vomiting, abdominal pain,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>candidiasis, photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Mefloquine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>750 mg salt oral loading dose</td>
<td>Nausea, vomiting, vivid dreams,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>followed by 500 mg salt orally</td>
<td>hypophoria, mood changes, QT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-12 h after initial dose</td>
<td>prolongation, mandatory</td>
<td></td>
</tr>
<tr>
<td>Chloroquine-sensitive</td>
<td>Chloroquine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Nausea, vomiting, headache, dizziness,</td>
<td></td>
</tr>
<tr>
<td>area (Central America</td>
<td>1000 mg salt oral loading dose</td>
<td>pruritis (usually in African patient),</td>
<td></td>
</tr>
<tr>
<td>west of Panama Canal,</td>
<td>followed by 500 mg salt orally at</td>
<td>photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Haiti, Dominican Republic,</td>
<td>6 h, 24 h, and 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and parts of the Middle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>800 mg salt oral loading dose</td>
<td>Retinal toxicity unlikely with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>followed by 400 mg salt orally at 6 h,</td>
<td>short-term use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h, and 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria—severe</td>
<td>Artesunate per CDC protocol</td>
<td>2.4 mg/kg IV at 0 h, 12 h, 24 h, and</td>
<td>Can be requested from CDC Malaria Hotline&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Usually</td>
<td></td>
<td>48 h, then once per day if IV still</td>
<td></td>
</tr>
<tr>
<td><em>P falciparum</em></td>
<td></td>
<td>necessary</td>
<td></td>
</tr>
<tr>
<td><em>plus</em> Atovaquone-proguanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxycycline, clindamycin,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or mefloquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Loading dose of 10 mg/kg salt IV over 1-2 h followed by 0.02 mg/kg/min</td>
<td>Infusion-related hypotension, QT and</td>
<td>Continuous ECG and close BP and blood glucose</td>
</tr>
<tr>
<td></td>
<td>salt continuous infusion for 24 h</td>
<td>QRS prolongation, arrhythmias,</td>
<td>monitoring mandatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Once improved, switch</td>
<td>625 mg salt orally 3 times a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>to oral quinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>plus</em> Doxycycline</td>
<td>100 mg IV/orally twice daily for 7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Tetracycline</td>
<td>250 mg orally 4 times daily for 7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Clindamycin</td>
<td>10 mg/kg IV loading dose then 5 mg/kg IV every 8 h (or oral dose as</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>as above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total duration of quinidine</td>
<td></td>
<td>7 d for patients infected in Southeast</td>
<td></td>
</tr>
<tr>
<td>quinine therapy is 7 d</td>
<td></td>
<td>Asia, 3 d for elsewhere</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic protozoa (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria—uncomplicated <em>Plasmodium vivax</em> or <em>Plasmodium ovale</em></td>
<td>Chloroquine Followed by primaquine</td>
<td>See <em>P. falciparum</em> 52.6 mg salt orally every day for 14 d</td>
<td>Nausea and vomiting, hemolytic anemia with G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine Followed by primaquine</td>
<td>See <em>P. falciparum</em></td>
<td></td>
</tr>
<tr>
<td>Malaria—uncomplicated <em>P. vivax</em> or <em>P. ovale</em></td>
<td>Quinine plus Doxycycline, tetracycline, or clindamycin Followed by primaquine or Atovaquone-proguanil Followed by primaquine</td>
<td>See <em>P. falciparum</em></td>
<td></td>
</tr>
<tr>
<td>Malaria—uncomplicated <em>Plasmodium malariae</em> or <em>Plasmodium knowlesi</em></td>
<td>Chloroquine or Hydroxychloroquine</td>
<td>See <em>P. falciparum</em></td>
<td></td>
</tr>
<tr>
<td>African trypanosomiasis Early (hemolymphatic stage) <em>Trypanosoma brucei gambiense</em></td>
<td>Pentamidine 4 mg/kg/d IM for 7-10 d</td>
<td>Hypotension (with IV infusion), hypoglycemia, hepatitis, pancreatitis, leukopenia, sterile abscesses, nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suramin 100-200 mg IV (test dose) followed by 1 g IV on days 1, 3, 7, 14, and 21</td>
<td>Nephrotoxicity, rash (including exfoliative dermatitis), fatal hypersensitivity reaction (1 in 20,000 doses), peripheral neuropathy, myelosuppression</td>
<td>Available from CDC Drug Service</td>
</tr>
<tr>
<td>Trypanosoma brucei rhodesiense</td>
<td>Suramin Dosed as above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late (CNS stage) <em>T. b. gambiense</em></td>
<td>Eflornithine 100 mg/kg IV every 6 h for 14 d</td>
<td>Fever, seizures, myelosuppression, peripheral neuropathy, diarrhea, hypertension, rash</td>
<td>Given as prolonged infusion. Contact CDC Drug Service regarding availability</td>
</tr>
<tr>
<td></td>
<td>or Eflornithine 200 mg/kg IV every 12 h for 7 d</td>
<td>Nausea, vomiting, anorexia, abdominal pain, insomnia, peripheral neuropathy, hepatitis. Avoid alcohol</td>
<td>Available from CDC Drug Service</td>
</tr>
<tr>
<td></td>
<td>plus Nifurtimox 5 mg/kg orally 3 times a day for 10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melarsoprol 2.2 mg/kg/d IV for 10 d</td>
<td>Vomiting, nephrotoxicity, hepatitis, myocardial damage, peripheral neuropathy, fever, thrombocytopenia, reactive encephalopathy (often fatal). Encephalopathy risk reduced by coadministration of corticosteroids. Contraindicated with G6PD deficiency</td>
<td>Available from CDC Drug Service</td>
</tr>
</tbody>
</table>

(continued on next page)
TABLE 1. **Continued**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic protozoa (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>T b rhodesiense</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melarsoprol</td>
<td>2.0-3.6 mg/kg/d IV for 3 d. Repeat course after 7 d and then again 7 d after the completion of the 2nd course</td>
<td>Nausea, vomiting, anorexia, insomnia, peripheral neuropathy, dermatitis, myelosuppression. Disulfiram-like reaction with alcohol</td>
<td>Available from CDC Drug Service[6]</td>
</tr>
<tr>
<td>Benznidazole</td>
<td>2.5-3.5 mg/kg orally twice a day for 60 d</td>
<td>Nausea, vomiting, anorexia, insomnia, peripheral neuropathy, dermatitis, myelosuppression.</td>
<td>Contact CDC Drug Service[6] regarding availability Should be taken with food</td>
</tr>
<tr>
<td>Nifurtimox</td>
<td>2-3 mg/kg orally every 6-8 h for 90 d</td>
<td></td>
<td>Should be taken after meals Available from CDC Drug Service[6]</td>
</tr>
<tr>
<td>Liposomal amphotericin</td>
<td>Immunocompetent adults: 3 mg/kg IV once a day on days 1-5, 14, and 21</td>
<td>Nephrotoxicity, electrolyte wasting, hypertension, infusion reaction, chills/rigors</td>
<td>Multiple regimens used, including shorter-course amphotericin-based regimens and combination regimens</td>
</tr>
<tr>
<td>Liposomal amphotericin</td>
<td>Immunocompromised adults: 4 mg/kg IV once a day on days 1-5, 10, 17, 24, 31, and 38</td>
<td>Nephrotoxicity, electrolyte wasting, hypertension, infusion reaction, chills/rigors</td>
<td>Multiple regimens used, including shorter-course amphotericin-based regimens and combination regimens</td>
</tr>
<tr>
<td>Sodium stibogluconate or Miltefosine</td>
<td>20 mg/kg IV or IM once a day for 28 d</td>
<td>Nausea, vomiting, severe vertigo, headache, diarrhea</td>
<td>Not commercially available in the US; contact Caligor Rx, Inc, for availability[7]</td>
</tr>
<tr>
<td>or Paromomycin</td>
<td>2.5 mg/kg/d (maximum 150 mg/d) orally for 28 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Paromomycin</td>
<td>15 mg/kg/d IM for 21 d</td>
<td>Nephrotoxicity, ototoxicity, hepatitis</td>
<td></td>
</tr>
<tr>
<td>Sodium stibogluconate</td>
<td>20 mg/kg/d IV or IM for 20 d</td>
<td>Pentavalent antimonials: nausea, vomiting, abdominal pain, pancreatitis, hepatitis, myalgias, myelosuppression, ECG abnormalities</td>
<td>Available from CDC Drug Service[6] Decision whether to use systemic therapy for cutaneous leishmaniasis is complex. When used, most appropriate drug depends in part on infecting species and region acquired</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>2.5 mg/kg/d (maximum 150 mg/d) orally for 28 d</td>
<td>Headache, anorexia, hepatitis, alopecia</td>
<td>Optimal dosing regimen not defined</td>
</tr>
<tr>
<td>or Fluconazole</td>
<td>200 mg orally once a day for 6 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Liposomal amphotericin</td>
<td>3 mg/kg IV once a day on days 1-5, 14, and 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Pentamidine</td>
<td>2-3 mg/kg IV or IM once a day or every other day for 4-7 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
### Systemic protozoa (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucocutaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium stibogluconate</td>
<td>20 mg/kg/d IV or IM for 28 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin</td>
<td>3 mg/kg IV once a day</td>
<td></td>
<td>Multiple regimens used</td>
</tr>
<tr>
<td>or Amphotericin deoxycholate</td>
<td>0.5-1.0 mg/kg IV once a day for 1 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Miltefosine</td>
<td>2.5 mg/kg (maximum 150 mg/d) orally once a day for 28 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Babesiosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>750 mg orally twice a day</td>
<td>Rash, abdominal pain, diarrhea, nausea, vomiting, headache, insomnia, methemoglobinemia, hepatotoxicity</td>
<td>Higher doses, longer duration of therapy for immunosuppressed patients (see text)</td>
</tr>
<tr>
<td><em>plus</em> Azithromycin</td>
<td>500 mg orally for 1 d then 250 mg orally once a day for 7-10 d</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, headache, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Quinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>plus</em> Clindamycin</td>
<td>650 mg orally 3 times a day 300-600 mg IV every 6 h or 600 mg orally 3 times a day for 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxoplasmosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>200 mg orally once followed by 50 mg (if &lt;60 kg) or 75 mg (if &gt;60 kg) orally once a day</td>
<td>Myelosuppression, abdominal pain, rash, headaches, dysgeusia</td>
<td>No treatment for acute illness in nonpregnant/immunosuppressed pregnant patients</td>
</tr>
<tr>
<td><em>plus</em> Sulfadiazine</td>
<td>1 g/kg (if &lt;60 kg) or 1.5 g/kg (if &gt;60 kg) orally 4 times a day</td>
<td>Myelosuppression, rash, crystal-induced nephropathy</td>
<td>Duration of therapy based on clinical situation</td>
</tr>
<tr>
<td><em>plus</em> Folic acid</td>
<td>10-25 mg orally once a day</td>
<td></td>
<td>Consider concomitant systemic corticosteroids for chorioretinitis</td>
</tr>
<tr>
<td><strong>TMP-SMX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/25 mg/kg orally or IV every 12 h</td>
<td>Higher doses have been used in some cases</td>
<td>Rash, urticaria, nausea, vomiting, myelosuppression. Rarely: Stevens-Johnson syndrome, renal insufficiency, hyperkalemia, hepatitis</td>
<td></td>
</tr>
<tr>
<td>For patients with sulfa allergy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Doses as above</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>plus</em> Folic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>plus</em> either</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600 mg IV every 6 h or 450 mg orally 4 times a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Atovaquone</td>
<td>750 mg orally every 6 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acquired during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider spiramycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Pyrimethamine/sulfadiazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>depending on clinical situation and gestational age (see text)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suggest expert consultation (see box to right)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Spiramycin: nausea, abdominal pain, diarrhea</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider prolonged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pyrimethamine/sulfadiazine</td>
<td></td>
<td></td>
<td>University of Chicago Congenital Toxoplasmosis Study Group may be able to provide clinical guidance&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Suggest expert consultation (see box to right)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
## Antiparasitic Therapy

### Intestinal/Genitourinary Protozoa

**Giardiasis**
- **Tinidazole**
  - Dose: 2 g orally once
  - Adverse effects: Anorexia, metallic taste, alcohol-induced disulfiram-like reaction, headache, peripheral neuropathy, seizures, neutropenia
- **Metronidazole**
  - Dose: 250 mg orally 3 times a day for 5-7 d

**Nitazoxanide**
- Dose: 500 mg orally twice a day for 3 d
  - Adverse effects: Nausea, vomiting, abdominal pain, diarrhea

**Amebiasis (Entamoeba histolytica)**
- **Asymptomatic carrier**
  - Luminal agent: Paromomycin or Iodoquinol
    - Dose: 8-12 mg/kg orally 3 times a day for 7 d or 650 mg orally 3 times a day for 20 d
    - Adverse effects: Nausea, vomiting, abdominal pain

**Diloxanide**
- Dose: 500 mg orally 3 times a day for 10 d
- Commercially unavailable in the US but may be available through Abbott India Ltd

**Amebic colitis**
- **Metronidazole**
  - Dose: 500-750 mg orally 3 times a day for 10 d or 2 g orally once a day for 3 d

**Amebic liver abscess or other disseminated disease**
- **Metronidazole**
  - Dose: 750 mg orally or IV 3 times daily or 2 g orally once a day
  - Adverse effects: Nausea, vomiting, diarrhea, pruritis, headache

**Cryptosporidiosis**
- **Non-AIDS-associated**
  - **Nitazoxanide**
    - Dose: 500 mg orally twice a day for 3 d

**Cyclosporiasis**
- **Non-AIDS-associated**
  - **TMP-SMX**
    - Dose: 1 DS tablet orally twice a day for 7-10 d or 1 DS tablet orally 4 times a day for 10 d followed by twice a day for 3 wk
  - **Ciprofloxacin**
    - Dose: 500 mg orally twice a day for 7 d followed by 1 tablet orally 3 times a week for 2 wk
    - Adverse effects: Nausea, vomiting, abdominal pain. Rarely: tendinopathy, neuropsychiatric effects

**Isosporiasis**
- **Non-AIDS-associated**
  - **TMP-SMX**
    - Dose: 1 DS tablet orally twice a day for 10 d or 1 DS tablet orally 4 times a day for 10 d followed by twice a day for 3 wk

**Dientamoebiasis**
- **Iodoquinol**
  - Dose: 650 mg orally 3 times a day for 20 d

**Blastocystis hominis**
- **Nitazoxanide**
  - Dose: 500 mg orally twice a day for 3 d

### Table 1. Continued

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 1. Continueda

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intestinal/genitourinary protozoa (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinidazole</td>
<td>2 g orally once</td>
<td>Sexual partners should be treated</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2 g orally once or 500 mg orally twice a day for 7 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Free-living amebae**

*Naegleria fowleri*

- Therapy should include amphotericin B
- Consider intrathecal amphotericin
- Combination systemic therapy is essential: consider addition of azoles, rifampin, or other anti-microbial agents (see text)

**Acanthamoeba species**

*GAE and disseminated disease*

- Combination therapy is essential and should include pentamidine, azoles, sulfonamides, and possibly flucytosine (see text)

**Acanthamoeba keratitis**

- Topical chlorhexidine
- Polyhexamethylene biguanide
- 0.02%
- May be available via compounding pharmacies1

**Balamuthia mandrillaris**

- Combination therapy is essential and should likely include flucytosine, pentamidine, fluconazole, sulfadiazine, macrolides (see text)

---

*a BP = blood pressure; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; DS = double-strength; ECG = electrocardiography; GAE = granulomatous amebic encephalitis; G6PD = glucose-6-phosphate dehydrogenase; HAART = highly active antiretroviral therapy; IM = intramuscular; IV = intravenous; TMP-SMX = trimethoprim-sulfamethoxazole; PAMF-TSL = Palo Alto Medical Foundation Toxoplasma Serology Laboratory; US = United States.

*b Dosing conversion for base formulation dose based on salt formulation dose: oral quinine 625 mg salt = 542 mg base; IV quinidine 10 mg/kg salt = 6.25 mg/kg base and 0.02 mg/kg/min salt = 0.0125 mg/kg/min base; oral methoquine 750 mg salt = 684 mg base, and 500 mg salt = 456 mg base; oral chloroquine 1000 mg salt = 600 base, and 500 mg salt = 300 mg base; oral hydroxychloroquine 800 mg salt = 620 mg base and 400 mg salt = 310 mg base; oral primaquine 52.6 mg salt = 30 mg base.

*c Symptoms of cinchonism include nausea, vomiting, dizziness, tinnitus, and high-frequency hearing loss.

*d CDC Malaria Hotline (770-488-7788 M-F 9:00 am to 5:00 pm EST or 770-488-7100 other hours).

*e CDC Drug Service (404-639-3670).

*f Caligor Rx, Inc, New York, NY (212-369-6000 or for emergencies 917-692-0195).

*g PAMF-TSL (650-853-4828).

*h University of Chicago Congenital Toxoplasmosis Study Group (773-834-4152).

*i Diloxanide may be available from Abbott India Ltd, Mumbai, India (+91 22 67978888).

*j A compounding pharmacy that specializes in ophthalmic drugs is Leiter’s Park Avenue Pharmacy in San Jose, CA (800-292-6773).

Pentamidine, an aromatic diamidine, is preferred for early-stage disease. Pentamidine reduces the mitochondrial membrane potential and binds to nucleic acids. It is given intramuscularly and can cause hypotension, hypoglycemia, leukopenia, nephrotoxicity, hepatitis, and pancreatitis.

Suramin, a sulfonated naphthylamine, inhibits multiple trypanosome metabolic enzymes. It is a second-line treatment for early-stage disease because of toxicity, including exfoliative dermatitis, peripheral neuropathy, nephrotoxicity, myelosuppression, and a potentially fatal hypersensitivity reaction. Suramin is active against *Onchocerca volvulus*, and reactions (from dying parasites) can occur in coinfected patients.14

Efornithine, which inhibits ornithine decarboxylase, is the preferred drug for late-stage *T b gambiense* disease. It is less toxic than melarsoprol but not reliably effective...
against *T. b. rhodesiense.* Adverse reactions include fever, myelosuppression, hypertension, rash, peripheral neuropathy, and diarrhea.

Melarsoprol, an organic arsenical agent, remains the most widely used drug against late-stage HAT despite being the most toxic. Its mechanism of action is unknown. The most feared adverse effect is reactive encephalopathy, which occurs in 5% to 10% of patients and is fatal in half of cases. Co-administration of corticosteroids lowers the risk of encephalopathy. Other adverse effects include vomiting, abdominal pain, thrombophlebitis, peripheral neuropathy, fever, and thrombocytopenia.

Nifurtimox-eflornithine combination therapy was more effective than eflornithine monotherapy for late-stage *T. b. gambiense* and enabled shorter treatment courses in 2 clinical trials. Another trial found that melarsoprol-nifurtimox combination therapy was more effective than melarsoprol alone. However, a subsequent study found that patients with late-stage *T. b. gambiense* disease who were treated with melarsoprol-nifurtimox had higher death rates than those treated with other combination regimens.

**T. b. rhodesiense.** There is little new clinical evidence regarding the treatment of *T. b. rhodesiense.* Suramin is used for early-stage disease, and melarsoprol is used for late-stage disease (Table 1).

**Resistance.** Up to 30% of patients infected with *T. b. gambiense* do not respond to melarsoprol, and 6% to 8% may receive no benefit from eflornithine in some regions. Suramin and melarsoprol resistance have occurred in clinical isolates of *T. b. rhodesiense* from Tanzania.

**Drugs in Development.** Clinical trials with fenixidazole, an oral 5-nitroimidazole active against *T. b. gambiense* and *T. b. rhodesiense,* are under way.

**American Trypanosomiasis.** American trypanosomiasis (Chagas disease) is caused by *Trypanosoma cruzi,* which is endemic only to Latin America and is usually transmitted by blood-feeding triatomine insects. Acute infection is often asymptomatic, but patients may have unilateral palpebral edema or an erythematous, indurated skin lesion with regional lymphadenopathy. Fever, diffuse lymphadenopathy, hepatosplenomegaly, and (less commonly) meningoencephalitis and myocarditis may occur. Acute disease is generally self-limited. Most patients are subsequently asymptomatic (a state termed indeterminate Chagas). Years to decades later, 20% to 40% of cases progress to chronic Chagas disease, which affects the heart (eg, cardiomyopathy, chronic heart failure, and arrhythmias) and the gastrointestinal tract (eg, achalasia, megaesophagus, constipation, obstruction, and megacolon). The nitroheterocyclic compounds nifurtimox and benznidazole are used to treat Chagas disease (Table 1). Benznidazole is better tolerated and generally considered the drug of choice. Contraindications to treatment include pregnancy and renal and hepatic insufficiency.

Nifurtimox is a 5-nitrofuran derivative; its mechanism of action is not well understood. Adverse effects include anorexia, abdominal pain, vomiting, insomnia, paresthesias, peripheral neuropathy, and hepatitis. Discontinuation due to intolerance is common. During therapy, clinicians should screen for peripheral neuropathy, monitor liver and renal function, and obtain a complete blood cell count (CBC).

Benznidazole is a nitroimidazole derivative that may increase phagocytosis. Adverse effects include vomiting, anorexia, dermatitis, and myelosuppression. Dose-dependent peripheral neuropathy, severe rash, fever, or lymphadenopathy should prompt discontinuation. Clinicians should check for rash and monitor CBCs as well as liver and renal function test results during treatment.

Although clinical evidence supporting treatment for Chagas disease is limited, most authorities recommend treatment for acute and congenital infections, infections in children, and reactivated infections in immunocompromised patients. The role of therapy in indeterminate and chronic Chagas disease in adults is more controversial, but evidence is emerging that select patients in these groups may benefit. Recent studies suggest that benznidazole for indeterminate or early chronic Chagas disease may improve parasite clearance rates and prevent progression to cardiomyopathy. A multicenter, placebo-controlled trial involving benznidazole for the treatment of chronic Chagas disease is under way.

**Resistance and Drugs in Development.** Although strains of *T. cruzi* resistant to both nifurtimox and benznidazole can be generated in vitro, documentation of clinical resistance is scarce. Several new triazoles, squalene sym- thase inhibitors, and cysteine protease inhibitors have shown efficacy in animal models. A phase 2 clinical trial of posaconazole vs benznidazole for chronic Chagas disease is under way.

**Leishmaniasis.** *Leishmania* species are transmitted primarily by sandflies and cause 3 clinical syndromes: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (ML).

**Visceral Leishmaniasis.** Visceral leishmaniasis is caused predominantly by *Leishmania donovani* on the Indian subcontinent and East Africa and by *Leishmania infantum/chagasi* elsewhere. Infection with these species results in subclinical infection in most patients and kala-azar (fever, weight loss, hepatosplenomegaly, hyperglobulinemia, neutropenia, and death) in a minority. Ninety percent of VL cases occur in India, Bangladesh, Nepal, Sudan, and...
Brazilians. The drug of choice for VL in the United States is liposomal amphotericin (Table 1). Multiple dosing schedules and other treatment regimens are used globally.

Liposomal amphotericin, a polynene, forms pores in cell membranes. In India, single-dose liposomal amphotericin was as effective as 29 days of amphotericin B deoxycholate in a recent trial. Amphotericin causes nephrotoxicity, electrolyte loss, fever, and rashes; however, these occur less frequently with liposomal formulations.

Miltefosine, a synthetic phospholipid analogue and the only orally available drug for VL, causes apoptosis-like cell death. Cure rates appear similar to those obtained with other treatment regimens. Combination therapy with miltefosine and other treatment regimens is used globally.

Antimonial agents, such as sodium stibogluconate, were previously the therapeutic choice for VL. Currently, resistance limits their use, especially in South Asia. Antimonial agents inhibit several parasitic enzymes, but they are poorly tolerated. Adverse effects include anorexia, vomiting, vertigo, diarrhea, hepatitis, renal insufficiency, and teratogenicity. There is concern that mono therapy may lead to drug resistance.

Pentavalent antimonial agents, such as sodium stibogluconate, were previously the therapeutic choice for VL. Currently, resistance limits their use, especially in South Asia. Antimonial agents inhibit several parasitic enzymes, but they are poorly tolerated. Adverse effects include anorexia, vomiting, vertigo, diarrhea, hepatitis, renal insufficiency, and teratogenicity. There is concern that monotherapy may lead to drug resistance.

Paromomycin, an aminoglycoside that inhibits metabolism and mitochondrial respiration, is an alternative for VL. Paromomycin was noninferior to amphotericin in India in a recent study. Adverse effects include ototoxicity, nephrotoxicity, and hepatotoxicity.

Combination therapy for VL may shorten treatment duration, decrease toxicity, and prevent resistance. In Sudan, paromomycin plus antimony was more effective than antimony alone. Single-dose liposomal amphotericin plus short-course miltefosine was effective and well tolerated in India, as was single-dose liposomal amphotericin plus short-course paromomycin and short-course miltefosine plus paromomycin.

Cutaneous Leishmaniasis. Cutaneous leishmaniasis usually presents as nodular skin lesions that slowly enlarge and ulcerate. Ninety percent of CL cases occur in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil, and Peru. Because the lesions of CL usually heal spontaneously, the decision to treat depends on lesion location and size, the region of acquisition and infecting species, the risk of progression to ML (limited to some New World CL infecting species), and patient preference.

New World CL is commonly caused by Leishmania braziliensis, Leishmania mexicana, and Leishmania panamensis. When the decision is made to treat, antimonial agents are usually used (Table 1). Combination therapy with allopurinol or pentoxifylline plus antimonial agents may be more effective than antimonial agents alone. A 4-week course of miltefosine was as effective as antimonial agents in Colombia but less effective than antimonial agents in Guatemala. Pentamidine has been used for CL caused by Leishmania guyanensis in French Guyana, Surinam, and Brazil but is toxic and less effective.

Old World CL is caused mainly by Leishmania major, Leishmania tropica, or Leishmania aethiopica. When systemic treatment is deemed necessary, antimonial agents are usually used (Table 1). Fluconazole cured 79% of CL patients in Saudi Arabia with L major at 3 months; however, a subsequent observational study showed no benefit from fluconazole. Miltefosine has been used successfully to treat Old World CL. Topical therapy, such as 15% paromomycin-12% methylbenzethonium ointment and intraleral antimonial agents, may be an alternative treatment option for Old World CL. Imiquimod, a topical immunomodulator, improved cure rates in Peru when given with parenteral antimonial agents; however, no benefit was seen in a similar trial in Iran.

Amphotericin (particularly liposomal formulations) has been used successfully in a growing number of CL patients infected in both the Old and New World. Infections caused by at least 5 different Leishmania species have been successfully treated with liposomal amphotericin; however, experience remains limited, and the optimal dosing regimen has not yet been determined.

Mucocutaneous Leishmaniasis. Patients with CL caused by certain New World Leishmania species (eg, L braziliensis) can develop ML (ulcerative lesions in the nose, mouth, and pharynx). Mucocutaneous leishmaniasis is usually treated with a 28-day course of antimonial therapy, but response rates are variable and relapses common (Table 1). Cure rates with antimonial agents plus pentoxifylline were higher than with antimonial agents alone in Brazil. Amphotericin and pentamidine have also been used. Oral miltefosine cured 83% of patients with mild ML and 58% with more extensive ML in Bolivia.

Resistance. Resistance to pentavalent antimonial agents occurs in 40% to 60% of patients with VL in Bihar, India. Resistance has also been reported from Sudan.

Drugs in Development. Sitamaquine (an oral 8-aminoquinoline) cured 50% to 90% of patients with VL in phase 2 trials. Adverse effects included nephrotoxicity and methemoglobinemia (with G6PD deficiency). Trials with azithromycin, amphotericin, miltefosine, and low-dose antimonial agents for CL are ongoing.

Babesiosis. Babesia microti is the most common cause of babesiosis. This predominantly tick-borne zoonosis is endemic to southern New England, New York, the north...
central American Midwest, and Europe. Babesia species parasitize red blood cells. Infections are commonly asymptomatic but can be associated with a mild to moderate febrile illness or fulminant hemolytic anemia (usually in patients with immunosuppression or splenectomy). Treating asymptomatic, immunocompetent patients is generally unnecessary unless parasitemia persists for 3 months or more. For mild to moderate illness, atovaquone plus azithromycin is as effective (and better tolerated) than the previous standard, oral quinine plus clindamycin (Table 1). Severe disease can be treated with a 7- to 10-day course of oral quinine plus intravenous clindamycin. Relapse is common in immunocompromised patients, and some authors recommend 6 or more weeks of therapy (including 2 weeks after blood smears are negative). Exchange transfusion is indicated for severe babesiosis (parasitemia of 10% or more; significant hemolysis; or renal, hepatic, or pulmonary compromise). Coinfection with Lyme disease or anaplasmosis should be considered in patients with babesiosis because the same tick transmits all 3 pathogens.

Atovaquone monotherapy can induce resistance in animal models, and resistance emerged during atovaquone and azithromycin treatment in 3 immunocompromised patients.

Toxoplasmosis. Toxoplasmosis is most commonly acquired by consuming undercooked meat or other food or water containing Toxoplasma gondii cysts. After acute infection, T gondii remains latent and persists for life. Although acute infection is usually asymptomatic, 10% to 20% of patients develop lymphadenopathy or a self-limited mononucleosis-like syndrome. T gondii can also cause chorioretinitis. Immunocompromised patients can develop toxoplasmic encephalitis (usually reactivation of latent disease) and, less commonly, disseminated disease. Toxoplasmosis acquired during pregnancy can cause spontaneous abortion, hydrocephalus, intracranial calcifications, mental retardation, and seizures in the baby. Nonpregnant, immunocompetent patients with acute toxoplasmosis generally do not require antimicrobial therapy. For eye disease, treatment usually includes anti-Toxoplasma agents plus systemic corticosteroids. Immunocompromised patients with toxoplasmosis should be treated with 2 antimicrobial agents.

Pyrimethamine (the most effective anti-Toxoplasma agent available) plus sulfadiazine (with folinic acid) is preferred (Table 1). Pyrimethamine inhibits dihydrofolate reductase, depleting folate and impairing nucleic acid synthesis. Adverse effects include dose-dependent myelosuppression (which can be ameliorated with concurrent folinic acid), abdominal pain, rash, and headaches. Pyrimethamine is combined with sulfadiazine, another folate antagonist. In addition to rash and myelosuppression, sulfadiazine can cause crystal-induced nephropathy. Trimethoprim-sulfamethoxazole (TMP-SMX) has similar efficacy to pyrimethamine-sulfadiazine for toxoplastic encephalitis and chorioretinitis; however, unlike pyrimethamine-sulfadiazine, it is also available intravenously. Pyrimethamine plus clindamycin is also effective. If none of these drugs can be used, clarihromycin, azithromycin, atovaquone, and dapsone are alternatives.

Toxoplasmosis During Pregnancy. In the United States, spiramycin is generally recommended for toxoplasmosis acquired during pregnancy to reduce the risk of congenital toxoplasmosis (Table 1). Although its efficacy is controversial, spiramycin, a macrolide that inhibits protein synthesis, is well tolerated. Its main adverse effects are abdominal pain and diarrhea. When maternal infection occurs at 18 weeks of gestation or later, or fetal transmission is confirmed, pyrimethamine-sulfadiazine plus folinic acid is usually recommended. Congenitally infected infants are generally treated for 12 months with pyrimethamine-sulfadiazine plus folinic acid (Table 1).

New Developments. A clinical trial comparing spiramycin with pyrimethamine-sulfadiazine for the prevention of congenital toxoplasmosis in the babies of women infected at 14 weeks of gestation or later is under way.

Infectious and Genitourinary Protozoa

Giardiasis. Giardia lambia (also called Giardia duodenalis and Giardia intestinalis) infects the small intestine. It is found worldwide and is a common cause of travelers’ diarrhea and childhood diarrhea in areas with poor sanitation. Water-borne transmission is most common, followed by person-to-person and food-borne spread. Some infections are asymptomatic, but most cause diarrhea (often lasting several weeks). Abdominal cramps, bloating, flatulence, weight loss, lactose intolerance, and malabsorption with oily, foul-smelling stools can occur.

Giardiasis can be treated with a single dose of tinidazole (Table 1), which cures more than 90% of cases. This 5-nitroimidazole is converted into toxic radicals that damage DNA. Adverse effects include dysgeusia, nausea, abdominal discomfort, and alcohol-induced disulfiram-like reactions. Rarely, peripheral neuropathy, seizures, and neutropenia occur. Metronidazole, widely used to treat giardiasis in the United States, has a similar mechanism of action and similar adverse effects; a 5- to 7-day course has slightly lower efficacy. Nitazoxanide, an oral nitrothiazolyl-salicylamide, appears to inhibit pyruvate:ferredoxin oxidoreductase. A 3-day course cures 80% to 85% of patients. It is generally well tolerated but can cause nausea and vomiting. A recent meta-analysis found that albenda-
zole had comparable efficacy and was better tolerated than metronidazole.62

**Amebiasis.** Entamoeba histolytica, a protozoan transmitted by the fecal-oral route, is most common in tropical regions. Most infected persons remain asymptomatic, but 10% annually develop invasive disease that presents as nonbloody diarrhea or amebic dysentery. Most adults have gradually worsening diarrhea and abdominal pain; rare complications include liver abscess, toxic megacolon, and ameboma. Asymptomatic persons infected with *E histolytica* are treated to prevent transmission and invasive disease (Table 1). For asymptomatic infections, a “luminal agent” (that is active against cysts), such as paromomycin or iodoquinol, is sufficient. Iodoquinol is an 8-hydroxyquinoline; both it and paromomycin are poorly absorbed and can cause nausea and abdominal cramps. Optic and peripheral neuropathy can occur with prolonged use. Diloxanide is an alternative luminal agent. Symptomatic infections should be treated with a tissue amebicide (eg, metronidazole or tinidazole) plus a luminal agent. Tinidazole may be better tolerated and more effective than metronidazole.63 Cure rates of greater than 90% have been seen with nitazoxanide,64 but comparative data with nitroimidazoles are limited.

**Cryptosporidiosis.** Cryptosporidium parvum and *Cryptosporidium hominis*, the most common causes of cryptosporidiosis, are found worldwide. They cause diarrhea, which is usually self-limited in immunocompetent hosts. In immunocompromised hosts (particularly patients with AIDS), diarrhea may be severe and persistent. Nitazoxanide accelerates symptom resolution in human immunodeficiency virus–negative patients, but results have anide accelerates symptom resolution in human immuno-

**Amebiasis.** Entamoeba histolytica, a protozoan transmitted by the fecal-oral route, is most common in tropical regions. Most infected persons remain asymptomatic, but 10% annually develop invasive disease that presents as nonbloody diarrhea or amebic dysentery. Most adults have gradually worsening diarrhea and abdominal pain; rare complications include liver abscess, toxic megacolon, and ameboma. Asymptomatic persons infected with *E histolytica* are treated to prevent transmission and invasive disease (Table 1). For asymptomatic infections, a “luminal agent” (that is active against cysts), such as paromomycin or iodoquinol, is sufficient. Iodoquinol is an 8-hydroxyquinoline; both it and paromomycin are poorly absorbed and can cause nausea and abdominal cramps. Optic and peripheral neuropathy can occur with prolonged use. Diloxanide is an alternative luminal agent. Symptomatic infections should be treated with a tissue amebicide (eg, metronidazole or tinidazole) plus a luminal agent. Tinidazole may be better tolerated and more effective than metronidazole.63 Cure rates of greater than 90% have been seen with nitazoxanide,64 but comparative data with nitroimidazoles are limited.

**Cryptosporidiosis.** Cryptosporidium parvum and *Cryptosporidium hominis*, the most common causes of cryptosporidiosis, are found worldwide. They cause diarrhea, which is usually self-limited in immunocompetent hosts. In immunocompromised hosts (particularly patients with AIDS), diarrhea may be severe and persistent. Nitazoxanide accelerates symptom resolution in human immunodeficiency virus–negative patients, but results have been mixed in HIV-infected patients, with efficacy greatest in those with CD4 cell counts higher than 50/μL (Table 1).55 In patients with AIDS, initiation of antiretroviral agents, particularly protease inhibitors, improves symptoms.55 Paromomycin, nitazoxanide, macrolides, and rifamycins appear to be ineffective in HIV-infected patients.66 Several thiazolides have in vitro activity against *C parvum*.67

**Cyclosporiasis.** Cyclospora cayetanensis is found worldwide, with highest prevalence in Haiti, Guatemala, Peru, and Nepal. It causes watery diarrhea with abdominal cramps, fatique, and anorexia. Diarrhea can persist for months, particularly in HIV-infected patients. Cyclosporiasis is treated with TMP-SMX (Table 1). Ciprofloxacin is a less effective alternative; limited data suggest nitazoxanide may also be effective.68,69

**Isosporiasis.** Found most commonly in tropical and subtropical regions, isosporiasis is caused by *Isospora belli*. Symptoms are similar to those of cyclosporiasis. Diarrhea is often self-limited in immunocompetent hosts but may be prolonged in those who are immunocompromised. Treatment is with TMP-SMX, and, as with cyclosporiasis, higher doses are used in patients with AIDS (Table 1). Ciprofloxacin, pyrimethamine (with folinic acid),70 and nitazoxanide71 are alternatives.

**Dientamoeba fragilis.** *D fragilis* is a trichomonad that may cause diarrhea and may be associated with irritable bowel syndrome. Iodoquinol is the preferred treatment; metronidazole, paromomycin, and tetracyclines have also been used successfully (Table 1).72

**Blastocystis hominis.** *B hominis* is a protozoan that has also been linked to irritable bowel syndrome. Whether it truly causes disease is controversial, but some evidence supports a trial of antiparasitic therapy in infected patients with abdominal pain or diarrhea and no alternative explanation for their symptoms.73 Therapeutic options include nitazoxanide, metronidazole, and iodoquinol (Table 1).

**Trichomonas vaginalis.** Trichomoniasis is a common sexually transmitted infection caused by *T vaginalis*. In women, *T vaginalis* can cause vaginal discharge and pruritis, but 50% of infections may be asymptomatic. In men, infections are usually asymptomatic but can cause urethritis. Treatment with a single dose of tinidazole cures 86% to 100% of patients; metronidazole is an alternative (Table 1).74 Sexual partners should also be treated.

In one study, 10% of *Trichomonas* isolates were resistant to metronidazole and less than 1% were resistant to tinidazole.75 Patients who do not respond to single-dose metronidazole should be treated with 500 mg of metronidazole twice daily for 7 days. If no improvement is seen, 2 g of metronidazole or tinidazole daily for 5 days is recommended.74 Other successful regimens have included high-dose tinidazole plus doxycycline or ampicillin with clotrimazole pessaries76 and intravaginal paromomycin.77

**Free-Living Amebae**

*Naegleria fowleri.* *N fowleri* is a thermophilic protist found worldwide in soil and fresh water. It causes primary amebic meningoencephalitis, which is almost universally fatal within days of infection via the nasopharynx from warm fresh water. Symptoms may begin with altered taste or smell, followed by fever, vomiting, and rapid progression to confusion, coma, and death. Most survivors have received amphotericin, and drugs used successfully in combination with amphotericin include miconazole, fluconazole, ornidazole, rifampin, sulfisoxazole, and chloramphenicol.78,79 Miltefos-
Helminths and the Diseases They Cause

Helminths are multicellular worms that do not reproduce in humans (with the exceptions of Strongyloides and Capillaria). They often provoke an eosinophilic response in their human hosts, particularly when they invade tissue. Helminths are broadly categorized as cestodes, trematodes, or nematodes.

Cestodes (Tapeworms)

Cestodes cause disease as segmented, ribbon-like adult tapeworms in the gastrointestinal lumen or as juvenile tissue cysts. The preferred treatment is praziquantel for most intestinal cestodes and benzimidazoles for tissue/larval cestodes.

Taenia saginata. Also known as beef tapeworm, *T. saginata* is the most common *Taenia* species that infects humans. It is found worldwide, with highest prevalence in Latin America, Africa, the Middle East, and Central Asia. Humans become infected after consuming undercooked/raw infested beef. Most infections are asymptomatic, but some patients have abdominal cramps or malaise. Treatment is with praziquantel; niclosamide and nitazoxanide are alternatives (Table 2). Praziquantel is very effective for taeniasis. It is an oral pyrazinoisoquinolone derivative that damages the tegument and causes paralysis. Adverse effects include dizziness, headache, abdominal pain, vomiting, diarrhea, and hepatitis. Niclosamide works by uncoupling oxidative phosphorylation. Adverse effects include nausea and abdominal pain.

*Taenia solium*. Also known as pork tapeworm, *T. solium* is endemic to Latin America, sub-Saharan Africa, and Asia, where free-range pigs are raised. Taeniasis, intestinal infection with the adult tapeworm, results from eating undercooked pork containing cysticerci (larval cysts). Cysticercosis (tissue infection with *T. solium* larval cysts) results from ingestion of *T. solium* eggs, which are spread from a person with intestinal taeniasis or via fecal-oral autoinfection. Cysticercosis involving subcutaneous tissue or skeletal muscle is usually asymptomatic. With neurocysticercosis (NCC), cysts in the CNS can cause seizures, hydrocephalus, or chronic meningitis.

Although *T. solium* intestinal infection is usually asymptomatic, patients are treated to prevent cysticercosis. Praziquantel is first-line treatment, and niclosamide is an alternative (Table 2). The decision to treat NCC with antiparasitic agents is complex; the location, number, and type of cysts and clinical manifestations should be considered. Corticosteroids are given concurrently to decrease the inflammatory response and risk of seizures as the parasite degenerates. In general, patients with intraparenchymal cysts should be treated with albendazole plus corticosteroids. Patients with only intraparenchymal calcifications generally do not require antiparasitic therapy. Patients with subarachnoid cysts should generally receive prolonged courses of albendazole plus corticosteroids. Surgical removal is indicated for intraventricular, intraocular, and spinal cysts. Intraocular cysts should be excluded before initiating antiparasitic therapy for cysticercosis. If present, intraocular cysts should be surgically removed before administration of antiparasitic treatment to avoid irreversible eye damage due to the resulting inflammatory response.
## TABLE 2. Treatment Regimens for Helminth Infections in Adults

<table>
<thead>
<tr>
<th>Additional Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cestodes

**Intestinal tapeworm infection**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
</table>
| **Taenia saginata** | Praziquantel 5-10 mg/kg orally once | Dizziness, headache, abdominal pain, nausea, hepatitis | Not commercially available in the US but may be obtained from Expert Compounding Pharmacy
| **Taenia solium** | Niclosamide 2 g orally once | Nausea, vomiting, diarrhea, headache | Tablets should be chewed before swallowing |
| **Diphyllobothrium latum** | Nitazoxanide 500 mg orally twice a day for 3 d | Nausea, vomiting, abdominal pain, diarrhea | |

### Hymenolepis nana

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praziquantel</td>
<td>25 mg/kg orally once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niclosamide</td>
<td>2 g orally once, followed by 1.5 g orally once a day for 6 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>500 mg orally once a day or twice a day for 3 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cysticercosis

(see above for intestinal *T solium* infection)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
</table>
| Albendazole | 400 mg orally twice a day for 2-4 wk with corticosteroids given before, during, and after treatment to decrease seizure risk | Abdominal pain, nausea, vomiting, myelosuppression, alopecia, hepatitis. Can precipitate seizures in patients with neurocysticercosis | Should be taken with food
| | Praziquantel 33 mg/kg orally 3 times a day for 1 d followed by 15 mg/kg orally 3 times a day for 2-4 wk with corticosteroids given before, during, and after treatment to decrease seizure risk | Can precipitate seizures in patients with neurocysticercosis | |

### Echinococcosis

**Echinococcus granulosus**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole</td>
<td>400 mg orally twice a day for 1-6 mo; consider PAIR</td>
<td></td>
<td>Treatment decision is complex; management strategies depend in part on cyst stage (see text)</td>
</tr>
</tbody>
</table>

**Echinococcus multilocularis**

Consider albendazole; definitive therapy is surgical

### Trematodes

**Schistosomiasis**

- *Schistosoma mansoni*, *Schistosoma haematobium*, or *Schistosoma intercalatum*
- *Schistosoma japonicum* or *Schistosoma mekongi*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praziquantel</td>
<td>20 mg/kg orally twice a day for 1 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Praziquantel</td>
<td>20 mg/kg orally 3 times a day for 1 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)


<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trematodes (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>Triclabendazole</td>
<td>10 mg/kg orally once or twice</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Bithionol</td>
<td>30-50 mg/kg orally every other day for 20-30 d</td>
<td>Nausea, vomiting, abdominal pain</td>
</tr>
<tr>
<td>or Nitazoxanide</td>
<td>500 mg orally twice a day for 7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonorchiasis/ opisthorchias</td>
<td>Praziquantel</td>
<td>25 mg/kg orally 3 times a day for 2 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>10 mg/kg/d orally for 7 d</td>
<td></td>
</tr>
<tr>
<td>Paragonimiasian</td>
<td>Praziquantel</td>
<td>25 mg/kg orally 3 times a day for 2 d</td>
<td></td>
</tr>
<tr>
<td>or Triclabendazole</td>
<td>10 mg/kg orally twice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Bithionol</td>
<td>30-50 mg/kg orally every other day for 20-30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal flukes</td>
<td>Praziquantel</td>
<td>25 mg/kg orally 3 times a day for 1 d</td>
<td></td>
</tr>
<tr>
<td><strong>Nematodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascariasis</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally once or twice</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>or Mebendazole</td>
<td>500 mg orally once or 100 mg orally twice a day for 3 d</td>
<td>Nausea, diarrhea, hepatitis, or dizziness</td>
<td></td>
</tr>
<tr>
<td>or Ivermectin</td>
<td>150-200 μg/kg orally once</td>
<td></td>
<td>Can be obtained from Expert Compounding Pharmacyb</td>
</tr>
<tr>
<td>or Pyrantel pamoate</td>
<td>11 mg/kg (maximum 1 g) orally for 3 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichuriasis (whipworm)</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally once a day for 3-7 d</td>
<td></td>
</tr>
<tr>
<td>or Mebendazole</td>
<td>100 mg orally twice a day for 3-7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Ivermectin</td>
<td>200 μg/kg orally once for 3 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hookworm (Necator americanus, Ancylostoma duodenale)</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally once</td>
<td></td>
</tr>
<tr>
<td>or Mebendazole</td>
<td>100 mg orally twice for 3 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Pyrantel pamoate</td>
<td>11 mg/kg (maximum 1 g) orally once for 3 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobiasis (pinworm)</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally once</td>
<td>Treatment course should be repeated 2 wk later</td>
</tr>
<tr>
<td>or Mebendazole</td>
<td>100 mg orally once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Ivermectin</td>
<td>200 μg/kg orally once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongyloidesis</td>
<td>Ivermectin</td>
<td>200 μg/kg orally once for 2 d</td>
<td></td>
</tr>
<tr>
<td>Chronic intestinal infection</td>
<td>Alabendazole or Thiabendazole</td>
<td>400 mg orally twice a day for 10-14 d</td>
<td>Similar to albendazole</td>
</tr>
<tr>
<td>or Thiabendazole</td>
<td>25 mg/kg orally twice a day for 3-7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated/ hyperinfection</td>
<td>Ivermectin</td>
<td>200 μg/kg orally once a day until 7-14 d after clearance of parasite</td>
<td></td>
</tr>
<tr>
<td>Possible role for subcutaneous (veterinary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>formulations of Ivermectin or combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or combination Ivermectin or albendazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
### Extra-intestinal nematodes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication 1</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichinellosis</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally twice a day for 8-14 d</td>
<td></td>
<td>Consider concomitant corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200-400 mg orally 3 times a day for 3 d, followed by 400-500 mg orally 3 times a day for 10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>Albendazole or Mebendazole</td>
<td>400 mg orally twice a day for 5 d</td>
<td></td>
<td>Consider concomitant corticosteroids</td>
</tr>
<tr>
<td>Visceral larva migrans</td>
<td></td>
<td>100-200 mg orally twice a day for 5 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular larva migrans</td>
<td>Albendazole</td>
<td>400-800 mg orally twice a day for 28 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filarial infections</td>
<td>DEC</td>
<td>2 mg/kg orally 3 times a day for 1 d or 12 d</td>
<td>Nausea, fever, asthma-like symptoms, and arthralgias</td>
<td></td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Ivermectin</td>
<td>150-400 μg/kg orally once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tropical pulmonary eosinophilia</td>
<td>Ivermectin</td>
<td>400 mg orally once</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 μg/d for 4-8 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Ivermectin</td>
<td>150 μg/kg orally once, repeated every 6-12 mo until asymptomatic</td>
<td>DEC contraindicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 μg/kg for 4-8 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loaiasis</td>
<td>DEC</td>
<td>2-3 mg/kg orally 3 times a day for 2-3 wk</td>
<td></td>
<td>Available from CDC Drug Service</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antiparasitic therapy associated with encephalopathy in patients with high-grade parasitemia; consider pretreatment apheresis</td>
</tr>
</tbody>
</table>

### Other tissue nematodes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication 1</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous larva migrans</td>
<td>Albendazole</td>
<td>400 mg orally once a day for 3 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ivermectin</td>
<td>200 μg/kg orally once a day for 1-2 d</td>
<td></td>
</tr>
<tr>
<td>Angiostrongylus cantonensis</td>
<td>Albendazole</td>
<td>400 mg orally twice a day for 2-3 wk (plus corticosteroids)</td>
<td></td>
</tr>
<tr>
<td>(eosinophilic meningitis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baylisascarisasis</td>
<td>Albendazole</td>
<td>400 mg orally twice a day for 1-2 wk (plus corticosteroids)</td>
<td></td>
</tr>
<tr>
<td>Gnathostomiasis</td>
<td>Albendazole</td>
<td>400 mg orally twice a day for 21 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ivermectin</td>
<td>200 μg/kg orally once a day for 2 d</td>
<td></td>
</tr>
<tr>
<td>Capillariasis</td>
<td>Mebendazole</td>
<td>200 mg orally twice a day for 20 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>400 mg orally twice a day for 10 d</td>
<td></td>
</tr>
</tbody>
</table>

---

a CDC = Centers for Disease Control and Prevention; DEC = diethylcarbamazine; PAIR = percutaneous puncture, aspiration, injection, reaspiration.
b Expert Compounding Pharmacy, Lake Balboa, CA (800-247-9767).
c Contact CDC Drug Service (404-639-3670).
Albendazole is a broad-spectrum benzimidazole that inhibits microtubule formation. It can cause nausea, abdominal pain, rash, alopecia, leukopenia, and hepatitis. Emerging evidence suggests that antiparasitic therapy decreases seizures in patients with live intraparenchymal cysts. Praziquantel is a second-line agent for NCC. Disadvantages of praziquantel include lower efficacy, lower drug levels when coadministered with corticosteroids, and more drug-drug interactions.

**Dwarf Tapeworm.** The dwarf tapeworm *Hymenolepis nana* is found worldwide, with highest prevalence in Asia, southern/eastern Europe, Latin America, and Africa. Transmission is usually fecal-oral. Infections are usually asymptomatic, but some patients have abdominal discomfort and diarrhea. Treatment is with praziquantel at higher doses and longer courses than for taeniasis (Table 2). Niclosamide and nitazoxanide are alternatives.

**Diphyllobothrium latum.** Infection with *D. latum* results from eating raw or undercooked fish. Outbreaks have occurred in South America, Japan, Siberia, Europe, and North America. Infection is usually asymptomatic, but some patients have weakness, dizziness, salt craving, diarrhea, and passage of proglottids in their stool. The parasite interferes with vitamin B12 absorption and can cause megaloblastic anemia. Treatment is with praziquantel or, alternatively, niclosamide (Table 2).

**Drugs in Development.** Tribendimidine is a diamidine derivative of amidantel, an older acetylcholine receptor agonist used to treat hookworm. Treatment with tribendimidine has yielded cure rates similar to albendazole for intestinal taeniasis.

**Echinococcosis.** *Echinococcus granulosus* and *Echinococcus multilocularis* cause cystic and alveolar echinococcosis, respectively. *E. granulosus* infection results from ingesting food or water contaminated with *Echinococcus* eggs or from contact with infected dogs. The disease affects pastoral communities, particularly in South America, the Mediterranean littoral, Eastern Europe, the Middle East, East Africa, Central Asia, China, and Russia. After infection, the parasites encyst, usually in the liver, or less commonly in the lungs. Initially, cysts are asymptomatic, but over the course of months to years they enlarge and cause symptoms. Cyst rupture can cause anaphylaxis. With *E. multilocularis* infection (which is less common than *E. granulosus*), cysts usually form in the liver. They are aggressive, eventually invading contiguous structures with tumor-like progression and can metastasize, usually to the lungs and brain.

Management strategies depend on the cyst stage and include percutaneous puncture, aspiration, injection, and reaspiration (PAIR); surgery; antiparasitic chemotherapy; and expectant management. Select patients may be treated with albendazole alone (Table 2). A prolonged course is recommended to prevent recurrence after surgery or percutaneous treatment. There may be some benefit to combination praziquantel plus albendazole before and after surgical interventions.

**Trematodes (Flatworms)**

With the exception of fascioliasis, the preferred treatment for trematodes (flukes) is praziquantel.

**Schistosomiasis.** More than 200 million people globally are infected by *Schistosoma* species. The 3 species of primary medical importance are *Schistosoma mansoni* (found primarily in Africa, the Arabian Peninsula, and South America), *Schistosoma japonicum* (China, the Philippines, Southeast Asia, and Indonesia), and *Schistosoma haematobium* (Africa and the Arabian peninsula).

Infection occurs after skin contact with infested fresh water; 1 to 2 days later, patients may develop a papular, pruritic rash. About 1 to 2 months later, a minority develop Katayama fever, with myalgias, cough, eosinophilia, abdominal pain, fever, and hepatosplenomegaly. *S. mansoni* and *S. japonicum* can cause chronic hepatic/intestinal disease (abdominal pain, hepatic fibrosis, and portal or pulmonary hypertension). *S. haematobium* can cause genitourinary disease (hematuria, genital lesions, urinary strictures/obstruction, and bladder cancer). In endemic areas, schistosomiasis contributes to anemia and growth retardation in children.

The treatment of choice for schistosomiasis is praziquantel (Table 2). Higher doses are recommended for *S. japonicum* and *Schistosoma mekongi* infections compared with the other *Schistosoma* species. Praziquantel has little activity against eggs or immature worms (schistosomulae) and cannot abort early infection. Patients treated early in their infection must be retreated with praziquantel after the adult worms have matured (usually in 6 to 12 weeks). Although artemesunate has activity against schistosomulae, it is not usually used for schistosomiasis, in part because of concern about causing artemisinin-resistant malaria. For Katayama fever, corticosteroids are often coadministered with praziquantel. *S. mansoni* resistance to praziquantel has been observed. *S. mansoni* can also be treated with oxamniquine, and *S. haematobium* with metrifonate (Table 2); however, these drugs are not currently available in the United States.

**Fascioliasis.** Fascioliasis, caused mainly by *Fasciola hepatica*, is endemic to more than 60 countries and is most highly prevalent in sheep-raising areas of Peru, Bolivia, France, Portugal, Egypt, and Iran. Infection results from...
Antiparasitic Therapy

Eating freshwater plants infested with metacercariae. About 6 to 12 weeks after infection, larvae enter the liver. This acute (migratory) stage of infection can last 2 to 4 months and presents with marked eosinophilia, abdominal pain, fever, and weight loss. Computed tomography reveals multiple migratory, branching hepatic abscesses. F. hepatica later moves to the bile ducts, where it produces eggs after 3 to 4 months. Some patients develop intermittent biliary obstruction, but many are asymptomatic during the chronic (biliary) stage of infection. Unlike other trematodes, F. hepatica responds poorly to praziquantel, and triclabendazole (a benzimidazole that inhibits microtubule formation) is the treatment of choice (Table 2). Efficacy is 80% to 90%, but resistance has been reported.97 Triclabendazole is well tolerated aside from abdominal pain. Bithionol is an alternative but requires longer courses and causes more adverse effects. Cure rates are 60% with a 7-day course of nitazoxanide and 70% with a 10-day course of artesunate.98

Clonorchiasis and Opisthorchiasis. The Opisthorchiidae family of liver flukes contains 3 major species: Clonorchis sinensis, Opisthorchis viverrini, and Opisthorchis felineus. Infection results from eating undercooked freshwater fish infested with metacercariae. C. sinensis is endemic primarily to East Asia, O. viverrini to Southeast Asia, and O. felineus to Russia and other former Soviet republics. Adult worms deposit eggs in the biliary system; symptoms are uncommon, but patients may have fever, abdominal pain, hepatomegaly, and eosinophilia. Complications include ascending cholangitis, pancreatitis, and biliary pigment stones. Infection may increase the risk of cholangiocarcinoma. The treatment of choice is praziquantel (Table 2)99; albendazole is an alternative.100 Tribendimidine preliminarily appears to be as efficacious as praziquantel.101

Paragonimiasis. Paragonimiasis is caused by Paragonimus species lung flukes, of which Paragonimus westermani is the best described. It is most common in East and Southeast Asia. Infection results from eating undercooked crabs or crayfish infested with metacercariae. Adult worms lay eggs in the lung, and acute infection can cause diarrhea, abdominal pain, fever, chest pain, eosinophilia, and cough. Subsequently, patients may develop eosinophilic pleural effusions or bronchictatic and cavitory lung disease with cough and hemoptysis, often mimicking tuberculosis. Less commonly, lesions develop in the CNS, skin, or other sites. Treatment with praziquantel results in rapid clinical improvement and has high cure rates (Table 2).102 Triclabendazole is also effective.103 Bithionol is an alternative but requires longer courses and is more toxic.104

Intestinal Flukes. More than 60 flukes infect the human intestinal tract. The best known are Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai, and Echinostoma species. Most cases occur in Asia, but there are foci in Africa and the Middle East. All intestinal flukes are food-borne, and most result in asymptomatic infection. Praziquantel is the preferred treatment; however, triclabendazole is also effective (Table 2).105

Nematodes (Roundworms)

Nematodes are a diverse group of parasites that are among the most prevalent of human infections. They are categorized as intestinal or extraintestinal. Except for Strongyloides and filarial infections, benzimidazoles are the treatments of choice.

Intestinal Nematodes

Soil-Transmitted Helminths. The most common intestinal nematodes are Ascaris lumbricoides, Trichuris trichiura (whipworm), and the human hookworms Ancylostoma duodenale and Necator americanus. These organisms are also termed soil-transmitted helminths (STHs) because their eggs or larvae must develop in soil before becoming infectious. More than 1 billion people are infected with Ascaris, and nearly as many with whipworm or hookworm, most commonly in tropical areas with poor sanitation. Humans acquire Ascaris and Trichuris primarily through the fecal-oral route and hookworm primarily by walking barefoot on infested soil. Although pulmonary symptoms can occur early after infection with Ascaris or hookworm, adult worms in the bowel lumen generally cause no symptoms or only mild abdominal pain, nausea, or diarrhea. Ascaris can rarely cause intestinal or biliary obstruction, appendicitis, and intestinal perforation. Whipworm can cause rectal prolapse, and hookworm causes chronic anemia. Chronic infection with the STHs can impair growth and cognitive development in children and adversely affect pregnancies.

Short-course albendazole (or mebendazole) cures 88% to 95% of infections with Ascaris (Table 2).106 For Trichuris, short-course cure rates are low, and patients should receive 3 to 7 days of therapy.107 Preliminary data suggest mebendazole may be superior to albendazole for whipworm and that combination therapy with ivermectin may be superior to benzimidazole monotherapy.107 For hookworm, albendazole is preferred over mebendazole.106 Soil-transmitted helminths may be developing resistance to benzimidazoles.108

None of the available alternative therapies is superior to albendazole or mebendazole for all 4 STH species. The acetylcholine receptor agonist pyrantel pamoate is an alternative for Ascaris and hookworm, and ivermectin is an
alternative for *Ascaris* and whipworm. Newer treatments include nitazoxanide for *Ascaris* and whipworm and tribendimidine for *Ascaris* and hookworm.109,110

**Enteroübias vermicularis.** *E. vermicularis* (pinworm) causes enterobiasis, which occurs worldwide and does not disproportionately affect residents of tropical countries. The worms live in the proximal colon and migrate to the perianal region to lay eggs that become infectious after 6 hours. Transmission is mainly person-to-person, often via fecal-oral contamination of hands or fomites. Institutional or familial spread is common. Although most infections are asymptomatic, perianal pruritis can be severe. Single-dose albendazole or mebendazole is highly effective (Table 2).111 Alternatives include ivermectin or pyrantel pamoate. Household and other close contacts should be treated, and treatment should be repeated after 2 weeks because of frequent reinfection and autoinfection.112

**Strongyloëides stercoralis.** Strongyloidiasis is caused by *S. stercoralis*, an intestinal nematode usually acquired by walking barefoot on infested soil. *S. stercoralis* is found in the tropics, subtropics, and limited foci in the United States and Europe, where poor sanitation and a warm, moist climate coexist. Unlike nearly all other helminths, Strongyloëides can complete its life cycle within humans, allowing for amplification of the parasite, person-to-person transmission, and lifelong persistence. Chronic infection is usually asymptomatic, although abdominal pain, nausea, eosinophilia, and diarrhea can occur. Acute infection causes eosinophilia and sometimes rash or cough. In immunosuppressed patients, hyperinfection (a dramatic increase in the worm burden) and dissemination can occur, causing abdominal pain, diarrhea, polymicrobial sepsis, bronchopneumonia, or meningitis. Hyperinfection risk is highest in patients receiving corticosteroids or cancer chemotherapy, and in those coinfected with human T-cell lymphotropic virus.

Uncomplicated strongyloidiasis should be treated with oral ivermectin, which cures 70% to 85% of chronically infected patients (Table 2).113 This monogenic lactone binds chloride channels in helminth nerve and muscle cells, resulting in paralysis and death. Ivermectin is well tolerated, only rarely causing nausea, diarrhea, hepatitis, or dizziness when used for intestinal nematodes. Resistance is rare. Less effective alternatives include thiabendazole and albendazole.114 Hyperinfection or disseminated strongyloidiasis should be treated with oral ivermectin, usually in prolonged courses.115 Experimental use of veterinary parenteral ivermectin has been successful in treating disseminated strongyloidiasis.116,117 Patients have also been successfully treated with ivermectin plus albendazole.118 Screening should be considered in anyone (particularly patients with current or impending immunosuppression) with any history of exposure to endemic areas, even if many years before. Due to the risk of hyperinfection, all patients infected with *Strongyloëides* should be treated.

**Extraintestinal (Tissue) Nematodes**

**Trichinellosis.** Trichinellosis is caused by multiple species in the *Trichinella* genus, of which *Trichinella spiralis* is the best described. Infection results from eating undercooked meat containing *Trichinella* cysts (traditionally pork, but most US cases are now due to bear or other wild game meat). Symptoms include diarrhea, myositis, periorbital edema, conjunctivitis, fever, and eosinophilia. Rarely, patients can die of myocarditis or encephalitis. The benefit of antiparasitic therapy is uncertain, but most patients are treated with albendazole (or mebendazole) plus corticosteroids (Table 2).119

**Toxocariasis.** Toxocariasis is usually caused by *Toxocara canis* or *Toxocara cati*, the eggs of *T. canis* or *T. cati*, which are the most common causes of toxocariasis, are passed in dog or cat (respectively) feces into the environment, where they become infectious after 3 to 4 weeks. Human infections, which result from ingesting eggs in contaminated soil, can be asymptomatic (covert toxocariasis) or present as a larva migrans syndrome. Visceral larva migrans (VLM) occurs most commonly in young children. It is usually asymptomatic but can cause cough, fever, and wheezing. Visceral larva migrans causes eosinophilia and often hepatomegaly; splenomegaly and lymphadenopathy are less common. It is usually self-limited, and treatment with antihelminthic agents is controversial. If antiparasitics are used, albendazole is the drug of choice (Table 2); alternatives include mebendazole, thiabendazole, ivermectin, or the piperazine diethylcarbamazine (DEC).120,121 Corticosteroids are usually added in severe cases. Ocular larva migrans usually presents as a chorioretinal granuloma. Albendazole may be effective but in higher doses and longer courses than for VLM (Table 2).122 Surgery is sometimes required.

**Filariasis.** The filariae are vector-borne tissue nematodes generally found in residents of endemic areas, although travelers occasionally become infected.

**Lymphatic filariasis (LF).** Caused by the mosquito-borne nematodes *Wuchereria bancrofti* and *Brugia* species. More than 120 million people have LF, mainly in Southern Asia, sub-Saharan Africa, Oceania, and parts of Latin America. Adult worms reside in lymphatics and release microfilariae, which circulate nocturnally in the blood. These parasites harbor rickettsia-like *Wolbachia* endosymbionts, which female worms require to reproduce. Most patients have asymptomatic eosinophilia, but fever, adenolymph-
ginitis, lymphedema, hydrocele, or elephantiasis can occur. Some patients develop tropical pulmonary eosinophilia, with nocturnal asthma, cough, fever, weight loss, and high-grade eosinophilia.

Parasitic patients should receive DEC. A 1-day course appears to be as effective as the traditional 12-day regimen (Table 2). Antiparasitic treatment in patients with lymphedema or elephantiasis who are not actively infected is controversial. Patients with tropical pulmonary eosinophilia should receive a 2- to 3-week course of DEC. Adverse effects include nausea, fever, asthma-like symptoms, and arthralgias. Therapy for all filarial infections may be associated with allergic-like reactions resulting from degenerating filariae and Wolbachia, for which anti-histamines and corticosteroids may be useful. Diethylcarbamazine kills microfilariae but has only modest activity against adult worms. It should not be given to persons from areas coendemic for onchocerciasis or Loa loa unless these infections have been excluded. Alternatives for LF include ivermectin and albendazole. Prolonged courses of doxycycline (which kills and sterilizes adult worms as a result of anti-Wolbachia activity) may have a role.

Onchocerciasis, also known as river blindness, is caused by Onchocerca volvulus. Transmitted by Simulium blackflies, onchocerciasis is found in equatorial Africa and limited foci in Latin America and the Arabian Peninsula. Infection can cause dermatitis, subcutaneous nodules, keratitis, chorioretinitis, and blindness. Ivermectin is the treatment of choice (Table 2), although it kills only microfilariae, not adult worms. Ivermectin must be used with caution if coinfected with L. loa is possible. The adverse effects of ivermectin include fever, rash, dizziness, pruritis, myalgias, arthralgias, and lymphadenopathy, mostly due to dying filariae and Wolbachia. Suramin is active against adult worms, but toxicity precludes use in most cases. Moxidectin, a drug in development that is closely related to ivermectin but with higher potency, is also active against onchocerciasis. Prolonged doxycycline therapy may have a role because of its anti-Wolbachia activity. Diethylcarbamazine should not be administered to persons infected with onchocerciasis because blindness can result from the subsequent ocular inflammatory response.

Loaiasis is caused by L. loa, a helminth that is transmitted by Chrysops flies and is endemic to Central and West Africa. Adult worms migrate in subcutaneous tissues, and microfilariae circulate diurnally in the blood. L. loa does not harbor Wolbachia. Most infected persons have asymptomatic eosinophilia; some have urticaria, Calabar swellings (migratory, subcutaneous, angioedematous lesions), and visible “eye worms” migrating across the conjunctivae. Hematruia, proteinuria, and encephalitis (usually precipitated by treatment) also occur. Diethylcarbamazine is effective against loaiasis, although multiple courses may be necessary (Table 2). Treatment can cause pruritis, arthralgias, Calabar swellings, fever, eye worms, diarrhea, and renal failure. Patients with detectable microfilaremia (particularly >2500 microfilariae/mL) are at risk of treatment-associated encephalopathy, which may be ameliorated by pretreatment apheresis. Ivermectin is active against L. loa, but albendazole (which acts more slowly) is associated with a lower risk of encephalopathy than DEC or ivermectin.

Other Tissue Nematodes

Cutaneous Larva Migrans. Migration of dog and cat hookworms (eg, Ancylostoma braziliense) in the dermis can cause a serpiginous rash termed cutaneous larva migrans. The rash occurs after skin contact with infested soil and is usually seen on the lower extremities. Cutaneous larva migrans can be associated with eosinophilia or pulmonary infiltrates but is self-limited. Albendazole or ivermectin may hasten resolution (Table 2).

Angiostrongylus cantonensis. Human infection with A. cantonensis occur after ingesting snails, slugs, or leafy vegetables containing snails, slugs or slime trails with larvae. Endemic primarily to Asia and Oceania, infection can cause a prolonged (but usually self-limited) eosinophilic meningitis. Although antiparasitic therapy is controversial, albendazole plus corticosteroids is often used (Table 2).

Baylisascaris procyonis. B. procyonis (ie, raccoon roundworm) can rarely cause a form of VLM. Human infections result from contact with soil contaminated with raccoon feces. Severe meningoencephalitis can occur, usually in children. Treatment is not well defined, but albendazole plus corticosteroids has been used successfully (Table 2).

Gnathostoma spinigerum. G. spinigerum, which is acquired by eating undercooked freshwater fish, chicken, or pork, is the most common cause of gnathostomiasis. Although it is endemic primarily to Southeast Asia, infections also occur in Latin America and elsewhere. Symptoms include eosinophilia, migratory subcutaneous swellings, and (rarely) fulminant meningoencephalitis. Treatment is with albendazole or ivermectin (Table 2).

Capillaria philippinensis. C. philippinensis is the most common cause of capillariasis, which results from eating infected freshwater fish. Endemic primarily to Southeast Asia and the Middle East, the parasite inhabits the small bowel, causing diarrhea, malabsorption, and (uncommonly) fever and eosinophilia. As with Strongyloides, these helminths can multiply in humans, sometimes causing overwhelming infection. Mebendazole or albendazole can be life-saving (Table 2).
CONCLUSION

A wide array of parasites infect humans, causing some of the most prevalent infectious diseases globally. Recent advances in the treatment of malaria, leishmaniasis, and Chagas disease have brought needed improvements to the management of these diseases. Helminth infections are managed with a smaller pharmaceutical armamentarium than protozoal infections, but good treatment options are now available for many trematode, intestinal cestode, and intestinal nematode infections. Despite a relatively narrow therapeutic pipeline for new antiparasitic drugs, there have been significant improvements in the treatment of these widespread infections in the past 2 decades.

REFERENCES

Antiparasitic Therapy

The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are now a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
Antimicrobial prophylaxis in Adults

Mark J. Enzler, MD; Elie Berbari, MD; and Douglas R. Osmon, MD, MPH

On completion of this article, readers should be able to: (1) identify common surgical and nonsurgical indications for the use of antimicrobial prophylaxis in adults, (2) formulate selected surgical and nonsurgical antimicrobial prophylaxis regimens for adults, and (3) summarize the arguments for and against the use of antimicrobial prophylaxis in adults.

Antimicrobial prophylaxis is commonly used by clinicians for the prevention of numerous infectious diseases, including herpes simplex infection, rheumatic fever, recurrent cellulitis, meningococcal disease, recurrent uncomplicated urinary tract infections in women, spontaneous bacterial peritonitis in patients with cirrhosis, influenza, infective endocarditis, pertussis, and acute necrotizing pancreatitis, as well as infections associated with open fractures, recent prosthetic joint placement, and bite wounds. Perioperative antimicrobial prophylaxis is recommended for various surgical procedures to prevent surgical site infections. Optimal antimicrobial agents for prophylaxis should be bactericidal, nontoxic, inexpensive, and active against the typical pathogens that can cause surgical site infection postoperatively. To maximize its effectiveness, intravenous perioperative prophylaxis should be administered within 30 to 60 minutes before the surgical incision. Antimicrobial prophylaxis should be of short duration to decrease toxicity and antimicrobial resistance and to reduce cost.


AAOS = American Association of Orthopedic Surgeons; ADA = American Dental Association; ANP = acute necrotizing pancreatitis; AP = antimicrobial prophylaxis; AUA = American Urological Association; CP = chemoprophylaxis; FDA = US Food and Drug Administration; HIV = human immunodeficiency virus; IDSA = Infectious Diseases Society of America; IE = infective endocarditis; IS = Information Statement; MRSA = methicillin-resistant Staphylococcus aureus; PJI = prosthesis joint infection; PJJ = prosthetic joint replacement; RF = rheumatic fever; SBP = spontaneous bacterial peritonitis; SCIP = Surgical Care Improvement Project; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed; UGI = upper gastrointestinal; UTI = urinary tract infection

Antimicrobial prophylaxis (AP) can be used effectively to prevent infection, but its use should be limited to specific, well-accepted indications to avoid excess cost, toxicity, and antimicrobial resistance. Antimicrobial prophylaxis may be considered primary (prevention of an initial infection) or secondary (prevention of the recurrence or reactivation of an infection), or it may also be administered to prevent infection by eliminating a colonizing organism. This article reviews widely accepted indications for AP in nonsurgical and surgical patients and is an update of a previously published review of this topic.1 In selected situations, vaccination may be recommended as part of a prophylaxis regimen. This article is meant to be a point-of-care overview topic for the busy clinician. Many of these recommendations are based on expert opinion rather than on prospective clinical trials. Most of the recommended antimicrobial agents are not approved by the US Food and Drug Administration (FDA) for prophylaxis. Current full prescribing information available in the package insert of each drug should be consulted before prescribing any product. Detailed information on individual topics can be found in the cited references.

The potential risks and benefits of AP should be discussed in detail with the patient. Potential risks include allergic reactions that may be severe or life-threatening as well as Clostridium difficile colitis with the use of antimicrobial agents.2 Patients taking fluoroquinolones should be warned of the risk of developing tendinitis, including Achilles tendon rupture.3 For all antibiotic dosing recommended in this article, normal hepatic and renal function are assumed.

NONSURGICAL AP

Rheumatic Fever

Rheumatic fever (RF), which is associated with tonsillopharyngitis caused by the group A β-hemolytic streptococci, may result in carditis with or without valvulopathy. Primary prevention of RF involves prompt and appropriate antibiotic treatment of group A β-hemolytic streptococcal pharyngitis with a penicillin (drug of choice) or alternative antibiotic.4 Continuous secondary AP prevents recurrent episodes of RF, which could otherwise lead to worsening of the severity of rheumatic heart disease that developed after the initial attack or the development of rheumatic carditis in those who did not develop carditis with the initial RF episode. Guidelines for secondary AP of RF have recently been updated (recommendations for AP regimens are summarized in Table 1).4 Penicillins are the antibiotics of choice for secondary prophylaxis for RF, and intramus-

From the Division of Infectious Diseases, Mayo Clinic, Rochester, MN.

Address correspondence to Mark J. Enzler, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (enzler.mark@mayo.edu).

Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

© 2011 Mayo Foundation for Medical Education and Research

For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
cular penicillin is superior to oral penicillins. Macrolides (eg, erythromycin, clarithromycin, azithromycin) should be reserved for patients who are allergic to both penicillin and sulfonamide antibiotics. The duration of secondary prophylaxis for RF is reviewed in detail elsewhere and is summarized in Table 2. Physicians should tailor the duration of secondary prophylaxis to the individual patient, taking into account the patient’s risk factors for RF recurrence, such as exposure to young children and the presence of carditis with or without underlying valvular disease. Antimicrobial prophylaxis should be considered for at least 10 years or until age 40 years (whichever is longer) for patients with carditis with persistent valvular disease. Prophylaxis should be continued in patients even after prosthetic valve replacement surgery. Antibiotic suppression for the prevention of RF is not adequate for infective endocarditis (IE) prophylaxis before dental procedures.

**Recurrent Cellulitis**

Patients with lymphedema or severe venous insufficiency of their extremities are at increased risk of recurring β-streptococcal cellulitis. Common scenarios for recurrent cellulitis of the lower extremity include patients with venous insufficiency after saphenous vein graft harvesting or pelvic lymphadenectomy. Recurrent cellulitis has been observed in the upper extremity after lymphadenectomy performed at the time of mastectomy for breast cancer. Antimicrobial prophylaxis may be a useful addition to the control of lymphedema with local measures and treatment of concurrent tinea pedis in the prevention of recurrent cellulitis. However, this recommendation is based on small, uncontrolled studies. Typically, more than 2 or 3 episodes per year should occur before AP is initiated. Recommended prophylactic antibiotics for recurrent cellulitis are summarized in Table 1. Oral penicillin V (phenoxymethylpenicillin) is a reasonable first choice, but optimal dosing of this agent is not well established. Although monthly administration of 1.2 MU of intramuscular benzathine penicillin is recommended as an alternative to oral penicillin V, this dosing regimen was shown to be effective only in those patients not at risk of cellulitis recurrence. Some experts recommend intramuscular administration of benzathine penicillin every 2 to 3 weeks for individuals who break through once-monthly intramuscular benzathine penicillin regimens.

Recurrent pyogenic skin infections caused by *Staphylococcus aureus*, including methicillin-resistant *S aureus* (MRSA), may be managed by encouraging good personal hygiene, the avoidance of shared personal items, and the diligent cleaning of high-touch environmental surfaces. If a patient is found to be colonized by *S aureus*, nasal decolonization with mupirocin for 5 to 10 days with or without a topical body decolonization with a skin antiseptic solution such as 4% chlorhexidine for 5 to 14 days may be reasonable in an attempt to decolonize the patient. Antimicrobial prophylaxis options are listed in Table 1 for recurrent methicillin-susceptible *S aureus* skin infections. Long-term oral AP of recurrent MRSA skin infections is not well studied, and formal recommendations for this situation were not included in recently published MRSA treatment guidelines.

**Meningococcal Disease**

Antimicrobial prophylaxis for meningococcal diseases should be offered to close contacts of sporadic cases of *Neisseria meningitidis* infection (Table 1). Close contacts include household members, day care center staff, and any person directly exposed to an infected person’s oral secretions (for example, through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management). Public health authorities may recommend population-based prophylaxis in the event of an outbreak. Prophylaxis should be offered as soon as possible. Close contacts should be offered meningococcal vaccination if the outbreak strain is one that is contained in the currently available meningococcal tetravalent conjugate vaccine.

**Asplenic Patients**

Penicillin prophylaxis is recommended in children during the first few years after splenectomy to prevent overwhelming *Streptococcus pneumoniae* sepsis. French and American authorities have advocated this form of prophylaxis (eg, 250 mg of oral penicillin V or amoxicillin twice daily) in adults for 1 to 2 years after splenectomy, although data showing the efficacy of this approach are lacking. *Haemophilus influenzae* type B, meningococcal, and pneumococcal vaccinations should be current in asplenic adults.

**Urinary Tract Infection**

Several prophylactic antibiotic options are available to non-pregnant women with recurrent (≥3 per year), uncomplicated urinary tract infections (UTIs) (Table 1). Continuous low-dose AP and patient-initiated treatment after onset of symptoms are both effective. During AP, monthly urine cultures should be performed to monitor for bacteriuria and the development of antibiotic resistance. Structural abnormality of the urinary tract, renal involvement with infection, or chronic prostatitis (in men) should be considered in the setting of recurrent UTIs. Methenamine hippurate (dosage, 1 g twice daily) has been approved by the FDA for UTI prophylaxis. A recent Cochrane review concluded that methenamine hippurate may be effective for short-term prophylaxis (≤1 week) in patients without known renal tract abnormalities. The typical duration of an initial trial of continuous AP is 6 months. Patients with prolonged exposure to nitrofurantoin should be counseled...
TABLE 1. Selected Nonsurgical Antimicrobial Prophylaxis Regimens for Adults\(^{a,b}\)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Antimicrobial agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever(^{4})</td>
<td>Primary prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Appropriately treated group A streptococcal pharyngitis</td>
<td>Preferred</td>
<td></td>
</tr>
<tr>
<td>Penicillin G benzathine</td>
<td>1.2 million U IM every 4 wk (every 3 wk for patients at high risk(^{4}))</td>
<td></td>
</tr>
<tr>
<td>Secondary prophylaxis(^{6})</td>
<td>Preferred oral agents</td>
<td></td>
</tr>
<tr>
<td>Penicillin V (preferred)</td>
<td>250 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>or Sulfadiazine</td>
<td>1 g orally daily</td>
<td></td>
</tr>
<tr>
<td>or Sulfasoxazole</td>
<td>1 g orally daily</td>
<td></td>
</tr>
<tr>
<td>Alternative oral agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>250 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>or Clarithromycin(^{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Azithromycin(^{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent cellulitis in conjunction with upper or lower extremity lymphedema or erysipelas(^{5,7})</td>
<td>Penicillin V</td>
<td>250-1000 mg orally twice daily(^{f})</td>
</tr>
<tr>
<td>or Penicillin G benzathine</td>
<td>1.2 million U IM every 2 to 4 wk</td>
<td></td>
</tr>
<tr>
<td>Penicillin allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>250-500 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>Recurrent pyogenic or staphylococcal soft tissue infection(^{8,10})</td>
<td>Etiology unknown or methicillin-susceptible Staphylococcus aureus suspected</td>
<td></td>
</tr>
<tr>
<td>or Penicillin G benzathine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G benzathine</td>
<td>1.2 million U IM every 4 wk (every 3 wk for patients at high risk(^{4}))</td>
<td></td>
</tr>
<tr>
<td>Travelers' diarrhea(^{12})</td>
<td>Bismuth subsalicylate</td>
<td>2 tablets (262 mg/tablet) chewed 4 times daily</td>
</tr>
<tr>
<td>or Ciprofloxacin(^{b})</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td>or Ceftiraxone</td>
<td>500 mg</td>
<td></td>
</tr>
<tr>
<td>Meningococcal disease (close contacts of sporadic cases)(^{11})</td>
<td>Rifampin</td>
<td>600 mg usually 12 h for 2 d</td>
</tr>
<tr>
<td>or Ciprofloxacin(^{b})</td>
<td>500 mg orally for 1 dose (adults)</td>
<td></td>
</tr>
<tr>
<td>or Ceftiraxone</td>
<td>250 mg IM once</td>
<td></td>
</tr>
<tr>
<td>Travelers' diarrhea(^{12})</td>
<td>Daily oral dose(^{5})</td>
<td></td>
</tr>
<tr>
<td>Recurrent uncomplicated urinary tract infections in nonpregnant women(^{11,13})</td>
<td>Continuous prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Postcoital regimens</td>
<td>Trimepsoprim-sulfamethoxazole</td>
<td>Daily oral dose (at bedtime)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>½ SS tablet (or 3 times/wk)</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>125 mg</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50-100 mg</td>
<td></td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis(^{16})</td>
<td>125-250 mg</td>
<td></td>
</tr>
<tr>
<td>Preferred (if taking a quinolone for long-term SBP prophylaxis)</td>
<td>Single oral dose</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>½-1 SS tablet</td>
<td></td>
</tr>
<tr>
<td>or Norfloxacin</td>
<td>125-250 mg</td>
<td></td>
</tr>
<tr>
<td>or Ciprofloxacin</td>
<td>50-100 mg</td>
<td></td>
</tr>
<tr>
<td>or Ofloxacin</td>
<td>125 mg</td>
<td></td>
</tr>
<tr>
<td>or Norfloxacin</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>Intermittent self-treatment</td>
<td>Oral dose</td>
<td></td>
</tr>
<tr>
<td>Trimepsoprim-sulfamethoxazole</td>
<td>1 DS tablet daily</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>250 mg twice daily for 3 d</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>200 mg twice daily for 3 d</td>
<td></td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis(^{16})</td>
<td>1 DS tablet daily</td>
<td></td>
</tr>
<tr>
<td>or Norfloxacin</td>
<td>250 mg orally twice daily for 7 d</td>
<td></td>
</tr>
<tr>
<td>or Ciprofloxacin</td>
<td>400 mg orally twice daily for 7 d</td>
<td></td>
</tr>
<tr>
<td>or Ifloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(continued on next page)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
about the rare but serious complications associated with this agent, including hepatitis, pulmonary reactions, and neuropathy. Cranberries contain 2 substances that prevent fimbrinated *Escherichia coli* from adhering to uroepithelial cells. Clinical studies have shown that cranberry juice and cranberry products may reduce the recurrence of UTIs in women. A recent Cochrane review noted limitations in these studies, including variable cranberry products and dosing used in the various studies, as well as high study participant dropout rates. Other patients who may be considered for prophylaxis of frequent UTIs include pregnant women, persons with spinal cord injuries, persons with immunocompromised or nonadherent to treatment.

---

**TABLE 1. Continued**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Antimicrobial agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk dog, cat, or human bite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial IV antibiotics</td>
<td>Ampicillin-sulbactam 3 g IV every 6 h</td>
<td></td>
</tr>
<tr>
<td>or Piperacillin-tazobactam 3.375 g IV every 6 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Ertapenem 1 g IV once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Metronidazole 500 mg orally or IV every 8 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus ceftriaxone, 1 g IV every 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levofloxacin, 500 or 750 mg IV once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or ciprofloxacin 400 mg IV every 12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antibiotic for 3-5 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>Amoxicillin-clavulanate 875 mg orally twice daily for 3-5 d</td>
<td></td>
</tr>
<tr>
<td>Penicillin allergy</td>
<td>Moxifloxacin monotherapy 400 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>or Clindamycin 300-450 mg orally 4 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or levofloxacin 500 mg orally daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary agents</td>
<td>Azithromycin 500 mg orally day 1, then 250 mg per day on days 2-5</td>
<td></td>
</tr>
<tr>
<td>or Clarithromycin 500 mg orally twice daily for 7 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Erythromycin 2000 mg orally in 4 divided doses for 14 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative agent</td>
<td>Trimethoprim-sulfamethoxazole, DS 1 table every 12 h for 14 d</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A or B</td>
<td>Oseltamivir 75 mg orally daily</td>
<td></td>
</tr>
<tr>
<td>or Zanamivir 5 mg/blister for inhalation: 2 inhalations (10 mg) daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimantadines (amantadine and rimantadine) are no longer recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

4 DS = double-strength; GI = gastrointestinal; IM = intramuscularly; IV = intravenously; MRSA = methicillin-resistant *Staphylococcus aureus*; SBP = spontaneous bacterial peritonitis; SS = single-strength; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed.

5 Antibiotic doses assume normal renal and hepatic function; the choice of therapy should be guided by the patient’s history of allergy or intolerance to a specific agent.

6 See Table 2 and text for duration of prophylaxis.

7 Administration of benzathine penicillin every 3 wk is recommended in the United States only for those who have recurrent acute rheumatic fever despite adherence to a once-monthly regimen.

8 Dosing of these agents was not specified in the recently published guidelines. However, a clarithromycin dose of 250 mg twice daily was proposed by us one of the authors of those guidelines, Stanford T. Schulman, MD (written communication, January 5, 2011).

9 There is a wide range of recommended penicillin V dosing for this purpose; 250-500 mg twice daily would be a reasonable starting point.

10 Duration of prophylaxis for travelers’ diarrhea should be limited to 2-3 wk and should be stopped 2 d after returning from travel.

11 Other fluoroquinolones are likely to be effective but have not been studied for use in prophylaxis for travelers’ diarrhea.

12 Rifaximin prophylaxis has only been studied in travelers to Mexico.

13 Primary prophylaxis for SBP is indicated in patients with ascitic fluid protein ≥1.5 g/dL and at least 1 of the following criteria: serum creatinine level, ≥1.2 mg/dL (to convert to μmol/L, multiply by 88.4); blood urea nitrogen level, ≥22 mg/dL (to convert to mmol/L, multiply by 0.357); serum sodium level, ≥130 mEq/L (to convert to mmol/L, multiply by 1); or Child-Pugh score, ≥9 points with bilirubin level ≥3 mg/dL (to convert to μmol/L, multiply by 17.104).

14 Consider IV antibiotics for animal bites as initial dose in the emergency department and with hospitalized patients. Consider hospitalization and IV antibiotics as an initial therapy for human bites and in patients with fever, sepsis, spread of cellulitis, significant edema or crush injury, or loss of function and in those who are immunocompromised or nonadherent to treatment.

15 Use oral antibiotics if treatment occurs soon after a dog or cat bite and only mild to moderate signs of infection are present.

16 Avoid penicillins in patients with a history of severe penicillin allergy.

17 Vaccinate with Tdap if indicated.

18 Choice of therapy should be dictated by resistance patterns of the circulating influenza virus; see text for discussion of treatment duration.

19 Common adverse effects include nausea, vomiting, and headaches. Taking oseltamivir with food may reduce the likelihood of nausea and vomiting.

20 A clarithromycin dose of 250 mg twice daily was proposed by us one of the authors of those guidelines, Stanford T. Schulman, MD (written communication, January 5, 2011).

21 Rifaximin prophylaxis has only been studied in travelers to Mexico.

22 Other fluoroquinolones are likely to be effective but have not been studied for use in prophylaxis for travelers’ diarrhea.

23 Rifaximin prophylaxis has only been studied in travelers to Mexico.

24 Consider IV antibiotics for animal bites as initial dose in the emergency department and with hospitalized patients. Consider hospitalization and IV antibiotics as an initial therapy for human bites and in patients with fever, sepsis, spread of cellulitis, significant edema or crush injury, or loss of function and in those who are immunocompromised or nonadherent to treatment.

25 Use oral antibiotics if treatment occurs soon after a dog or cat bite and only mild to moderate signs of infection are present.

26 Avoid penicillins in patients with a history of severe penicillin allergy.

27 Vaccinate with Tdap if indicated.

28 Choice of therapy should be dictated by resistance patterns of the circulating influenza virus; see text for discussion of treatment duration.

29 Common adverse effects include nausea, vomiting, and headaches. Taking oseltamivir with food may reduce the likelihood of nausea and vomiting.

30 A clarithromycin dose of 250 mg twice daily was proposed by us one of the authors of those guidelines, Stanford T. Schulman, MD (written communication, January 5, 2011).

31 Rifaximin prophylaxis has only been studied in travelers to Mexico.

32 Other fluoroquinolones are likely to be effective but have not been studied for use in prophylaxis for travelers’ diarrhea.

33 Consider IV antibiotics for animal bites as initial dose in the emergency department and with hospitalized patients. Consider hospitalization and IV antibiotics as an initial therapy for human bites and in patients with fever, sepsis, spread of cellulitis, significant edema or crush injury, or loss of function and in those who are immunocompromised or nonadherent to treatment.

34 Use oral antibiotics if treatment occurs soon after a dog or cat bite and only mild to moderate signs of infection are present.

35 Avoid penicillins in patients with a history of severe penicillin allergy.

36 Vaccinate with Tdap if indicated.

37 Choice of therapy should be dictated by resistance patterns of the circulating influenza virus; see text for discussion of treatment duration.

38 Common adverse effects include nausea, vomiting, and headaches. Taking oseltamivir with food may reduce the likelihood of nausea and vomiting.

39 A clarithromycin dose of 250 mg twice daily was proposed by us one of the authors of those guidelines, Stanford T. Schulman, MD (written communication, January 5, 2011).

40 Rifaximin prophylaxis has only been studied in travelers to Mexico.

41 Other fluoroquinolones are likely to be effective but have not been studied for use in prophylaxis for travelers’ diarrhea.

42 Consider IV antibiotics for animal bites as initial dose in the emergency department and with hospitalized patients. Consider hospitalization and IV antibiotics as an initial therapy for human bites and in patients with fever, sepsis, spread of cellulitis, significant edema or crush injury, or loss of function and in those who are immunocompromised or nonadherent to treatment.

43 Use oral antibiotics if treatment occurs soon after a dog or cat bite and only mild to moderate signs of infection are present.

44 Avoid penicillins in patients with a history of severe penicillin allergy.

45 Vaccinate with Tdap if indicated.

46 Choice of therapy should be dictated by resistance patterns of the circulating influenza virus; see text for discussion of treatment duration.

47 Common adverse effects include nausea, vomiting, and headaches. Taking oseltamivir with food may reduce the likelihood of nausea and vomiting.

48 A clarithromycin dose of 250 mg twice daily was proposed by us one of the authors of those guidelines, Stanford T. Schulman, MD (written communication, January 5, 2011).

49 Rifaximin prophylaxis has only been studied in travelers to Mexico.

50 Other fluoroquinolones are likely to be effective but have not been studied for use in prophylaxis for travelers’ diarrhea.
neurogenic bladders, renal transplant recipients, and men with chronic bacterial prostatitis. Postcoital regimens may be appropriate for female patients with UTIs temporally related to sexual intercourse. Patients who use postcoital regimens should be informed that only 1 dose per day is recommended, regardless of the frequency of intercourse. Postcoital AP in pregnancy can be managed with a single dose of either cephalexin (250 mg) or nitrofurantoin (50 mg). Tetracyclines and fluoroquinolones should be avoided during pregnancy, and sulfonamides should be avoided during the last weeks of gestation to minimize the risk of hyperbilirubinemia and kernicterus in the newborn. Topical vaginal estrogen therapy has been shown to reduce the risk of recurrent UTIs in postmenopausal women who are not receiving estrogen replacement therapy and who have no contraindications to estrogen therapy.

### Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) in patients with cirrhosis is associated with increased morbidity and mortality. Aerobic gram-negative organisms and streptococci are the most frequent causes of this infection. In a recent Cochrane review of 12 treatment trials, empirical oral or parenteral antimicrobial treatment of patients with cirrhosis and upper gastrointestinal (UGI) bleeding reduced the incidence of bacterial infections and was associated with shortened hospital stays and reduced rates of overall mortality, mortality from bacterial infections, and rebleeding. No one antibiotic regimen or route of administration was found to be superior. On the basis of these data, 7 days of empirical antibiotics are recommended for patients with ascites and UGI bleeding (Table 1). In prospective randomized clinical trials, primary prophylaxis in high-risk patients and secondary prophylaxis after an initial episode of SBP have been shown to be effective in preventing SBP. A recent Cochrane review of 7 trials of empirical AP to prevent SBP in cirrhotic patients with ascites without UGI bleeding revealed a pooled reduction in SBP and mortality but noted issues with trial methodology and findings suggestive of systematic bias in publication and design. A 1998 analysis concluded that prophylaxis in high-risk patients (serum bilirubin level >2.5 mg/dL [to convert to μmol/L, multiply by 17.104]; asitic fluid protein level, <1 g/dL) is cost-effective. The American Association for the Study of Liver Diseases has published guidelines that recommend long-term daily AP for patients with previous SBP and for primary prophylaxis in those with an ascitic fluid protein level of less than 1.5 g/dL and at least 1 of the following criteria: a serum creatinine level of 1.2 mg/dL or higher (to convert to mmol/L, multiply by 88.4), a blood urea nitrogen level of 25 mg/dL or higher (to convert to mmol/L, multiply by 0.357), a serum sodium level of 130 mEq/L or less (to convert to mmol/L, multiply by 1), or a Child-Pugh score of 9 points or higher with a bilirubin level of 3 mg/dL or higher (Table 1). Before initiation of AP, SBP should be ruled out in all patients with ascites at hospital admission and in cirrhotic patients with ascites with signs, symptoms, or laboratory abnormalities suggestive of infection.

### Acute Necrotizing Pancreatitis

Severe pancreatitis with necrosis is associated with an overall mortality rate of 17% and a mortality rate of 25% to 30% with infected necrosis. Debate is ongoing as to whether AP in the setting of acute necrotizing pancreatitis (ANP) leads to improved outcomes (some consider the use of antibiotics in this setting preemptive). A recent Cochrane database review of 7 randomized studies concluded that patients randomized to receive AP for ANP had no statistically significant reduction in infections. Recent practice guidelines published by the American College of Gastroenterology do not recommend AP for ANP. If AP is initiated, a broad-spectrum β-lactam such as imipenem-cilastatin is often recommended and should be limited to computed tomography–documented pancreatic necrosis involving 30% or more of the pancreas for 14 days or less.

### Bite Wound Infection

Five percent of dog bites and 30% of cat bites become secondarily infected because these wounds are highly contaminated by microorganisms present in the oral cavity of these animals. These infections can lead to septic arthritis, tenosynovitis, severe soft tissue infection, or sepsis. The microbiology of dog and cat bite infections is typically polymicrobial and includes Pasteurella species as the most common isolate, followed by staphylococci, streptococci, and anaerobes. Although AP for animal bites remains controversial, a meta-analysis of 8 clinical trials by Cummings found that AP significantly protects against subsequent wound infection. Antimicrobial prophylaxis of a...
contaminated wound may be more accurately considered expectant therapy to prevent the development of a wound infection in a contaminated but not yet infected wound. No clinical trials have shown superiority of one antibiotic regimen over another; choices should be based on the likely microbiology of dog and cat bite infections. Antimicrobial prophylaxis for bite wounds has recently been reviewed and should be offered to all patients who are thought to have an increased risk of infection (Table 1). High-risk situations include, but are not limited to, bites to body areas where deeper structures (tendons and bones) can become easily injured, bites to the hand(s) or close to a bone or joint, crush injuries, puncture wounds (difficult to clean), bites in which treatment is delayed more than 8 to 10 hours, wounds requiring closure, bites in compromised persons (diabetic patients, persons with no spleen, immunocompromised patients), bites in persons with indwelling prosthetic devices, and all cat bites. Consideration for hospitalization and intravenous antibiotics may be reasonable for patients in the setting of fever, sepsis, spread of cellulitis, significant edema or crush injury, loss of function, compromised immunity, or patient nonadherence to treatment. All dog and cat bites should be appropriately irrigated and debrided, and rabies prophylaxis should be administered, if indicated. Delayed primary closure of heavily contaminated wounds should be considered to decrease the risk of wound infection.

Human bite wounds, including clenched fist injuries, are considered to be at high-risk of infection with organisms such as Streptococcus anginosus, S aureus, Eikenella corrodens, and anaerobes. Recommended AP is similar to that for animal bite wounds (Table 1). Patients who have sustained human bites should be assessed for human immunodeficiency virus (HIV) and hepatitis B infection risk, and prophylaxis should be offered as indicated according to published guidelines. Tetanus immune globulin and tetanus toxoid should be administered to patients who have not been immunized or tetanus toxoid alone to any patient who has not received a tetanus booster within the past 5 years.

**Pertussis**

Pertussis (whooping cough), an upper respiratory tract infection caused by *Bordetella pertussis*, is associated with prolonged bouts of coughing that may last 1 to 6 weeks. Numerous pertussis outbreaks have occurred in the United States during the past 6 years among adolescents and adults as immunity from childhood vaccination has waned. Because pertussis is spread by aerosolized respiratory droplets, it is recommended that all household and other close contacts of infected patients who did not use respiratory precautions while in contact with an infected patient receive AP, regardless of age or immunization status (Table 1).

The first tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap) licensed for adults was approved by the FDA in 2005 (ADACEL; Sanofi Pasteur; Swiftwater, PA [US Headquarters]; Lyon, France [Global Headquarters]) as a single-dose booster vaccine for persons aged 11 to 64 years to provide protection against tetanus, diphtheria, and pertussis. Tdap was initially recommended to replace the next adult booster dose of tetanus- and diphtheria-toxoid vaccines in patients whose last tetanus booster was 10 years or more earlier. The interval between the most recent tetanus vaccination and Tdap for persons with contact with infants, child care providers, or health care professionals with direct patient contact could be as short as 2 years or less. Given the poor adult pertussis vaccine coverage (5.9% in 2008), and in the setting of increasing numbers of pertussis cases in the United States (16,858 cases in 2009, including 14 infant deaths), the Pertussis Vaccine Working Group of the Advisory Committee on Immunization Practices recommends the administration of a single Tdap (either ADACEL or BOOSTRIX [GlaxoSmithKline Biologicals; Morrisville, NC]), when indicated, for any adult, at any interval since the previous tetanus-diphtheria vaccination. A single Tdap should be considered for adults 65 years or older who have or anticipate having close contact with an infant younger than 12 months as well as for children aged 7 through 10 years who are not fully vaccinated against pertussis. Tdap is not licensed for revaccination. A provisional recommendation from the Advisory Committee on Immunization Practices (February 23, 2011) states that the data on the need for postexposure AP for Tdap-vaccinated health care professionals are inconclusive. In view of this, Tdap-vaccinated health care professionals may still be at risk of acquiring pertussis and should be considered for chemoprophylaxis (CP) after a significant pertussis exposure, particularly if they are likely to be exposed to a patient at risk of severe pertussis, such as hospitalized neonates and pregnant women.

**INFECTIVE ENDOCARDITIS**

Infective endocarditis is a relatively rare endocardial infection that can lead to catastrophic complications and death. Guidelines for the prevention of IE have been published by the American Heart Association for more than 50 years. The first 9 guidelines (1955-1997) were based on low-level evidence; more recently, guidelines have been stratified according to the lifetime risk of IE. The recommendations of the most recent (2007) guidelines reflected a new reticence about using AP for IE based on the following premises: (1) cumulative bacteremia risk is much greater with daily activities than dental procedures; (2) antibiotics do not eliminate bacteremia or clearly reduce IE risk; (3) there are no prospective, placebo-controlled AP trials; and (4) even if
Although many respiratory tract procedures reportedly cause bacteremia involving a wide variety of microorganisms, no published data conclusively demonstrate a link between these procedures and IE. Antimicrobial prophylaxis (for regimens, see Table 5) is thought to be reasonable for patients at highest risk of complications from IE (Table 3) who undergo invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa (eg, tonsillectomy, adenoidectomy). Patients at highest risk of complications from IE who undergo an invasive respiratory tract procedure to treat an established infection, such as drainage of an abscess or empyema, should receive an antibiotic that is active against the viridans group streptococci. If an infection is known or suspected to be caused by *S. aureus*, the antibiotic regimen should contain an antistaphylococcal penicillin or a cephalosporin for patients who are unable to tolerate a penicillin. Vancomycin should be used in those in whom an infection is known or suspected to be caused by a methicillin-resistant strain of *S. aureus* or in those who have a history of a severe reaction to β-lactam antibiotics.61

**Prosthetic Joint Infections**

By 2030, an estimated 4 million total knee or hip arthroplasties will be performed annually in the United States.62 Prosthetic joint infections (PJIs), which are rare but serious complications of prosthetic joint replacements (PJRs), occur in 0.3% to 1.0% of patients after primary total hip replacement and 1.0% to 2.0% of patients after primary total knee replacements, with the greatest risk occurring during the first 2 postoperative years (6.5, 3.2, and 1.4 infections per 1000 patient-years during the first year, second year, and after the second year, respectively).63,64 These infections may be associated with devastating financial and personal consequences. Most PJIs are acquired in the operating room as a result of colonization of the prosthesis at the time of implantation or airborne contamination of the wound.63 Infection of a prosthesis via hematogenous seeding is a less common cause of PJI. Among PJIs occurring via the hematogenous route, most are the result of *S. aureus* bacteremia, skin infections, or urosepsis.65-67 The development of a PJI due to hematogenous seeding after dental procedures is thought to be a rare event. According to a recent literature review, this occurred in 0.04% to 0.20% of reported PJR case series; many of these infections were seen in patients with dental disease.68 Pins, plates, and screws not within the synovial joint are not thought to be at increased risk of hematogenous seeding by microorganisms. No studies have shown that AP before dental procedures prevents PJI.69 A recently published prospective case-control study concluded that dental procedures were not risk factors for subsequent total hip or knee infection. Additionally, the use

### TABLE 3. Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis For Which Prophylaxis With Dental Procedures Is Reasonable

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reasonable Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic cardiac valve or prosthetic material used for cardiac valve repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
<td>Yes</td>
</tr>
<tr>
<td>Congenital heart disease (CHD)*</td>
<td>Yes</td>
</tr>
<tr>
<td>Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
<td>Yes</td>
</tr>
<tr>
<td>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure</td>
<td>Yes</td>
</tr>
<tr>
<td>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Except for the conditions listed above, antimicrobial prophylaxis is no longer recommended for any other form of CHD.

### TABLE 4. Dental Procedures for Which Endocarditis Prophylaxis Is Reasonable for Patients in Table 3

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Reasonable Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prostodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

From *Circulation*, with permission from the American Heart Association.
of AP before dental procedures did not decrease the risk of subsequent total hip or knee infection.70

Despite the lack of data supporting AP before dental procedures, many surveys of health care professionals have shown that a substantial number of them recommend AP before dental procedures in patients with a PJR.71,72 Antimicrobial prophylaxis for patients with a prosthetic joint undergoing a dental procedure or other invasive medical procedure has been controversial for decades.67,71,73-75 Consensus guidelines for this practice were initially published in 1997 and affirmed in 2003 by the American Dental Association (ADA) and the American Association of Orthopedic Surgeons (AAOS) on the basis of low-level evidence.69,76 It was proposed that AP be administered before dental procedures thought most likely to be associated with bacteremia for patients who were considered to be at highest risk of bacteremia-associated PJI. High-risk patients are thought to include all patients during the first 2 years after joint replacement, immunocompromised or immunosuppressed patients, patients with comorbid conditions (eg, diabetes, obesity, HIV infection, smoking), and patients with inflammatory arthropathies (eg, rheumatoid arthritis), systemic lupus erythematosus, medication- or radiation-induced immunosuppression, previous PJI, malnourishment, hemophilia, HIV infection, insulin-dependent (type 1) diabetes, megaprosthesis, or malignancy. More recently (February 2009), the Patient Safety Committee of the AAOS posted an Information Statement (IS) advising that “clinicians consider antibiotic prophylaxis for…all total joint replacement patients prior to any invasive procedure that may cause bacteremia.”77 The ADA no longer supports the 2003 AAOS/ADA Guidelines and the AAOS IS (Karen London, American Dental Association, written communication, March 28, 2011).77 Although specific dental procedures that may cause bacteremia are not listed in the AAOS IS, the ADA lists the dental procedures that may cause bacteremia in the AAOS/ADA 2003 guidelines.76,77 The antibiotics recommended in the AAOS IS to be administered to patients with PJR before dental procedures include 2 g of oral cephalexin, cephradine, or amoxicillin 1 hour before dental procedures. The AAOS IS makes no mention of parenteral antibiotic options or antibiotic alternatives for penicillin-allergic patients. The 2003 AAOS/ADA advisory statement recommended 1 g of intravenous cefazolin or ampicillin as parenteral antibiotic alternatives or 600 mg of clindamycin (intravenous or oral) for penicillin-allergic patients, to be administered 1 hour before the dental procedure; in our opinion, these remain valid antibiotic alternatives.76

A panel that included representatives from the ADA, AAOS, and IDSA was recently convened with the goal of producing an evidence-based antimicrobial guideline for patients with PJR before dental procedures (D.R.O. is a member of the working group). It is hoped that this will lead to a simpler consensus guideline for patients and health care professionals to the AAOS IS (Karen London, American Dental Association, written communication, March 28, 2011).77 Antimicrobial prophylaxis in patients undergoing invasive gastrointestinal procedures is not recommended by the American Society of Colon and Rectal Surgeons78 or the American Society for Gastrointestinal Endoscopy.79

### TABLE 5. Regimens for a Dental Procedure*

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen: single dose 30 to 60 min before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2 g</td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Ampicillin 2 g IM or IV 50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin—oral</td>
<td>Cefazolin or ceftriazone 1 g IM or IV 50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Cephalexin 2 g OR 50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Clindamycin 600 mg 20 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Azithromycin or clarithromycin 500 mg 15 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin—oral</td>
<td>Cefazolin or ceftriazone 1 g IM or IV 50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>and unable to take oral medication</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Clindamycin 600 mg IM or IV 20 mg/kg IM or IV</td>
<td></td>
</tr>
</tbody>
</table>

---

*IM = intramuscularly; IV = intravenously.

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

* Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Adapted from Circulation,61 with permission from the American Heart Association.
matrogenous PJIs in these patients, they should discuss with them the possibility of life-threatening adverse reactions (rare) and the more common drug toxicities. If used, antimicrobial agents should be chosen on the basis of the expected flora at the site of the procedure.

The American Urological Association (AUA) and the AAOS first published consensus- and expert opinion–based AP guidelines in 2003 for patients with total joint replacement who were undergoing urologic procedures.89 Antimicrobial prophylaxis is recommended for patients at increased risk of hematogenous PJIs who undergo urologic procedures associated with an increased risk of bacteremia. The details of these recommendations can be found in the 2007 AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis, which is available on the AUA Web site.80,81 The guidelines assume that the urine is sterile preoperatively. If bacteriuria is present, it should be treated with appropriate antibacterial agents before manipulation of the urinary tract.

TRAVELERS’ DIARRHEA
Antibacterial agents have been shown to decrease the risk of travelers’ diarrhea by up to 84%.82-84 Antimicrobial agents are not routinely recommended for the prevention of travelers’ diarrhea because antibiotic self-treatment is so rapidly effective. The traveler may be instructed to carry a supply of an antibiotic (often a 1- to 3-day course of a fluoroquinolone for travel to Central or South America or Africa or of azithromycin when traveling to Asia or the Indian subcontinent) to be taken on an as-needed basis.12 In certain circumstances (risk-averse travelers, athletes, persons taking antacids, or persons with diabetes, an elevated gastric pH, or inflammatory bowel disease), a daily oral antibiotic regimen may be considered on a short-term basis (ideally <2-3 weeks) to prevent travelers’ diarrhea. Fluoroquinolones may be less effective in areas with quinolone-resistant Campylobacter species infections (eg, India, Southeast Asia), so an agent such as azithromycin (250 mg once daily) may be considered, although this has not been studied. In a 14-day study among travelers to Mexico, rifaximin (200 mg 1-3 times daily) was 72% effective in preventing travelers’ diarrhea.21 Bismuth subsalicylate prophylaxis (Pepto-Bismol [Proctor & Gamble; Cincinnati, OH]: two 262-mg chewable tablets 4 times daily, with meals and once in the evening) is less effective (62%-65% effective) than antibiotics, is inconvenient to take, contains a salicylate (to be avoided if receiving anticoagulant therapy or high-dose salicylates), causes a black tongue, and may interfere with the absorption of medications such as doxycycline.12 Probiotics containing Lactobacillus GG or Saccharomyces boulardii are of limited efficacy (0%-60% effective) in the prevention of travelers’ diarrhea and generally are not recommended for this purpose.85,86

OPEN FRACTURES
Open fractures, particularly Gustilo grade 3 fractures, are at an increased risk of infection.87 The key to infection avoidance of open class III fractures is wound irrigation, surgical débridement of devitalized tissue, and delayed wound closure. A recent Surgical Infection Society Guideline recommended AP with a first-generation cephalosporin after open fracture until 24 to 48 hours after wound closure.88 Some groups recommend adding gram-negative coverage for class III open fractures.89

HERPES SIMPLEX VIRA L INFECTION
Frequent recurrent genital herpes simplex viral infections (>5-6 episodes per year) are amenable to prophylaxis with continuous acyclovir (400 mg twice daily), famciclovir (250 mg twice daily), or valacyclovir (500-1000 mg once daily).90,91 Famciclovir may be less effective for suppression of viral shedding, and 500 mg of valacyclovir once daily might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (ie, ≥10 episodes per year).91 Patients should be counseled regarding consistent condom use and avoidance of sexual activity during recurrences in addition to suppressive antiviral therapy.

INFLUENZA
Chemoprophylaxis of influenza A and B infection with a neuraminidase inhibitor (zanamivir [inhaled] or oseltamivir [oral]) is 70% to 90% effective92,93 (Table 1). These agents are particularly useful for prophylaxis after exposure in unvaccinated high-risk patients and unvaccinated health care professionals in an outbreak setting in a medical institution or community. Chemoprophylaxis is recommended for persons who are at high risk of influenza complications (Table 6) and those who are hospitalized or have severe, complicated, or progressive illness.94 Low-risk, healthy persons who are not in contact with high-risk patients do not typically require CP. Adults for whom antiviral CP should be considered during periods of increased influenza activity in the community are listed in Table 7. Zanamivir and oseltamivir are classified as category C (risk cannot be ruled out) for use during pregnancy. Influenza CP should be considered as an adjunct to influenza vaccination. Chemoprophylaxis should not be administered 48 hours before or 2 weeks after administration of the intranasal live-attenuated FluMist influenza vaccine (MedImmune, Gaithersburg, MD); CP has no effect on the inactivated influenza vaccine.21 Chemoprophylaxis may be stopped 10 days after exposure for household contacts and 7 days after other exposures.94 For control of outbreaks in long-term care facilities and hospitals, the Centers for Disease Control and Prevention recommends CP for a mini-
TABLE 6. Persons at High Risk of Influenza Complications

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged &lt;5 y (especially &lt;2 y)</td>
<td></td>
</tr>
<tr>
<td>Adults aged &gt;65 y</td>
<td></td>
</tr>
<tr>
<td>Persons with chronic disorders, including the following:</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (including asthma)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (except hypertension alone)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td>Hematologic (including sickle cell disease)</td>
<td></td>
</tr>
<tr>
<td>Metabolic (including diabetes mellitus)</td>
<td></td>
</tr>
<tr>
<td>Persons with neurologic and neurodevelopment conditions, including the</td>
<td></td>
</tr>
<tr>
<td>following:</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Intellectual disability (mental retardation)</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe developmental delay</td>
<td></td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td></td>
</tr>
<tr>
<td>Persons who are immunosuppressed as a result of medication or HIV infection</td>
<td></td>
</tr>
<tr>
<td>Women who are pregnant or postpartum (within 2 wk after delivery)</td>
<td></td>
</tr>
<tr>
<td>Persons aged ≤18 y who are receiving long-term aspirin therapy</td>
<td></td>
</tr>
<tr>
<td>American Indians and Alaska Natives</td>
<td></td>
</tr>
<tr>
<td>Persons who are morbidly obese (ie, BMI ≥40)</td>
<td></td>
</tr>
<tr>
<td>Residents of nursing homes and other long-term care facilities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a BMI = body mass index; HIV = human immunodeficiency virus.</td>
</tr>
<tr>
<td>b Influenza vaccination is the primary tool to prevent influenza;</td>
</tr>
<tr>
<td>antiviral chemoprophylaxis is not a substitute for vaccination.</td>
</tr>
<tr>
<td>Chemoprophylaxis should be administered in conjunction with inactivated vaccination.</td>
</tr>
<tr>
<td>Highest risks for morbidity and mortality include the very elderly (aged &gt;65 y) residents of nursing homes and those severely immunosuppressed (eg, allogenic stem cell transplant recipients).</td>
</tr>
<tr>
<td>d Affecting brain, spinal cord, peripheral nerve, or muscle.</td>
</tr>
<tr>
<td>Adapted from Clin Infect Dis, with permission from Oxford University Press, and from MMWR Recomm Rep.</td>
</tr>
</tbody>
</table>

In patients who are able to receive influenza vaccination and who are at high risk of complications, treatment should be continued for the duration of the influenza season in the community. Oseltamivir- and zanamivir-resistant influenza A strains have been reported; one should monitor the Centers for Disease Control and Prevention influenza Web site (http://www.cdc.gov/flu) for seasonal updates. The adamantanes (amantadine and rimantadine) are active only against influenza A; with the emergence of adamantane resistance in most seasonal A H3N2 and pandemic 2009-2010 A H1N1 strains, these agents are no longer recommended for CP.

**SURGICAL AP**

Surgical site infections account for 14% to 18% of all health care infections and are the third most frequently reported nosocomial infection. Factors that may increase the risk of surgical site infection include those related to the patient (age, nutritional status, diabetes, smoking status, obesity, coexisting infections at a remote site, colonization with a pathogenic microorganism, altered immune response, and length of preoperative stay) and the operative procedure (duration of surgical scrub, skin antisepsis, preoperative shaving, preoperative skin preparation, duration of operation, AP; operating room ventilation, inadequate sterilization of instruments, foreign material at the surgical site, surgical drains, and surgical technique). The risk of surgical site infection also depends on whether the surgical procedure is clean, clean-contaminated, contaminated, or dirty-infected based on standard definitions of these terms. Improvements in operating room ventilation, sterilization methods, barriers, and surgical technique as well as the use of perioperative topical, oral, and intravenous AP have been important in decreasing the incidence of surgical site infection.

Perioperative antimicrobial surgical prophylaxis is recommended for operative procedures that have a high rate of postoperative wound infection, when foreign material is implanted, or when the wound infection rate is low but the development of a wound infection results in a disastrous event. Prophylactic antimicrobial agents should be bactericidal, nontoxic, and inexpensive and

TABLE 7. Adults for Whom Antiviral Chemoprophylaxis Should Be Considered During Periods of Increased Influenza Activity in the Community

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at high risk during the 2 wk after influenza vaccination</td>
<td></td>
</tr>
<tr>
<td>Persons at highest risk of influenza complications for whom influenza vaccine is contraindicated, unavailable, or a poor match (at particularly high risk are recipients of hematopoietic stem cell transplants, pregnant women, and those infected with the human immunodeficiency virus)</td>
<td></td>
</tr>
<tr>
<td>Family members or health care professionals who are unvaccinated and likely to have ongoing, close exposure to persons at high risk, unvaccinated persons, or infants aged ≤6 mo</td>
<td></td>
</tr>
<tr>
<td>Persons at high risk, their family members and close contacts, and health care professionals, when circulating strains of influenza virus in the community are not matched with the vaccine strains</td>
<td></td>
</tr>
<tr>
<td>Persons with immune deficiencies or those who might not respond to vaccination (eg, persons who are infected with the human immunodeficiency virus, who have other immunosuppressed conditions, or who are receiving immunosuppressive medications)</td>
<td></td>
</tr>
<tr>
<td>Vaccinated and unvaccinated staff and other persons during response to an outbreak in a closed institutional setting with residents at high risk (eg, extended-care facilities)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Chemoprophylaxis should be administered in conjunction with inactivated vaccination.</td>
</tr>
<tr>
<td>b Chemoprophylaxis does not need to be limited to these people.</td>
</tr>
<tr>
<td>c Updates or supplements to these recommendations might be required.</td>
</tr>
<tr>
<td>Health care professionals should be alert to the announcement of recommendation updates and should check the Centers for Disease Control and Prevention influenza Web site periodically for additional information.</td>
</tr>
<tr>
<td>Adapted from Clin Infect Dis, with permission from Oxford University Press, and from MMWR Recomm Rep.</td>
</tr>
</tbody>
</table>
## TABLE 8. **Antimicrobial Prophylaxis for Surgery**

<table>
<thead>
<tr>
<th>Nature of operation</th>
<th>Common pathogens</th>
<th>Recommended antimicrobial agents</th>
<th>Adult dosage before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiacd (prosthetic valve, coronary artery bypass, open heart surgery)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic (noncardiac)</td>
<td>S aureus, coagulase-negative staphylococci, enteric gram-negative bacilli</td>
<td>Cefazolin or Cefuroxime or Vancomycin</td>
<td>1-2 g IV every 8 h</td>
</tr>
<tr>
<td>Pacemaker or defibrillator implant</td>
<td>S aureus, coagulase-negative staphylococci</td>
<td>Cefazolin or Vancomycin</td>
<td>1-2 g IV every 8 h</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal, gastroduodenal</td>
<td>Enteric gram-negative bacilli, gram-positive cocci</td>
<td>High-risk patients only or Cefazolin</td>
<td>1-2 g IV every 8 h</td>
</tr>
<tr>
<td>Biliary tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteric gram-negative bacilli, enterococci, clostridia</td>
<td>High-risk patients only or Cefazolin</td>
<td>1-2 g IV every 8 h</td>
<td></td>
</tr>
<tr>
<td>Colorectal§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteric gram-negative bacilli, enterococci, anaerobes</td>
<td>Oral Neomycin sulfate or plus Erythromycin base or plus Metronidazole</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Appendectomy, nonperforatedk</td>
<td>Enteric gram-negative bacilli, enterococci, anaerobes</td>
<td>Cefoxitin or cefotetan or Cefazolin or Ampicillin-sulbactam or Metronidazole</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Genitourinary§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy alone</td>
<td>Enteric gram-negative bacilli, enterococci</td>
<td>High-risk patients only or Cefazolin or Trimehexoprim-sulfamethoxazole or Ciprofloxacin</td>
<td>500 mg orally or 400 mg IV</td>
</tr>
<tr>
<td>Cystoscopy with manipulation or upper tract instrumentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open or laparoscopic surgery§</td>
<td>Enteric gram-negative bacilli, enterococci</td>
<td>Cefazolin</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Gynecologic and obstetric§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal, abdominal, or laparoscopic hysterectomy</td>
<td>Gram-negative bacilli, enterococci, group B streptococci, anaerobes</td>
<td>Cefoxitin or cefotetan or Cefazolin or Ampicillin-sulbactam or Metronidazole</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Cesarean section §</td>
<td>Same as for hysterectomy</td>
<td>Cefazolin</td>
<td>3 g IV</td>
</tr>
<tr>
<td>Abortion §</td>
<td>Same as for hysterectomy</td>
<td>Doxycycline</td>
<td>300 mg orally</td>
</tr>
<tr>
<td>Head and neck§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incision through oral or pharyngeal mucosa</td>
<td>S aureus, oropharyngeal anaerobes, enteric gram-negative bacilli</td>
<td>Clindamycin</td>
<td>600-900 mg IV</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniotomy/spine §</td>
<td>S aureus, coagulase-negative staphylococci</td>
<td>Cefazolin or Vancomycin</td>
<td>1-2 g IV</td>
</tr>
<tr>
<td>Cerebrospinal fluid shunting§</td>
<td>S aureus, coagulase-negative staphylococci, streptococci, enteric gram-negative bacilli</td>
<td>Gentamicin, tobramycin, ciprofloxacin, ofloxacin, gatifloxacin, levofloxacin, moxifloxacin or Neomycin-gramicidin-polymyxin B Cefazolin</td>
<td>Multiple drops topically over 2 to 24 h</td>
</tr>
<tr>
<td>Ophthalmic§</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)

have in vitro activity against the common organisms that cause postoperative wound infection after a specific surgical procedure. Consensus panels most often recommend cefazolin and other cephalosporins because they meet the aforementioned criteria. Broad-spectrum antibiotics (eg, ertapenem) should be avoided for surgical prophylaxis. Perioperative antimicrobial surgical prophylaxis regimens for various surgical procedures adapted from the published recommendations of 2 consensus panels are summarized in Table 8. The use of vancomycin...
### TABLE 8. Continued a,b

<table>
<thead>
<tr>
<th>Nature of operation</th>
<th>Common pathogens</th>
<th>Recommended antimicrobial agents</th>
<th>Adult dosage before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic c,d,e</td>
<td><em>S. aureus</em>, coagulase-negative staphylococci</td>
<td>Cefazolin[^5] or cefuroxime[^5] or Vancomycin[^5]</td>
<td>1-2 g IV every 8 h for 24 h or 1.5 g IV every 12 h for 2 doses</td>
</tr>
<tr>
<td>Total joint replacement[^5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation of internal fixation device[^5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular[^6]</td>
<td><em>S. aureus</em>, coagulase-negative staphylococci, entecic gram-negative bacilli</td>
<td>Cefazolin or Vancomycin[^5]</td>
<td>1-2 g IV every 8 h for 24 h or 15 mg/kg IV every 12 h for 2 doses</td>
</tr>
<tr>
<td>Arterial surgery involving a prosthesis, the abdominal aorta, or a groin incision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremity amputation due to ischemia[^5]</td>
<td><em>S. aureus</em>, coagulase-negative staphylococci, enteric gram-negative bacilli, clostridia</td>
<td>Cefazolin or Vancomycin[^5]</td>
<td>1-2 g IV or 1 g IV (15 mg/kg)</td>
</tr>
</tbody>
</table>

---

[^5]: DS = double-strength; IV = intravenously; NA = not available.
[^6]: We agree with the *Medical Letter* consultants who do not recommend the use of broad-spectrum drugs (eg, ertapenem), third-generation cephalosporins (eg, cefotaxime, ceftriaxone, cefoperazone, cefixime), or fourth-generation cephalosporins (eg, cefepime) for routine surgical prophylaxis because they are expensive, the activity of some against staphylococcus is less than first- or second-generation cephalosporins, and their spectrum of activity includes organisms rarely encountered in elective surgery. These drugs should be reserved for treatment of serious infections, particularly those likely to be caused by organisms resistant to other antimicrobial agents.
[^7]: Parenteral prophylactic antimicrobial agents can be given as a single IV dose begun ≤60 min before the operation. For prolonged operations (>4 h) or those with major blood loss, additional intraoperative doses should be given at intervals 1 to 2 times the half-life of the drug: ampicillin-sulbactam, every 2-4 h; cefazolin, every 2-5 h; cefuroxime, every 3-4 h; cefotaxin, every 2-3 h; clindamycin, every 3-6 h; vancomycin, every 6-12 h; and metronidazole, every 6-8 h[^102] for the duration of the procedure in patients with normal renal function. If vancomycin or a fluoroquinolone is used, the infusion should be started 60-120 min before the initial incision to minimize the possibility of an infusion reaction close to the time of induction of anesthesia and to have adequate tissue levels at the time of incision.
[^8]: The Society of Thoracic Surgeons recommends vancomycin plus cefazolin in patients not allergic to penicillins who are at increased risk of methicillin-resistant staphylococcal surgical site infections and nasal mupirocin in all patients who are nasally colonized with *S. aureus* or in whom nasal *S. aureus* colonization status is unavailable.[^100] Adjunctive decolonization of *S. aureus* carriers may also decrease the incidence of surgical site infection.[^100] Treatment of prophylaxis up to 48 h may be appropriate.
[^9]: Some consultants recommend an additional dose when patients are removed from bypass during open heart surgery.
[^10]: Vancomycin can be used in hospitals in which methicillin-resistant *S. aureus* (MRSA) and *Staphylococcus epidermidis* are a frequent cause of postoperative wound infections, in patients previously colonized with MRSA, or in those who are allergic to penicillins or cephalosporins. Rapid IV administration may cause hypotension, which could be especially dangerous during induction of anesthesia. Even when the drug is administered for a period of 60 min, hypotension may occur; treatment with diphenhydramine and further slowing of the infusion rate may be helpful. Some experts would give 15 mg/kg of vancomycin to patients weighing more than 75 kg, up to a maximum of 1.5 g, with a slower infusion rate (1.5 g for 90 min). For operations in which enteric gram-negative bacilli are common pathogens, adding another drug, such as an aminoglycoside (gentamicin, tobramycin, or amikacin), may be reasonable.
[^11]: Patients with morbid obesity, esophageal obstruction, decreased gastric acidity, decreased gastrointestinal motility, hemorrhage, gastric cancer, gastric bypass, or percutaneous endoscopic gastrostomy are at high risk, as are those being treated with an H2 blocker or a proton pump inhibitor.[^130] Some experts recommend prophylaxis for all gastroduodenal operations in which there is entry into the lumen of the gastrointestinal tract.
[^12]: For patients allergic to penicillins and cephalosporins, clindamycin with either gentamicin, ciprofloxacin, levofloxacin, or aztreonam is a reasonable alternative.
[^13]: Risk factors for infection resulting from biliary procedures, including laparoscopic cholecystectomy: emergency procedures, diabetes, longer procedure duration, intraoperative gallbladder rupture, age >70 y, open cholecystectomy, conversion of laparoscopic to open cholecystectomy, higher American Society of Anesthesiologists (ASA) score, episode of colic within 30 d before surgery, reintervention in <1 mo for noninfectious complications, acute cholecystitis, bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, immunosuppression, obstructive jaundice, common duct stones, or insertion of a prosthetic device. Some experts recommend prophylaxis for all biliary operations.
[^14]: 1 g of neomycin plus 1 g of erythromycin at 1 PM, 2 PM, and 11 PM or 2 g of neomycin plus 2 g of metronidazole at 7 PM and 11 PM the day before an 8 AM operation.
[^15]: For a ruptured viscus, therapy is often continued for about 5 d (therapeutic course).
[^16]: Preoperative urine culture positive or unavailable, preoperative catheter, transrectal prostatic biopsy, or placement of prosthetic material.
[^17]: Shockwave lithotripsy, ureteroscopy.
[^18]: Including percutaneous renal surgery, procedures with entry into the urinary tract, and those involving implantation of a prosthesis. If manipulation of the bowel is involved, prophylaxis is given according to colorectal guidelines.
[^19]: Divided into 100 mg an hour before the abortion and 200 mg a half hour after.
[^20]: There is no consensus supporting a particular choice, route, or duration of antimicrobial prophylaxis for ophthalmic surgeries.
[^21]: If a tourniquet is to be used in the procedure, the entire dose of antibiotic must be infused before its inflation.
[^22]: Antibiotic containing polymethyl methacrylate cement in addition to cefazolin or vancomycin may be appropriate for high-risk procedures, including revision arthroplasty.[^7] Adjunctive decolonization of *S. aureus* carriers may also decrease the incidence of surgical site infection.[^11] Adapted from *Treatment Guidelines from the Medical Letter*,[^106] with special permission, and from *Am J Health Syst Pharm. ©1999. American Society of Health-System Pharmacists, Inc. All rights reserved. Distributed with permission (R1109).*
ANTIMICROBIAL PROPHYLAXIS IN ADULTS

The use of AP has led to the prevention of a large number and variety of infections and to substantial declines in surgical site infections. Antimicrobial prophylaxis should be limited to specific, well-accepted indications to avoid excess cost, toxicity, and antimicrobial resistance. Patients should understand the potential risks and benefits of any AP regimen. Although some AP practices are evidence-based, many are based on low-level evidence or expert opinion. More studies in the area of AP are needed.

REFERENCES

Antimicrobial Prophylaxis in Adults


ANTIMICROBIAL PROPHYLAXIS IN ADULTS


The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are now a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
The introduction of new antifungal agents (eg, echinocandins, second-generation triazoles) in the past decade has transformed the management of invasive mycoses to the point that drug toxicity is no longer the major limiting factor in treatment. Yet, many of these newer antifungal agents have important limitations in their spectrum of activity, pharmacokinetics, and unique predisposition for pharmacokinetic drug-drug interactions and unusual toxicities associated with long-term use. This article reviews key pharmacological aspects of systemic antifungal agents as well as evolving strategies, such as pharmacokinetic-pharmacodynamic optimization and therapeutic drug monitoring, to improve the safety and efficacy of systemic antifungal therapy.


AUC = area under the curve; CYP = cytochrome P450; 5-FC = flucytosine; GI = gastrointestinal; MIC = minimum inhibitory concentration; TDM = therapeutic drug monitoring

The era of systemic antifungal chemotherapy effectively began with the introduction of amphotericin B-deoxycholate in 1958 by Squibb Laboratories, after exhaustive attempts to develop orally bioavailable formulations of more than 200 polycyane macrolide antibiotics produced by the soil actinomycete Streptomyces.1 Although amphotericin B was to become the criterion standard treatment for serious fungal infections for more than 40 years, infusion-related adverse effects and dose-limiting nephrotoxicity prompted the continued search for equally effective but less toxic alternatives that could be administered both intravenously and orally.

This goal was not realized until more than 3 decades later with the introduction of fluconazole in 1990 (Figure 1). Unlike amphotericin B and the earlier imidazole antifungal agents (miconazole, ketoconazole), fluconazole possessed excellent oral bioavailability; predictable linear pharmacokinetics with wide distribution into many tissues, including the cerebral spinal fluid and vitreous chamber of the eye; and a much lower risk of drug interactions and toxicity in critically ill patients compared with earlier azoles.2 Fluconazole was also effective for the treatment of oropharyngeal candidiasis in patients with AIDS; however, resistance could be problematic in patients receiving prolonged treatment who had declining CD4+ cell counts.3 Fluconazole quickly became one of the most widely prescribed antifungal agents for mucosal and systemic yeast infections. However, the lack of activity against opportunistic molds (ie, Aspergillus, Mucorales, and Fusarium species) and intrinsic resistance among some Candida species (eg, Candida glabrata, Candida krusei) created a need for broader-spectrum alternatives. Itraconazole (1992) was a partial solution to the limitations of fluconazole because the drug had improved activity against endemic fungi and Aspergillus species, but the oral dosing formulations were plagued by erratic absorption (capsules)4 or adverse gastrointestinal (GI) effects (solution formulation)5 that limited its effectiveness in cancer patients with mucositis or nausea and vomiting.6

The introduction of the broader-spectrum triazoles voriconazole (2002) and posaconazole (2006) transformed the management of invasive mold infections in severely immunocompromised patients. Voriconazole was shown to be more effective than conventional amphotericin B for the treatment of invasive aspergillosis7 and is a useful agent for fusariosis,8 whereas posaconazole had a spectrum of activity that included not only Aspergillus and Fusarium species but also many Mucorales.9,10 Both agents could be administered orally, paving the way for their use not only for the treatment of suspected or documented mold infections but also as prophylaxis in severely immunocompromised patients.11-13 Unfortunately, the broader spectrum of activity with triazole antifungal agents often comes at the expense of increased pharmacokinetic variability and risk of drug interactions. Newer triazoles currently under investigation (ie, isavuconazole) appear to have a spectrum of activity...
similar to voriconazole and posaconazole, with less pharmacokinetic variability and drug interactions.14 Efforts under way to reformulate the posaconazole suspension into better oral and intravenous dosage forms could address many of the drug’s pharmacokinetic shortcomings.

The final milestone of antifungal drug discovery in the 20th century was the identification and development of echinocandin antifungal agents. Echinocandins are semisynthetic lipopeptides that inhibit synthesis of β-1,3-d-glucan in susceptible fungi, leading to damage of the fungal cell wall. Because a glucan-rich cell wall is a target not found in mammalian cells, these agents were predicted to be effective antifungal agents with very little collateral toxicity in mammalian cells—a prediction that has been proven true in clinical trials of patients with invasive candidiasis15-17 and aspergillosis.18 However, echinocandins still lack activity against some common opportunistic yeasts (Cryptococcus species) and less common molds (ie, Fusarium, Scedosporium, and Mucorales) that often develop as breakthrough infections in severely immunocompromised patients.

Therefore, although considerable progress has been achieved since the dawn of systemic antifungal therapy in the 1950s, the current antifungal armamentarium is far from perfect. No single antifungal agent is appropriate for all patients for a given mycosis because of patient-specific comorbid conditions, hypersensitivities, risk of drug interactions, immunosuppression, site of infection, and risk of infection with more intrinsically antifungal-resistant pathogens. This article reviews key aspects of the clinical pharmacology of older vs newer antifungal agents, with a particular emphasis on pharmacokinetic issues that arise with newer agents and emerging data on toxicity with longer-term therapy.

**OVERVIEW OF ANTIFUNGAL PHARMACOLOGY**

Despite differences in the composition of the cell membrane and the presence of the cell wall, fungi are metabolically similar to mammalian cells and offer few pathogen-specific targets. Systemic antifungal agents can be generally grouped on the basis of their site of action in pathogenic fungi (Figure 2). Azole and polyene antifungal agents exert their antifungal effects by targeting ergosterol—the principal cell membrane sterol of many pathogenic fungi. By inhibiting 14α-demethylase (lanosterol demethylase), a fungal cytochrome P450 (CYP)–dependent enzyme, azole antifungal agents deplete cell membrane ergosterol, impair membrane fluidity, and lead to accumulation of toxic 14α-methylated sterols, resulting in growth arrest and eventual fungal cell death. However, inhibition is not entirely selective to fungi; indeed, collateral inhibition of human CYP enzymes by azoles is often responsible for pharmacokinetic drug-drug interactions. The fungal target forazole binding is a heme-containing pocket on the 14α-demethylase enzyme.20 Differences in the conformation of the 14α-demethylase binding pocket and azole structure largely define the binding affinity of each drug, and in some fungal species, the potential for cross-resistance among triazoles.20 For molecules derived from ketoconazole (ie, itraconazole, posaconazole), extension of the nonpolar side chains enhances azole binding to the 14α-demethylase apoprotein, resulting in an enhanced

---

**FIGURE 1. Timeline of systemic antifungal drugs.**
Fuginulpharmacology

For para:Hnal use.

Antifungal agents have a spectrum of activity against molds (Figure 3). Voriconazole, a derivative of fluconazole, possesses an α-α-methyl group that confers activity against Aspergillus species and other filamentous fungi. Resistance to triazole antifungal agents is most commonly the result of mutations in the azole binding pocket of 14α-demethylase and/or the overexpression of MDR1 efflux pumps that expel fluconazole or the multidrug adenosine triphosphate–dependent efflux pumps CDR1 and CDR2, which expel all triazoles, thereby leading to cross-resistance. Because intrinsic resistance in C. krusei is a result of impaired binding of fluconazole to 14α-demethylase, newer triazoles with enhanced binding to the enzyme retain activity against fluconazole-resistant strains such as C. krusei. However, fluconazole resistance in C. glabrata is frequently a result of the expression of multidrug efflux pumps; hence, cross-resistance may be observed with all azole antifungal agents.

Similar to azole antifungal agents, the allylamine terbinafine inhibits ergosterol biosynthesis by inhibiting squalene monooxygenase—an enzyme in fungi responsible for conversion of squalene to squalene epoxide, which is a precursor to lanosterol in the ergosterol synthesis pathway. Although allylamines do not seem to have the same collateral effects on human CYP enzymes as azole antifungal agents, drugs such as rifampin that strongly induce CYP metabolism in mammals will increase the metabolism of terbinafine. Once taken orally, terbinafine concentrates in the skin and nail beds and has relatively low bloodstream concentrations. Consequently, its use as a systemic antifungal agent is primarily restricted to the treatment of onychomycosis and cutaneous fungal infections.

The broad-spectrum polyene amphotericin B is the only other antifungal agent that targets the fungal cell membrane (Figure 2). Amphotericin B directly binds to ergosterol, forming complexes that intercalate the cell membrane, thereby resulting in pore formation and leakage of intracellular contents. Amphotericin B has greater avidity for ergosterol-rich fungal cell membranes vs cholesterol-rich
mammalian cell membranes; however, this specificity may be lost when the drug accumulates to high concentrations in organs such as the kidney, where the drug causes direct damage to distal tubular membranes.28 Consequently, nephrotoxicity is a common dose-limiting adverse effect of amphotericin B therapy. Amphotericin B also directly stimulates release of proinflammatory cytokines by mononuclear phagocytic cells, often resulting in fever, rigors, and chills during drug infusion.29,30 This infusion reaction can be attenuated to varying degrees by reformulation of amphotericin B into lipid carriers. However, the principal advantage of lipid amphotericin B formulations are their reduced distribution of amphotericin B to the kidneys, which reduces but does not eliminate the nephrotoxicity of amphotericin B.31 Two formulations of amphotericin B—a liposomal formulation and a lipid complex—are now commonly used to treat a wide range of invasive fungal infections. Although development of amphotericin B resistance during therapy is a rare clinical phenomenon, substitution of alternative cell wall sterols33 and increased resistance to oxidative damage in the cell membrane through increased production of neutralizing enzymes35 are 2 mechanisms that have been identified in clinical isolates exhibiting innate or acquired resistance to amphotericin B.

Of the antifungal agents currently in clinical use, echinocandins are the only ones that target the fungal cell wall by competitively inhibiting the synthesis of β-1,3-d-glucan polymers—key cross-linking structural components of the cell wall in some pathogenic fungi (Figure 2).34 Echinocandins bind to the β-1,3-d-glucan synthase enzyme complex in susceptible fungi, resulting in a glucan-depleted cell wall that is susceptible to osmotic lysis, especially in rapidly growing cells.35 The degree of β-1,3-d-glucan polymerization in the fungal cell wall and the expression of the glucan synthase enzyme target largely define the spectrum of this antifungal class, which is generally considered to have fungicidal activity against Candida species and fungistatic activity against Aspergillus species (Figure 3).36 Although bona fide echinocandin resistance remains a relatively rare clinical phenomenon, mutations in defined “hot spot” regions of the FKS1 and FKS2 catalytic subunits of the glucan synthase are associated with reduced echinocandin inhibitory activity against the enzyme, higher minimum inhibitory concentrations (MICs), and an increased risk of treatment failure.37

Two groups of antifungal agents selectively target intracellular processes in fungi via mechanisms analogous to
those of cancer chemotherapeutic agents and are generally not effective as monotherapy for systemic mycoses (Figure 2). Fluconazole (5-FC) is selectively taken up by fungus-specific enzymes, cytosine permease and cytosine deaminase, and is converted to cytostatic 5-fluorouracil in fungal cells, where the active drug inhibits thymidylate synthase and causes RNA miscoding.28,38 However, resident intestinal bacterial flora in the human gut can convert 5-FC to 5-fluorouracil, resulting in nausea, vomiting, diarrhea, and bone marrow suppression.28,39 Flucytosine (5-FC) is primarily active against yeasts but must be given in combination with other drugs to avoid resistance that arises with mutations in cytosine permease and cytosine deaminase, resulting in decreased importation and conversion of the drug to its active form (Figure 3).39 Griseofulvin is a systemic antifungal agent that binds to tubulin, interfering with microtubule formation. Because the drug concentrates in keratinocytes, it is only used for noninvasive dermatophyte infections. Interestingly, griseofulvin inhibits the proliferation of many types of cancer cells in vitro, which has led to renewed interest in this agent as a potential adjunctive treatment for breast cancer.

**TABLE 1. Comparative Pharmacokinetic and Pharmacodynamic Properties of Systemic Antifungal Agents**

| Drug         | Typical adult dosing | Oral bioavailability | Cmax (μg/mL) | AUC (mg × h/L) | Protein (% CSF) | CSF (% Vitreous) | Urine (% Metabolism) | Elimation T1/2 (h) PK-PD (total drug unless indicated) |
|--------------|----------------------|----------------------|-------------|----------------|----------------|-----------------|----------------------|---------------------|-------------------------------------------------|
| AMB          | 0.6-1.0 mg/kg/d      | <5                   | 0.5-2.0     | 17.0           | >95.0          | 0-4             | 0-38h,c             | 3-20 Minimal        | Feces 50 Cmax MIC 4-10 or AUC:MIC >100 |
| ABCD         | 4 mg/kg/d            | <5                   | 4.0         | 43.0           | >95.0          | <5              | 0-38h,c             | <5 Minimal          | ND 30 Cmax MIC >40 or AUC MICH >100 |
| ABLC         | 5 mg/kg/d            | <5                   | 1.7         | 14.0           | >95.0          | <5              | 0-38h,c             | <5 Minimal          | ND 173 Cmax MIC >40 or AUC MICH >100 |
| LAMB         | 3-5 mg/kg/d          | <5                   | 83          | 555            | >95.0          | <5              | 0-38h,c             | 5 Minimal urine; feces Minor hepatic Renal 100-153 Cmax MIC >40 or AUC MICH >100 |
| FLU          | 6-12 mg/kg/d         | >90                  | 6-20        | 400-800        | 10.0           | >60             | 28-75h,c             | 90                   | Minor hepatic Renal 31 AUC MICH >25 |
| ITRAd        | 200 mg twice daily   | 50                   | 0.5-2.3     | 29.2           | 99.8           | <10             | 10b 38h,c             | 1-10 Hepatic Renal 24 AUC MICH >25 |
| VOR          | 6 mg/kg every 12 h   | >90                  | 3.0-4.6     | 20.3           | 58.0           | 60              | 38h,c 1-10 Hepatic Renal 6 AUC MICH >25 |
| POS          | 600-800 mg/d in      | ND                   | 1.5-2.2     | 8.9            | 99.0           | ND              | 26h,c 25                  | Minor hepatic Renal 25 AUC MICH >400 (8-25 free drug) |
| ANIe         | 200 mg x 1 loading   | <5                   | 6-7         | 99             | 84.0           | 50              | 0.1 25                  | None Feces 26 Cmax MIC >10 or serum (unbound) |
| CAS          | 70 mg loading dose   | <5                   | 8-10        | 119            | 97.0           | 50              | 0.1 25                  | None Feces 26 Cmax MIC >10 or serum (unbound) |
| MICA         | 100-150 mg/d; 50 mg/d (prophylaxis) | <5                   | 10-16       | 158            | 99.0           | 50              | 0.1 25                  | None Feces 26 Cmax MIC >10 or serum (unbound) |
| 5-FC         | 100 mg/kg/d in       | 80                   | 30-40       | 30-62          | 4.0            | 60-100          | 49h,c 90              | Minor 3-6 Hepatic 24 AUC MICH >20 Time > MIC 20%-40% |

**a** ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex; AMB = amphotericin B; ANI = anidulafungin; AUC = area under the curve; CAS = caspofungin; Cmax = maximum concentration; CSF = cerebrospinal fluid; 5-FC = flucytosine; FLU = fluconazole; ITRA = itraconazole; LAMB = liposomal AMB; MIC = minimum inhibitory concentration; MICA = micafungin; ND = not determined; PK-PD = pharmacokinetics-pharmacodynamics; POS = posaconazole; VOR = voriconazole; T1/2 = half-life.

b Data derived from human studies.
c Data derived from animal studies.
d Oral solution formulation.
e Data are for the 100-mg dose.

**PHARMACOKINETIC CONSIDERATIONS**

Besides spectrum of activity, antifungal pharmacokinetic properties are often the most important consideration in drug selection because impaired GI tract function or reduced renal/hepatic drug clearance can profoundly influence the safety and efficacy of antifungal therapy. Key pharmacokinetic characteristics of systemic antifungal agents are summarized in Table 1.

Several classes of antifungal agents must be administered intravenously, including amphotericin B and the echinocandins, because these agents are not sufficiently...
Absorbed from the GI tract. This problem has been solved with the introduction of triazole antifungal agents; however, the degree of absorption varies considerably from one drug to the next (Table 1). Fluconazole and voriconazole both have oral bioavailability exceeding 90% and can be administered without regard to food (fluconazole) or preferably on an empty stomach (voriconazole). Itraconazole capsules and posaconazole suspension require food to prolong gastric residence time to enhance drug dissolution, which is not an issue with the oral cyclodextrin formulation of itraconazole that is administered on an empty stomach. However, patients may prefer to take itraconazole solution with food because of GI intolerance and the unpalatable aftertaste of the solution.

The oral absorption of a posaconazole suspension can be unpredictable in patients with poor appetite, nausea, diarrhea, and GI dysfunction associated with cancer chemotherapy (mucositis) or transplant (graft-versus-host disease involving the gut, colitis) or in patients taking acid suppression therapy, especially with potent agents such as proton pump inhibitors. Absorption of posaconazole is dose limited at 800 mg/d but can be maximized when the drug is administered with a high-fat (>50% of the calories from fat) food or nutritional supplement. Administration of the drug in divided doses improved the exposure by 180% compared with a single daily dose. Therefore, posaconazole is usually initiated at doses of 200 mg 3 to 4 times daily with food in patients with suspected or documented infections until infection stabilizes or adequate serum levels can be verified (see Therapeutic Drug Monitoring section). Dosing can then be transitioned to 400 mg twice daily. Inadequate posaconazole concentrations are better addressed with clinical approaches that improve drug dissolution and absorption (eg, administration with acidic cola or fruit juice or a high-fat meal, discontinuation of acid suppression therapy) than increasing drug doses above 800 mg/d.

Unlike posaconazole, genetic variability in metabolism plays a more important role in the patient-to-patient pharmacokinetic variability of voriconazole. Polymorphisms in the CYP2C19-encoding gene result in 3 populations of patients with markedly different rates of nonlinear voriconazole clearance despite the administration of the same fixed daily dose: (1) homozygous patients who extensively metabolize voriconazole, (2) heterozygous patients with moderate clearance rates of voriconazole, and (3) homozygous patients who metabolize drug poorly through this pathway and have slow rates of voriconazole clearance. The poor metabolism genotype is more common in some ethnic groups, such as patients of Asian or Pan-Pacific origin (14%-19%), than in patients of African origin or whites (2%). In contrast, pediatric patients often exhibit more rapid linear clearance of voriconazole, which may result in low or undetectable serum drug concentrations at standard adult doses. Therefore, higher weight-based doses are recommended in children (7 mg/kg every 12 hours, sometimes increased up to 12 mg/kg every 12 hours without a loading dose) (Table 1).

Drug interactions are another important cause of pharmacokinetic variability because coadministration of any triazole or caspofungin with potent inducers of phase 1 (CYP) and phase 2 metabolism (ie, rifampin, phenytoin) can potentially result in low (fluconazole, caspofungin, posaconazole) or undetectable (itraconazole, voriconazole) bloodstream concentrations of the antifungal agent and an increased risk of treatment failure. In the case of itraconazole, voriconazole, and posaconazole, interactions with potent inducers of CYP3A4 cannot always be overcome with higher antifungal drug doses.

Pharmacokinetic drug-drug interactions are further compounded by the fact that some antifungal agents inhibit the clearance or metabolism of other drugs. Nephrotoxicity associated with amphotericin B therapy (often accelerated by calcineurin inhibitors, aminoglycosides, intravenous radiopaque contrast agents, foscarnet, or aggressive diuresis) will reduce the clearance of other renally eliminated drugs. Pharmacokinetic drug-drug interactions are most problematic, however, with triazole antifungal agents because all of these agents inhibit human CYP enzymes to varying degrees (Table 2). These interactions can be dangerous if not anticipated in patients receiving drugs with a narrow therapeutic index, such as chemotherapeutic agents, immunosuppressants, and some cardiovascular medications. Although a detailed discussion of drug interactions is beyond the scope of this review, several recent reviews have been published on this topic.

Finally, the site of infection is an important consideration in the selection of antifungal therapy because some antifungal agents have limited distribution to anatomically privileged sites, such as the central nervous system and vitreous fluid, or, in the case of oral itraconazole and

### Table 2. Cytochrome P450 (CYP) Inhibition Profile of Triazole Antifungal Agents

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>+</td>
<td></td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Substrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>+</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

– = no activity; + = minimal activity; ++ = moderate activity; +++ = strong activity.

Data are derived from reference 57.
posaconazole, may not achieve sufficient concentrations in the bloodstream to treat hematogenous infection (Table 1). Fungal infections involving the central nervous system are notoriously difficult to treat, and many antifungal agents have high molecular weights and a large degree of protein binding that limit their ability to penetrate the blood-brain barrier. \(^{60,61}\) Of the currently available antifungal agents, 5-FC, fluconazole, and voriconazole have the best penetration in the cerebrospinal fluid and vitreous chamber of the eye. \(^{62}\) However, liposomal amphotericin B and perhaps other triazoles and echinocandins may still achieve concentrations in the brain parenchyma sufficient to be clinically effective. \(^{28,63}\) Lipid formulations of amphotericin B, newer triazole antifungal agents, and echinocandins have no role in the treatment of candiduria because only small amounts of microbiologically active drug are excreted in the urine. \(^{58}\)

**PHARMACODYNAMIC CONSIDERATIONS**

Similar to antibacterial agents, antifungal agents display different patterns of activity in vivo (ie, concentration-independent or concentration-dependent as determined by the shape of the dose-response curve at clinically achieved concentrations). \(^{64}\) These patterns of activity in vivo can often be correlated with the drug dose and the pathogen MIC to identify dosing strategies that maximize antifungal efficacy while reducing the risk of toxicity. Pharmacodynamic data may also be useful for predicting sites of infection where antifungal drugs have a higher risk of treatment failure (ie, cerebrospinal fluid, vitreous fluid, urine) because inadequate distribution leads to ineffective drug concentrations.

Flucytosine displays concentration-independent pharmacodynamic characteristics in vitro and in vivo against *Candida* and *Cryptococcus* species; ie, increases in serum drug concentrations above the pathogen MIC do not appreciably increase the rate or extent of fungal killing. \(^{65}\) In dose fractionation studies in animals, the ability of a dosage regimen to maintain serum drug concentrations above the MIC (percent of time greater than MIC of 20%-40%) was the best predictor of 5-FC activity against *Candida albicans*. \(^{65}\) This realization led in part to studies that used lower doses of 5-FC (100 mg/kg daily) in combination with higher amphotericin B treatment doses for cryptococcal meningitis, even though pharmacodynamic data for 5-FC in the treatment of *Cryptococcus neoformans* are limited. \(^{66}\)

Both in vitro and in vivo amphotericin B and lipid amphotericin B formulations generally display concentration-dependent fungicidal activity that begins to plateau once concentrations surpass the MIC of the infecting pathogen by 4- to 10-fold. \(^{67,68}\) Animal models \(^{69}\) and limited clinical data \(^{70}\) suggest that a ratio of maximum concentration in serum to MIC of greater than 40 is associated with a higher probability of treatment response with liposomal amphotericin B. For most adults, standard liposomal amphotericin B doses of 3 to 5 mg/kg should surpass the maximum concentration to MIC ratio of 40 unless the pathogen has an MIC of 2 μg/mL or greater. Moreover, a recent study that examined the benefits of dosage escalation to 10 mg/kg daily of liposomal amphotericin B in patients with proven or probable aspergillosis found that the escalated dosage provided no benefit over the 3 mg/kg daily dosage and nearly doubled the rate of nephrotoxicity and severe hypokalemia. \(^{71}\)

The concentration-dependent activity of echinocandins against *Candida* \(^{72,73}\) and *Aspergillus* \(^{74}\) species is optimized when the free-drug (non–protein-bound) serum area under the curve (AUC):MIC ratio approaches 20 for *C. albicans* or 7 for less virulent isolates of *C. glabrata* and *Candida parapsilosis*. \(^{72}\) These pharmacokinetic-pharmacodynamic targets are generally achieved with currently recommended echinocandin dosages for greater than 90% of isolates with MICs less than 0.575 (Table 1). However, initial echinocandin breakpoints for defining nonsusceptible MICs were set at greater than 2 μg/mL, suggesting that a portion of isolates with MICs of 1 to 2 μg/mL that are classified as “susceptible” may not be treatable with currently recommended echinocandin dosages. \(^{75}\) A reassessment of echinocandin breakpoints on the basis of analysis of resistant isolates and molecular-biochemical resistance mechanisms suggested that nonsusceptibility breakpoints should be lowered to 0.25 μg/mL for susceptible, 0.5 μg/mL for intermediate, and 1 μg/mL for resistant *C. albicans*, with breakpoints of less than 2 μg/mL, 4 μg/mL, and greater than 8 μg/mL for susceptible, intermediate, and resistant *C. parapsilosis*, respectively. \(^{75}\)

Triazole antifungal agents have perhaps the largest body of experimental and clinical literature establishing a correlation between drug dose, organism MIC, and outcome. \(^{76}\) Experimental studies in animals and clinical studies with fluconazole in the treatment of mucosal and invasive candidiasis suggest that achieving a serum free-drug AUC:MIC ratio of greater than 25 is the parameter most closely linked to successful treatment. \(^{76-78}\) Although less data are available for other triazoles and mold infections, studies in animal models of aspergillosis also suggest that the AUC:MIC ratio is the best predictor of treatment response to posaconazole, with 50% survival at total-drug AUC:MIC ratios of 100 to 150 and maximal responses at a ratio greater than 440 (free-drug AUC:MIC ratio of approximately 8-25). \(^{79,80}\)

Clinical trial data for candidal infections have suggested that this pharmacokinetic-pharmacodynamic relationship may be helpful for predicting treatment efficacy in
humans and have formed the basis for susceptibility testing breakpoints in Candida species. For example, isolates with fluconazole MICs of 16 or greater would be difficult to treat with a standard dosage of 6 mg/kg daily (ie, 400 mg dose with an AUC of 400 μg/h per liter) because the AUC:MIC falls below 25 at this MIC with the standard dosage. Therefore, isolates with fluconazole MICs of 16 to 32 μg/mL are categorized as “susceptible-dose dependent” instead of “intermediate” because they may still be treatable provided higher daily dosages of fluconazole are used (ie, 12 mg/kg daily or approximately 800 mg/d). Candida isolates with MICs greater than 64 μg/mL would require fluconazole dosages of 1600 mg/d or greater and therefore are classified as “resistant.” Recent studies using epidemiological cut-off analysis of wild-type susceptible and fluconazole-resistant Candida species, however, have prompted reconsideration of these pharmacodynamics-driven breakpoints because they may not be sufficiently sensitive to detect emerging resistance, especially among non–C glabrata isolates. Therefore, new species-specific MIC breakpoints for fluconazole have been proposed for C albicans, C parapsilosis, and Candida tropicalis (susceptible, ≤2 μg/mL; susceptible-dose dependent, 4 μg/mL; resistant, ≥8 μg/mL) while maintaining current breakpoints for C glabrata (susceptible-dose dependent, ≤32 μg/mL; resistant ≤64 μg/mL).

**THERAPEUTIC DRUG MONITORING OF ANTIFUNGAL AGENTS**

Because some antifungal agents exhibit marked variability in bloodstream concentrations that are difficult to predict on the basis of dosing alone, recent treatment guidelines and expert reviews have recommended therapeutic drug monitoring (TDM) for some antifungal agents in select patient populations. Therapeutic drug monitoring has long played an important role in improving the safety of 5-FC because the drug is frequently administered with nephrotoxic agents such as amphotericin B that cause wide fluctuations in drug clearance. Bone marrow suppression and hepatotoxicity are the most common dose-limiting toxicities of 5-FC and have been strongly linked to serum peak concentrations greater than 100 μg/mL. In an analysis of 1000 5-FC concentrations from 233 patients with invasive fungal infections, only 20% of patients were found to have “therapeutic” serum concentrations, 5% had undetectable levels, and 39% had serum concentrations that are generally considered to be toxic (>100 μg/mL). Therefore, standard weight-based dosages of 5-FC (100 mg/kg daily) should be individualized on the basis of the patient’s renal function and serum 5-FC levels, which are determined 2 hours after the administration of an oral dose. Target blood concentrations should fall between 20 to 50 μg/mL and be checked during the first week of therapy and 1 to 2 times weekly thereafter if the patient is receiving other nephrotoxic agents or has fluctuations in renal function.

Mold-active triazole antifungal agents (itraconazole, voriconazole, and posaconazole) are the other antifungal class most frequently recommended for TDM because of erratic absorption (itraconazole and posaconazole), variable hepatic clearance (voriconazole), and propensity for multiple drug interactions. Several studies have examined the association between itraconazole efficacy and serum drug levels when the drug is administered as prophylaxis or for the treatment of documented infections due to Candida, Aspergillus, Cryptococcus, and Coccidioides immitis. All of these studies found a higher probability of treatment response when serum trough concentrations determined by bioassay surpassed 6 μg/mL (>1-2 μg/mL by high-performance liquid chromatography). According to studies by Glasmacher et al in patients with hematologic malignancy receiving itraconazole prophylaxis, patients who did not achieve trough concentrations of greater than 0.5 μg/mL (determined by high-performance liquid chromatography) by the first week were at significantly higher risk of subsequent breakthrough aspergillosis. A recent analysis of the association between itraconazole serum concentrations and toxicity reported that serum concentrations greater than 5 μg/mL (determined by high-performance liquid chromatography) or 17 μg/mL (determined by bioassay) were associated with an increased risk of GI adverse effects and peripheral edema.

Voriconazole serum concentrations may vary up to 100-fold from one patient to the next depending on age, drug dose, concurrent illness, underlying liver function, drug-drug interactions, and genetic polymorphisms affecting CYP2C19 metabolism. Pharmacokinetic variability can be especially problematic in patients undergoing hematopoietic or solid organ transplant because these patients have multiple concomitant conditions affecting voriconazole clearance and are at higher risk of severe drug interactions.

Common adverse effects reported with voriconazole (ie, photopsia, liver function test abnormalities) can be retrospectively correlated with serum drug concentrations, but data are conflicting as to whether specific threshold serum voriconazole concentrations are predictive of toxicity. For example, an analysis of the association between hepatotoxicity and serum voriconazole concentrations from phase 3 clinical trials revealed the odds of a greater than 3 times the upper limit of normal increase in levels of aspartate aminotransferase, alkaline phosphatase, and...
bilirubin to be 13.1%, 16.5%, and 17.2%, respectively, for every 1-μg/mL increase in voriconazole plasma concentrations, especially in recipients of hematopoietic stem cell transplants.88 However, no single concentration was predictive of subsequent hepatotoxicity by receiver operator curve analysis, suggesting that elevated voriconazole concentrations were a consequence (not necessarily a cause) of hepatic dysfunction. Although less common toxicities have been reported in the setting of high voriconazole exposures (eg, encephalopathy, hallucinations, hypoglycemia, electrolyte disturbances, pneumonitis), their association with plasma voriconazole concentrations are less well established.

A stronger case for TDM of voriconazole can be made on the basis of clinical efficacy because inadequate drug exposures that cannot be predicted on the basis of dose alone could increase the probability of treatment failure. Exploratory pharmacokinetic-pharmacodynamic analysis of 3736 plasma samples from 1053 patients enrolled in voriconazole therapeutic studies found that the rate of treatment success appeared proportionately lower in patients with mean plasma concentrations less than 0.5 μg/mL than in patients with concentrations between 0.5 and 5 μg/mL.97 The difference in clinical outcome was not statistically significant, however, because of the heterogeneous response rates in each quartile of drug exposure—a reflection of the varied response rate among different patient groups included in the analysis (ie, those receiving transplants, those with lymphoma, those with leukemia). Similarly, patients with possible or proven invasive aspergillosis who have random voriconazole serum concentrations less than 2.05 μg/mL were shown to have poorer treatment responses.100 Subsequent studies in adults101 and pediatric patients48 have also demonstrated that the probability of successful outcome while receiving voriconazole therapy declines when trough serum concentrations in patients are less than 1 μg/mL. Therefore, many experts currently recommend dosing voriconazole to achieve trough concentrations of 1 to 5 μg/mL.86

Collectively, most data from single-institution studies and randomized trials suggest that nearly one-third of patients who receive voriconazole at currently approved dosing may be at increased risk of therapeutic failure due to suboptimal drug exposures.86 The absolute threshold voriconazole concentration (ie, 0.5, 1.0, or 2.0 μg/mL) required for clinical efficacy is not well established and probably varies by infecting pathogen. However, trough concentrations of less than 0.5 μg/mL in patients receiving voriconazole prophylaxis, or trough concentrations of less than 1 to 2 μg/mL in patients receiving treatment for suspected or documented infection, should prompt an increase in the voriconazole dose by 50- to 100-mg increments or a switch to an alternative agent(s), especially if there is evidence of progressing infection.86

Risk factors for impaired posaconazole absorption and suboptimal serum concentrations include graft-vs-host disease of the gut or chemotherapy-associated mucositis, severe nausea and/or diarrhea, poor appetite, and treatment with potent acid suppression therapy or inducers of hepatic phase 1/2 metabolism.42,102-105 In 2 pivotal phase 3 trials that evaluated the effectiveness of posaconazole (200 mg 3 times daily) as antifungal prophylaxis in patients with graft-vs-host disease after hematopoietic stem cell transplant13 or with neutropenia after remission induction chemotherapy for acute myeloid leukemia/myeloid dysplastic syndrome,12 the probability of breakthrough infections while receiving posaconazole therapy increased significantly when random plasma concentrations fell below 0.719 μg/mL.106 Similarly, in an open-label study evaluating posaconazole as salvage therapy for invasive aspergillosis,105 the highest clinical response rates were observed in a cohort of patients who had plasma posaconazole exposures of at least 0.719 to 1.250 μg/mL.

Taken together, these studies indicate that plasma concentrations of posaconazole may serve as a useful surrogate end point for identifying patients at higher risk of drug failure due to inadequate drug absorption. In the absence of more definitive data, trough concentrations greater than 0.5 μg/mL could be considered a practical provisional target trough concentration for patients receiving posaconazole prophylaxis, with targets of 0.5 to 1.5 μg/mL for patients with documented mold infections.86

The frequency and timing of serum sampling for triazole TDM is not well established. Sampling of the trough concentration (immediately before the next dose) once the patient reaches steady state (5-7 days into therapy) is the most practical approach and is less prone to sampling error.86,87 Trough concentrations do not provide sufficient information about drug absorption or AUC but can help identify patients with overall low exposures and excessively rapid drug clearance.87 For drugs such as posaconazole that have a long half-life but are administered in divided daily doses, the serum concentration curve is relatively flat, so even random samples can identify patients with suboptimal plasma concentrations because of poor drug absorption.

TOXICITIES OF ANTIFUNGAL AGENTS

Although the safety and tolerability of systemic antifungal therapy has improved considerably, a growing proportion of heavily immunocompromised patients are receiving systemic antifungal agents for progressively longer treatment...
ANTIFUNGAL PHARMACOLOGY

As a result, clinicians need to be aware of not only the more familiar dose-limiting toxicities associated with systemic antifungal agents (ie, infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents) but also longer-term risks, including recurrent drug interactions, organ dysfunction, and cutaneous reactions and malignancies (Figure 4). Oral itraconazole can cause nausea and GI disturbances associated with the cyclodextrin excipient, making it difficult to tolerate for prolonged treatment courses. Itraconazole has also been described as causing (mostly in older adults) a unique triad of hypertension, hypokalemia, and edema that may be related to a negative inotropic effect of the drug or adrenal suppression. Therefore, prolonged administration of itraconazole is not recommended in patients with a history of heart failure.

Although rash is reported with all antifungal classes in 5% to 15% of patients, voriconazole treatment in ambulatory patients has been associated with unique retinoid-like phototoxic reactions that present with cheilitis, erythema, and occasional blistering. This phototoxic reaction is not prevented through the use of sunscreens but is generally reversible after discontinuation of therapy. However, recent reports have linked this phototoxic reaction to the subsequent development of squamous cell carcinoma and melanoma, suggesting that all patients who receive long-term voriconazole treatment should undergo careful screening for skin cancer, especially if they manifest evidence of photosensitivity or cutaneous photodamage.

CONCLUSION

The introduction of new systemic antifungal agents during the past decade has revolutionized the treatment of invasive mycoses. However, with these new therapies comes a need for increased awareness of the limitations in their spectrum of activity, pharmacokinetics, and risk for pharmacokinetic drug interactions. Newer broad-spectrum triazoles, in particular voriconazole and posaconazole, display significant variability in bloodstream concentrations from one patient to the next that may necessitate TDM in select situations to guide drug therapy and dosing. Long-term toxicities have become more of a concern because ambulatory patients with long-term immunosuppression are taking antifungal therapies for prolonged periods. For most patients, however, the benefits of safer and more effective antifungal therapy vastly outweigh the manageable risks of developing toxicity and undertreating a life-threatening systemic fungal infection.
REFERENCES


The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are now a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
Antiviral Drugs for Viruses Other Than Human Immunodeficiency Virus

RAYMOND R. RAZONABLE, MD

On completion of this article, you should be able to (1) discuss the different regimens for the prevention and treatment of human herpesviruses; (2) discuss options for the prevention and treatment of influenza virus, including infections with resistant strains; and (3) discuss antiviral drugs for the treatment of chronic hepatitis B and C infections, including novel nucleos(t)ide analogues and serine protease inhibitors, respectively.

Most viral diseases, with the exception of those caused by human immunodeficiency virus, are self-limited illnesses that do not require specific antiviral therapy. The currently available antiviral drugs target 3 main groups of viruses: herpes, hepatitis, and influenza viruses. With the exception of the antiviral molecule fomiviren, all antitherase drugs inhibit viral replication by serving as competitive substrates for viral DNA polymerase. Drugs for the treatment of influenza inhibit the ion channel M2 protein or the enzyme neuraminidase. Combination therapy with interferon-α and ribavirin remains the backbone treatment for chronic hepatitis C; the addition of serine protease inhibitors improves the treatment outcome of patients infected with hepatitis C virus genotype 1. Chronic hepatitis B can be treated with interferon or a combination of nucleos(t)ide analogues. Notably, almost all the nucleos(t)ide analogues for the treatment of chronic hepatitis B possess antiviral properties, and they inhibit replication of hepatitis B virus by serving as competitive substrates for its DNA polymerase. Some antiviral drugs possess multiple potential clinical applications, such as ribavirin for the treatment of chronic hepatitis C and respiratory syncytial virus and cidofovir for the treatment of cytomegalovirus and other DNA viruses. Drug resistance is an emerging threat to the clinical utility of antiviral drugs. The major mechanisms for drug resistance are mutations in the viral DNA polymerase gene or in genes that encode for the viral kinases required for the activation of certain drugs such as acyclovir and ganciclovir. Widespread antiviral resistance has limited the clinical utility of M2 inhibitors for the prevention and treatment of influenza infections. This article provides an overview of clinically available antiviral drugs for the primary care physician, with a special focus on pharmacology, clinical uses, and adverse effects.


From the Division of Infectious Diseases, Mayo Clinic, Rochester, MN.

The author has no conflicts of interest to declare.

Address correspondence to Raymond R. Razonable, MD, Division of Infectious Diseases, 200 First St SW, Rochester, MN 55905 (razonable.raymund@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

© 2011 Mayo Foundation for Medical Education and Research

Most diseases caused by viral pathogens are self-limited and do not require specific antiviral therapy. Other than therapies targeting the human immunodeficiency virus (HIV), currently available antiviral drugs in the clinical setting target 3 principal groups of viruses—the herpes, hepatitis, and influenza viruses. This review article is structured to discuss antiviral therapeutics on the basis of these 3 major antiviral categories, with the caveat that some drugs discussed in these sections possess other potential applications, such as ribavirin for the treatment of respiratory syncytial virus (RSV) and cidofovir for the treatment of cytomegalovirus (CMV) and other DNA viral infections. Nucleos(t)ide analogues for the treatment of chronic hepatitis B (CHB) may also possess anti-HIV properties, but their clinical utility for the treatment of HIV will be discussed in a separate article in this symposium. Experimental and novel therapies that have not reached clinical application will not be reviewed.

ANTITHERPES DRUGS

ACYCLOVIR

Acyclovir is a synthetic guanosine analogue used for treating herpes simplex virus (HSV) and varicella zoster virus (VZV) infections. Intravenous (IV) acyclovir provides excellent tissue and fluid penetration, including the cerebrospinal fluid (CSF), whereas oral acyclovir provides modest bioavailability of 15% to 30%. Bioavailability is improved with the use of valacyclovir, the valyl ester formulation of acyclovir. Acyclovir is excreted by glomerular filtration and tubular secretion.

Herpesviruses have varying degrees of susceptibility to acyclovir, with HSV type 1 (HSV-1) being most susceptible, followed by HSV type 2 (HSV-2) and VZV, and to a lesser extent Epstein-Barr virus (EBV). High acyclovir concentrations may also inhibit CMV in vitro, but acyclovir is not recommended clinically for CMV treatment. Acyclovir is not active against human herpesvirus (HHV) 6, 7, and 8.

To exert antiviral activity, acyclovir must be converted to acyclovir-triphosphate; this process is initially catalyzed by...
viral thymidine kinase (TK) and subsequently by human enzymes. Acyclovir-triphosphate serves as a competitive substrate for viral DNA polymerase, and its incorporation into the DNA chain results in termination of viral replication.

Acyclovir is approved for the treatment of primary and recurrent genital HSV infection (Table 1).\textsuperscript{2,4,5} Topical acyclovir may be used to treat genital herpes, but the oral formulation is generally recommended\textsuperscript{6}; IV acyclovir is used for severe cases.\textsuperscript{1,4} Suppressive therapy with oral acyclovir is also indicated to reduce the incidence of recurrent genital herpes.\textsuperscript{2,7}

Oral acyclovir is modestly efficacious against orolabial herpes. In immunocompetent individuals, orolabial herpes is often self-limited, and antiviral treatment is generally not recommended.\textsuperscript{7} However, oral acyclovir may be indicated for severe cases, for those with recurrent orolabial herpes, and in those who are immunocompromised.\textsuperscript{6,8}

Intravenous acyclovir is the first-line treatment for HSV encephalitis\textsuperscript{9} and should be started as soon as the disease is suspected clinically. Magnetic resonance imaging of the brain typically demonstrates temporal lobe involvement, and diagnosis is confirmed by detection of HSV DNA in the CSF. Major studies have evaluated the efficacy of 10 days of acyclovir treatment for HSV encephalitis; however, the recommended duration of treatment in the clinical setting is 2 to 3 weeks because shorter durations have been associated with relapse.\textsuperscript{10} The treatment duration may be further prolonged in immunocompromised patients.\textsuperscript{8}

Acyclovir is also approved by the US Food and Drug Administration (FDA) for the treatment of VZV\textsuperscript{11,12}; however, young immunocompetent patients with zoster may not require treatment if the lesions are localized and have been present for more than 72 hours. Intravenous acyclovir is recommended for patients with disseminated zoster disease or visceral involvement. Acyclovir treatment of zoster reduces duration of viral shedding, formation of new lesions, and short- and long-term neuralgia.\textsuperscript{3,13} Therapy should be started early, but even delayed initiation of acyclovir may still be beneficial in immunocompromised patients. Short-course prednisone may be added as an adjunct to acyclovir treatment of zoster to improve quality of life, especially in elderly patients.

Acyclovir has been used in the treatment of acute retinal necrosis (which is associated with HSV or VZV), eczema herpeticum, and oral hairy leukoplakia due to EBV. Oral acyclovir is used to prevent HSV during the early period after transplant in patients not receiving ganciclovir or valganciclovir prophylaxis.\textsuperscript{14}

Acyclovir is generally well tolerated. However, IV acyclovir may cause reversible nephrotoxicity in 5% to 10% of patients because of intratubular precipitation of acyclovir crystals. Acyclovir crystalline nephropathy is more common when acyclovir is given as a rapid infusion (reaching serum concentrations >25 µg/mL)\textsuperscript{15} and in patients with dehydration and preexisting renal impairment.\textsuperscript{16} Adequate hydration, a slower rate of infusion, and dosing based on renal function may reduce this risk. Reversible neurologic symptoms such as delirium and seizures may occur rarely in elderly people and those with renal impairment; this toxicity has been associated with high serum acyclovir concentrations\textsuperscript{17} and high CSF levels of its metabolite 9-carboxymethoxymethylguanine.\textsuperscript{16-19} Other adverse effects are gastrointestinal symptoms, myelosuppression, and rash.\textsuperscript{3,20,21}

Acyclovir-resistant HSV has been reported, especially in immunocompromised patients.\textsuperscript{22-24} Resistance occurs by selection of viral mutants that are deficient in TK (which results in an inability to activate acyclovir) or that have altered DNA polymerase with reduced affinity to acyclovir-triphosphate.\textsuperscript{23}

**Brivudin**

Brivudin is a 5′-halogenated thymidine nucleoside analogue that is highly active against HSV-1 and VZV.\textsuperscript{25,26} Brivudin is phosphorylated by viral TK and cellular kinases to brivudin-triphosphate, which serves as a competitive inhibitor of viral DNA polymerase, thereby terminating viral DNA synthesis. It is available in some countries for the treatment of herpes zoster and herpes simplex. However, concerns about its toxicity halted its clinical development in the United States. Its metabolite, bromovinyluracil, irreversibly inhibits dihydropyridine dehydrogenase, which regulates nucleoside metabolism. Coadministration with 5-fluorouracil has resulted in lethal bone marrow toxicity and severe gastrointestinal toxicity.\textsuperscript{25,26}

**Cidofovir**

Cidofovir is a nucleoside analogue used for the treatment of CMV, other herpesviruses, and other DNA viral infections.\textsuperscript{27} It is available as an IV formulation, and an oral prodrug of cidofovir (known as CMX-001) is under clinical development.\textsuperscript{28} This investigational lipid ester formulation of cidofovir has enhanced bioavailability, resulting in improved 50% inhibitory concentrations.\textsuperscript{29} Direct intraocular injection of cidofovir is contraindicated due to ocular hypopyon.\textsuperscript{27} Serum cidofovir concentrations decline rapidly after IV infusion, with a half-life of 2 hours; however, the intracellular half-life of active cidofovir-diphosphate is as long as 65 hours. Cidofovir is eliminated by glomerular filtration and tubular secretion; probenecid reduces its excretion by blocking tubular secretion.\textsuperscript{29,30}

Cidofovir is phosphorylated by cellular kinases into cidofovir-diphosphate, a competitive substrate for viral
### TABLE 1. Suggested Antiviral Drugs for the Treatment of Herpesvirus Infections

<table>
<thead>
<tr>
<th>Virus</th>
<th>Clinical disease</th>
<th>Drug name (route)</th>
<th>Recommended dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex viruses 1 and 2</td>
<td>Mucocutaneous disease</td>
<td>Acyclovir (IV)</td>
<td>5 mg/kg IV every 8 h</td>
<td>IV therapy is preferred for severe and disseminated disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400 mg orally 3 times daily</td>
<td>Risk of crystalline nephropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>800 mg orally twice daily</td>
<td>Localized disease and genital herpes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200 mg orally 5 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acyclovir (oral)</td>
<td>1 g orally twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500 mg orally twice daily</td>
<td>First episode of genital herpes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir (oral)</td>
<td>10 mg/kg IV every 8 h</td>
<td>Recurrent episodes of genital herpes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400 mg orally twice daily</td>
<td>Risk of crystalline nephropathy</td>
</tr>
<tr>
<td></td>
<td>HSV encephalitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-term suppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicella zoster virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicella zoster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV disease in transplant recipients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acyclovir (IV)</td>
<td>5 mg/kg IV every 12 h</td>
<td>IV therapy is preferred for severe CMV disease, gastrointestinal disease, pneumonia, and encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir (oral)</td>
<td>500 mg orally once daily</td>
<td>Recurrence of &lt;9 episodes per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-12 mg/kg IV every 12 h</td>
<td>Recurrence of &gt;9 episodes per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>600-800 mg orally 5 times daily</td>
<td>Less preferred than valacyclovir because of poor bioavailability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 g orally every 6 h</td>
<td>Preferred oral therapy for mild or localized disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir (oral)</td>
<td>1 g orally every 3 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV disease in transplant recipients</td>
<td>Ganciclovir (IV)</td>
<td>5 mg/kg IV every 12 h</td>
<td>IV therapy is preferred for severe CMV disease, gastrointestinal disease, pneumonia, and encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valganciclovir (oral)</td>
<td>900 mg orally twice daily</td>
<td>Recurrence of &lt;9 episodes per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence of &gt;9 episodes per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foscarnet (IV)</td>
<td>Induction: 90 mg/kg every 12 h OR</td>
<td>Risk of myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 90-120 mg/kg every 24 h</td>
<td>Second-line therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indicated for ganciclovir-resistant CMV disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cidofovir (IV)</td>
<td>Induction: 5 mg/kg per dose once weekly for 2 doses</td>
<td>Risk of nephrotoxicity and electrolyte abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 5 mg/kg every 2 wk</td>
<td>Duration of therapy is guided by CMV surveillance using PCR or pp65 antigenemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiviral prophylaxis for CMV prevention in transplant recipients</td>
<td>Valganciclovir (oral)</td>
<td>900 mg orally once daily</td>
<td>Preferred drug for CMV prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ganciclovir (IV)</td>
<td>5 mg/kg IV once daily</td>
<td>Duration is generally for 3-6 mo; may be longer for lung transplant recipients Myelosuppression is major adverse effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 g orally 3 times daily</td>
<td>Preferred for intestinal transplant recipients or in clinical situations in which absorption is a concern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ganciclovir (oral)</td>
<td>2 g orally 4 times daily</td>
<td>Effective for CMV prevention but no longer a preferred drug because of its poor bioavailability; valganciclovir is preferred</td>
</tr>
</tbody>
</table>

(continued on next page)
## CMV Preemptive therapy for asymptomatic CMV infection in transplant recipients

**Valganciclovir (oral)**

<table>
<thead>
<tr>
<th>Drug name (route)</th>
<th>Recommended dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg orally twice daily</td>
<td>CMV replication is detected by weekly CMV surveillance using PCR or pp65 antigenemia. Preferred drug for the treatment of asymptomatic CMV infection in solid organ and hematopoietic stem cell transplant recipients.</td>
<td></td>
</tr>
</tbody>
</table>

**Ganciclovir (IV)**

| 5 mg/kg IV every 12 h | Less preferred than valganciclovir because of the logistics of IV administration. Oral ganciclovir should not be used for treating active CMV infection. | |

**CMV retinitis in HIV-infected patients**

**Valganciclovir (oral)**

| Induction: 900 mg orally twice daily for 14-21 d | For sight-threatening retinitis, use in combination with ganciclovir intravitreal implant (see below). | |
| Maintenance: 900 mg orally once daily until immune reconstitution |  |

**Ganciclovir (IV)**

| Induction: 5 mg/kg IV every 12 h for 14-21 d | For sight-threatening retinitis, use in combination with ganciclovir intravitreal implant (see below). | |
| Maintenance: 5 mg/kg IV every 24 h until immune reconstitution |  |

**Ganciclovir (intraocular implant)**

| One sustained-release intravitreal implant (4.5 mg/implant) every 6-8 mo | Replace every 6-8 mo until immune reconstitution. Use in combination with systemic ganciclovir (or valganciclovir) because of the systemic nature of CMV disease. Second-line therapy indicated for ganciclovir-resistant CMV disease. High risk of nephrotoxicity and electrolyte abnormalities. Alternative treatment of CMV disease resistant to ganciclovir. Requires concomitant hydration and probenecid use. | |

**Foscarnet (IV)**

| Induction: 90 mg/kg every 12 h OR 60 mg/kg every 8 h | Second-line therapy indicated for ganciclovir-resistant CMV disease. High risk of nephrotoxicity and electrolyte abnormalities. Alternative treatment of CMV disease resistant to ganciclovir. Requires concomitant hydration and probenecid use. | |
| Maintenance: 90-120 mg/kg every 24 h |  |

**Cidofovir (IV)**

| Induction: 5 mg/kg per dose once weekly for 2 doses | High risk of nephrotoxicity; requires concomitant hydration and probenecid use. | |
| Maintenance: 5 mg/kg every 2 wk |  |

**CMV disease other than retinitis in HIV-infected patients**

**Valganciclovir (oral)**

| Induction: 900 mg orally twice daily for 14-21 d | Preferred for severe disease (e.g., pneumonitis, encephalitis) and for those with poor intestinal absorption. | |
| Maintenance: 900 mg orally once daily until immune reconstitution |  |

**Ganciclovir (IV)**

| Induction: 5 mg/kg IV every 12 h for 14-21 d | Preferred for severe disease (e.g., pneumonitis, encephalitis) and for those with poor intestinal absorption. | |
| Maintenance: 5 mg/kg IV every 24 h until immune reconstitution |  |

**Foscarnet (IV)**

| Induction: 90 mg/kg every 12 h OR 60 mg/kg every 8 h | Second-line therapy indicated for ganciclovir-resistant CMV disease. High risk of nephrotoxicity and electrolyte abnormalities. | |
| Maintenance: 90-120 mg/kg every 24 h |  |

**Cidofovir (IV)**

| Induction: 5 mg/kg per dose once weekly for 2 doses | Alternative treatment for CMV disease resistant to ganciclovir. Requires concomitant hydration and probenecid use. | |
| Maintenance: 5 mg/kg every 2 wk |  |

---

**DNA polymerase, thereby halting viral DNA synthesis.**

The major clinical indication for cidofovir is the treatment of CMV retinitis in HIV-infected patients (Table 1).31 Cidofovir is also used as rescue therapy for immunocompromised patients with CMV disease resistant or unresponsive to ganciclovir.32 Because activation of cidofovir does not rely on viral kinases, it retains activity against CMV with the UL97 mutation and HSV with the TK mutation.33 Resistance to cidofovir occurs when the virus develops mutations in the DNA polymerase gene (ie, CMV-UL54 gene...
mutations). Cidofovir has also been used off-label for various illnesses, such as acyclovir-resistant HSV disease, condyloma acuminatum, BK virus–associated hemorrhagic cystitis, JC virus–associated progressive multifocal leukoencephalopathy, and other infections due to double-stranded DNA viruses.

Nephrotoxicity is the most common serious adverse effect of cidofovir. The incidence and severity of nephrotoxicity may be reduced by hydration and probenecid. Blood cell counts should be monitored to assess myelosuppression, and ophthalmological surveillance is recommended because of the risk of ocular hypotony, uveitis, and iritis.

**FAMCICLOVIR**

Famiclovir is a diacetyl 6-deoxy analogue of penciclovir. Oral famciclovir is rapidly absorbed and achieves a bioavailability of 77%. Famiclovir is metabolized into penciclovir, reaching peak plasma penciclovir concentrations within 1 hour. Because of extensive hepatic metabolism, virtually no famciclovir is detectable in plasma. Famiclovir is excreted renally as penciclovir and its 6-deoxy precursor.

Famiclovir is active against HSV-1, HSV-2, and VZV, and, to a lesser extent, against EBV. Its mechanism of action is through penciclovir; penciclovir triphosphate inhibits herpes DNA synthesis by acting as a substrate for viral DNA polymerase. The major clinical indications for famciclovir use are treatment of herpes zoster, recurrent genital herpes, and EBV. Unlike ganciclovir, foscarnet does not require intracellular conversion to active triphosphate, thus maintaining activity against herpesviruses with TK or UL97 kinase mutations.

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS. It has been used to treat other CMV diseases in immunocompromised patients, especially those unable to tolerate ganciclovir and those infected with ganciclovir-resistant virus. Foscarnet is also used for treating acyclovir-resistant mucocutaneous HSV and VZV in immunocompromised patients. On rare occasion, it has been used for prevention of CMV in transplant recipients; however, its toxicity limits this clinical indication.

Nephrotoxicity is the most common serious adverse effect of foscarnet, affecting 30% of patients. It is caused by deposition of foscarnet crystals in the glomerular capillary lumen. Foscarnet may cause myelosuppression, with anemia as the most common effect. It can chelate bivalent metal ions and may lead to reductions in ionized calcium. Other electrolyte disturbances are hypokalemia, hypomagnesemia, and hypophosphatasemia, which could manifest as paresthesias, cardiac dysrhythmias, and neurologic symptoms, including seizures. Patients should be hydrated to prevent nephrotoxicity, and electrolyte abnormalities should be corrected to avoid cardiac and neurologic complications.

**GANCICLOVIR**

Ganciclovir is an acyclic 2′-deoxyguanosine analogue for the management of CMV. It is available in oral and parenteral formulations. Oral ganciclovir is poorly absorbed, with a bioavailability of only 5%. Management of active CMV disease is therefore with IV ganciclovir or its oral valyl prodrug valganciclovir. Intravitreal ganciclovir im-
plants are also available, with minimal systemic absorption. Ganciclovir is excreted renally.

Ganciclovir undergoes triphosphorylation to become active, with the initial monophosphorylation catalyzed by UL97-encoded kinase and subsequently by cellular kinases. Ganciclovir triphosphate inhibits viral DNA synthesis through competitive incorporation during viral DNA synthesis, thereby leading to DNA chain termination. In vitro, it is 10 times more potent than acyclovir against CMV and EBV and is just as effective as acyclovir against HSV-1, HSV-2, and VZV. Ganciclovir is active against HHV-6 and HHV-8 but not against HHV-7.

Ganciclovir is approved for the treatment of CMV retinitis in patients with AIDS, the treatment of herpes simplex keratitis, and CMV prophylaxis in transplant recipients. Intravenous ganciclovir may also be used to treat other forms of CMV disease, such as colitis or esophagitis. Induction therapy with IV ganciclovir for CMV retinitis in patients with AIDS has an efficacy of 85% to 95% in stabilizing disease. Because it is poorly absorbed, oral ganciclovir should not be used for induction treatment of CMV disease. Because CMV disease often recurs or progresses with AIDS, oral or IV ganciclovir (or valganciclovir) is given as maintenance therapy until immune reconstitution is achieved. Intravitreal ganciclovir may also be surgically implanted for the treatment of CMV retinitis, although this treatment should be used together with systemic therapy with IV ganciclovir or oral valganciclovir.

Oral ganciclovir may be used to prevent CMV in patients with AIDS; however, the benefit of this strategy is not as pronounced in the era of highly active antiretroviral therapy. Although IV and oral ganciclovir have also been used to prevent CMV disease in transplant recipients, valganciclovir is currently the preferred drug for this indication. Intravenous ganciclovir is also used as a first-line treatment of CMV disease in bone marrow and solid organ transplant recipients.

Reversible bone marrow suppression is the most common adverse effect of ganciclovir. Other adverse effects of the drug are rash, pruritus, diarrhea, nausea, vomiting, and increased levels of serum creatinine and liver enzymes. Neurotoxicity may occur occasionally.

Resistance to ganciclovir occurs most commonly in severely immunocompromised patients with prolonged exposure to the drug. The most common mechanism for ganciclovir resistance is UL97 gene mutation; this mutation leads to deficiency in the viral kinase that is necessary for the initial phosphorylation of ganciclovir into its active form. A less common mechanism is a mutation in the UL54 gene, which encodes for the CMV DNA polymerase.

Penciclovir

Penciclovir is an acyclic guanine analogue that is chemically similar to acyclovir. Because it is poorly absorbed from the gastrointestinal tract, it is only available as topical therapy for mucocutaneous herpes. For systemic use, penciclovir has been reformulated into the oral prodrug famiclovir.

The antiviral activity of penciclovir is similar to that of acyclovir, with efficacy against HSV-1, HSV-2, and VZV, and, to a lesser extent, against EBV. Penciclovir is monophosphorylated by TK and subsequently by cellular kinases into active penciclovir-triphosphate, which inhibits herpes DNA polymerase activity by serving as a competitive inhibitor of deoxyguanosine triphosphate. Penciclovir is approved as topical therapy for recurrent herpes labialis, resulting in a faster healing rate and reduction in pain and viral shedding.

Valacyclovir

Valacyclovir, an L-valyl ester prodrug of acyclovir, provides a higher bioavailability (55%) than oral acyclovir. After absorption, valacyclovir is hydrolyzed almost completely to acyclovir by first-pass intestinal and hepatic metabolism. It achieves peak serum concentration in 1 to 3 hours. Serum acyclovir levels are much higher with valacyclovir than with oral acyclovir.

The mechanism of action and spectrum of activity of valacyclovir is identical to those of acyclovir. It is approved for the treatment of initial or recurrent episodes of genital herpes and for the treatment of recurrent herpes labialis. Treatment is most efficacious when initiated at the earliest onset of symptoms. Suppressive therapy with valacyclovir is recommended to prevent recurrent genital herpes and has the potential to reduce transmission to sexual partners.

Valacyclovir is approved for treatment of VZV. Varicella often resolves without antiviral therapy in those who are immunocompetent. However, in immunocompromised patients, such as HIV-infected patients and transplant recipients, valacyclovir may be used to treat varicella, even if it is uncomplicated. Valacyclovir is the most commonly used drug for the treatment of zoster. In a randomized double-blind trial of older immunocompetent patients, valacyclovir was as effective as acyclovir, with similar resolution rates of cutaneous zoster but accelerated resolution of herpetic pain and a lower risk of postherpetic neuralgia. The typical course of zoster treatment is 7 days, and the first dose should be started within 48 hours of rash onset. Treatment can be prolonged, continuing until all lesions have crusted, in immunocompromised patients.

Valacyclovir has also been used to treat acute retinal necrosis and for prevention of CMV disease in kidney transplantation from donors with either CMV or EBV infection or from patients who have been seroconverted posttransplantation. In patients with advanced AIDS, oral or IV ganciclovir (or valganciclovir) is given as maintenance therapy until immune reconstitution is achieved. Intravitreal ganciclovir may also be surgically implanted for the treatment of CMV retinitis, although this treatment should be used together with systemic therapy with IV ganciclovir or oral valganciclovir.

Oral ganciclovir may be used to prevent CMV in patients with AIDS; however, the benefit of this strategy is not as pronounced in the era of highly active antiretroviral therapy. Although IV and oral ganciclovir have also been used to prevent CMV disease in transplant recipients, valganciclovir is currently the preferred drug for this indication. Intravenous ganciclovir is also used as a first-line treatment of CMV disease in bone marrow and solid organ transplant recipients.

Reversible bone marrow suppression is the most common adverse effect of ganciclovir. Other adverse effects of the drug are rash, pruritus, diarrhea, nausea, vomiting, and increased levels of serum creatinine and liver enzymes. Neurotoxicity may occur occasionally.

Resistance to ganciclovir occurs most commonly in severely immunocompromised patients with prolonged exposure to the drug. The most common mechanism for ganciclovir resistance is UL97 gene mutation; this mutation leads to deficiency in the viral kinase that is necessary for the initial phosphorylation of ganciclovir into its active form. A less common mechanism is a mutation in the UL54 gene, which encodes for the CMV DNA polymerase.
transplant recipients. Although ganciclovir is the backbone for CMV prevention in transplant recipients, the efficacy of valacyclovir prophylaxis for CMV prevention was demonstrated in kidney transplant recipients. However, valacyclovir has not been proven effective for preventing CMV in heart, liver, lung, pancreas, and small bowel transplant recipients.

The adverse effects of valacyclovir are similar to those of acyclovir. At very high doses, neurotoxicity characterized by confusion, hallucinations, and seizures may occur, especially in elderly patients and in those with dehydration and renal disease. The mechanism of resistance for valacyclovir is identical to that of acyclovir (TK mutation); however, achieving higher serum acyclovir levels with valacyclovir could reduce the risk of resistance compared with oral acyclovir.

**Valganciclovir**

Valganciclovir is the L-valyl ester prodrug of ganciclovir. Oral valganciclovir is well absorbed and converted to ganciclovir by first-pass intestinal or hepatic metabolism. The bioavailability of ganciclovir after valganciclovir administration is about 60%, and peak plasma concentrations are achieved in 1 to 3 hours.

Valganciclovir was first approved by the FDA for treatment of CMV retinitis in patients with AIDS. For immediate sight-threatening lesions, valganciclovir is used in combination with an intravitreal ganciclovir implant. Valganciclovir is also used for preventing CMV disease in high-risk CMV donor-positive/recipient-negative recipients of kidney, heart, or kidney-pancreas transplants.

In the United States, valganciclovir is not approved for preventing CMV disease in liver recipients because of a higher incidence of tissue-invasive CMV disease in patients who received valganciclovir vs oral ganciclovir prophylaxis. In other countries, valganciclovir is used for preventing CMV disease in all solid organ transplant recipients. It has recently gained approval for the prevention of CMV disease in pediatric heart and kidney transplant recipients. It can also be used to preemptively treat asymptomatic CMV infection in transplant recipients.

Valganciclovir was recently demonstrated to be as effective as IV ganciclovir for treating mild to moderate CMV disease in transplant recipients.

Bone marrow suppression is the most common adverse effect of valganciclovir. Gastrointestinal manifestations, such as diarrhea, nausea, and vomiting, may be observed. Resistance to valganciclovir occurs through mechanisms identical to those underlying ganciclovir resistance, ie, through mutations in the UL97 gene, which encodes for CMV kinase, and the UL54 gene, which encodes for CMV DNA polymerase.

**Vidarabine**

Vidarabine, a purine nucleoside obtained from *Streptomyces antibioticus*, was historically used for treating HSV and VZV. Acyclovir has since become the preferred drug for these conditions. Vidarabine is currently available only as an ophthalmic solution for treating recurrent epithelial keratitis and acute keratoconjunctivitis. Once phosphorylated into its active form, vidarabine inhibits viral DNA polymerase. Adverse effects of ophthalmic vidarabine include irritation, pain, photophobia, lacrimation, and occlusion of the lacrimal duct.

**Antiviral Drugs for Influenza**

**M₂ Inhibitors**

**Amantadine.** Amantadine is a symmetric tricyclic amine that inhibits replication of influenza A virus by impairing the function of the membrane protein M₂. Present only in influenza A virus, M₂ is an acid-activated ion channel required for nucleocapsid release. Amantadine is well absorbed after oral administration. It has an elimination half-life of 11 to 15 hours and is excreted by glomerular filtration and tubular secretion.

Amantadine is effective for treating susceptible influenza A virus infection. It results in a more rapid functional recovery and reduces the duration of fever and other symptoms by about 1 day, if given within 48 hours of disease onset. Amantadine is effective as prophylaxis for preventing symptomatic influenza A infection in exposed persons. It is usually given for 14 days or for at least 7 days after the last confirmed illness. Seasonal influenza vaccination, however, remains the preferred method for prevention.

Amantadine is generally well tolerated. Among its adverse effects are mild neurologic symptoms such as anxiety, disorientation, and headache, especially in elderly patients and those taking neuroaffective drugs. Emergence of amantadine resistance has limited its use in the clinical setting. Amantadine resistance, characterized by amino acid substitutions in the M₂ protein, emerges within 2 to 4 days of treatment. Because of widespread resistance, amantadine is no longer recommended for empiric treatment of influenza. M₂ mutation confers cross-resistance with rimantadine.

**Rimantadine.** Rimantadine is a symmetric tricyclic amine that inhibits influenza virus. It is well absorbed after oral administration, reaching peak plasma concentration...
in 3 to 5 hours. Rimantadine undergoes extensive hepatic metabolism before it is excreted in the urine.

The mechanism of action of rimantadine is similar to that of amantadine; it inhibits the ion channel function of M2, thereby inhibiting viral uncoating. Rimantadine is indicated for prevention and treatment of influenza A virus\(^\text{89}\); however, its clinical utility is currently limited by drug resistance.\(^\text{96,97}\) A few trials that compared amantadine and rimantadine suggested similar efficacy; however, neuropsychiatric adverse events are less severe and frequent with rimantadine.

**NEURAMINIDASE INHIBITORS**

**Oseltamivir.** Oseltamivir phosphate is a prodrug of oseltamivir carboxylate, which is an inhibitor of neuraminidase that is essential in the replication of influenza A and B viruses.\(^\text{98}\) Oral oseltamivir is well absorbed and reaches peak serum concentrations in 1 hour. Bioavailability of oseltamivir phosphate is at least 75%. The prodrug oseltamivir phosphate undergoes extensive hepatic metabolism via ester hydrolysis. More than 99% of active oseltamivir carboxylate is excreted renally.

Oseltamivir carboxylate, the active drug metabolite, selectively blocks viral neuraminidase, thereby preventing the release of virus from infected cells.\(^\text{98}\) Oseltamivir is approved for the treatment of children (≥1 year) and adults with influenza A or B viral infections.\(^\text{98}\) Treatment should start within 48 hours of disease onset and continue for 5 days. Oseltamivir is as effective as the other neuraminidase inhibitor, zanamivir, in reducing the febrile period during infection with influenza A (H1N1), influenza A (H3N2), and influenza B virus.\(^\text{99}\)

Oseltamivir is also used for postexposure prophylaxis against influenza A and B, including pandemic strains. For this indication, oseltamivir should be started within 48 hours of exposure and continued daily for at least 10 days or for up to 6 weeks during an outbreak. A systematic review reported no statistically significant difference between oseltamivir and zanamivir prophylaxis for preventing symptomatic influenza among immunocompetent adults.\(^\text{100}\)

The most common adverse effects of oseltamivir are nausea, vomiting, diarrhea, abdominal pain, insomnia, and vertigo. Neuropsychiatric adverse effects, including delirium, abnormal behavior, and hallucinations, have been reported. Oseltamivir-resistant influenza A virus has been reported.\(^\text{101-103}\) Mutations in the neuraminidase gene, such as R292K\(^\text{101}\) and H274Y,\(^\text{98}\) account for oseltamivir resistance. Surveillance conducted during the 2009 H1N1 influenza pandemic detected sporadic and infrequent incidence of oseltamivir-resistant pandemic (H1N1) 2009 influenza virus. All resistant viruses had neuraminidase mutations (most commonly H275Y mutation) that conferred resistance to oseltamivir, but not to zanamivir.\(^\text{104}\) Oseltamivir resistance among influenza B viruses occurs less frequently.\(^\text{105}\)

**Zanamivir.** Zanamivir is an inhaled neuraminidase inhibitor that is used for the treatment and prophylaxis of influenza A and B viruses.\(^\text{106}\) Zanamivir is not available orally since it is poorly absorbed.\(^\text{106}\) Inhaled zanamivir produces high concentrations in the respiratory tract where influenza virus infection occurs. About 4% to 20% of inhaled zanamivir is absorbed systemically, producing peak serum concentrations at 1 to 2 hours. The absorbed drug is not metabolized and is excreted unchanged in the urine, while the unabsorbed drug is excreted in the feces.\(^\text{106}\)

The mechanism of action of zanamivir is similar to oseltamivir, by inhibiting neuraminidase, which is essential for release of newly formed viral particles from infected cells.\(^\text{106}\) For treatment, zanamivir can be given once daily for 10 days as postexposure prophylaxis of influenza A and B in household or close contacts. Zanamivir prophylaxis during community outbreaks may be given for 28 days. Zanamivir has occasionally been given IV to treat critically ill patients with influenza.\(^\text{107,108}\)

Inhaled zanamivir is well tolerated.\(^\text{106}\) Acute bronchospasm with decline in respiratory function has been reported; a bronchodilator should be available if given as treatment for patients with underlying pulmonary disease. Other adverse effects include headache and gastrointestinal symptoms. Hypersensitivity reactions and neuropsychiatric adverse effects occur rarely.\(^\text{109}\)

**ANTIVIRAL DRUGS FOR HEPATITIS AND OTHER VIRUSES**

**INTERFERONS**

Interferons (IFNs) are naturally occurring proteins produced in response to viral infection.\(^\text{110}\) The 3 major classes of IFNs are α, β, and γ; IFN-α and IFN-β are further classified as type I, whereas IFN-γ is type II.\(^\text{110}\) Available only in parenteral formulation, more than 80% of a subcutaneous (SC) or intramuscular dose of IFN-α is absorbed.\(^\text{110}\) After an intramuscular injection, peak IFN concentrations occur within 4 to 8 hours and return to baseline levels in 16 to 24 hours.\(^\text{110}\) Pegylation, which is the process of attachment of IFN to a large inert polyethylene glycol, markedly reduces the rate of absorption and excretion of IFN and therefore increases its plasma concentration.\(^\text{111}\) For example, after an SC dose of peginterferon α-2b, the peak serum concentration occurs in 15 to 44 hours, high concentrations are maintained for 48 to 72 hours, and the mean terminal half-life is about 40 hours.\(^\text{110}\) In contrast, the peak serum concentration of peginterferon α-2a is reached in 72 to 96 hours after...
an SC dose, and the mean terminal half-life is 160 hours.\textsuperscript{110} Interferon-\(\alpha\) undergoes extensive renal catabolism, and negligible amounts of IFN are excreted in the urine.

Interferons have multiple overlapping biological activities, including antiviral, antiproliferative, and immunoregulatory functions. After binding to receptors, IFNs initiate a cascade of events that lead to various cellular responses, such as inhibition of virus replication, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Interferons have been used in treating multiple viral infections and are most commonly used for treating chronic viral hepatitis.\textsuperscript{112} Interferon-\(\alpha\) was the first drug approved for treatment of compensated liver disease due to CHB; it is not approved for treating acute hepatitis B. For CHB, IFN-\(\alpha\)-2a or \(\alpha\)-2b is given parenterally, depending on dosing schedule, for 4 to 6 months or up to 48 weeks.\textsuperscript{112,113} Interferon was most effective in patients with recently acquired hepatitis B virus (HBV), high pretreatment levels of alanine aminotransferase (ALT), and low levels of HBV DNA. Subcutaneous peginterferon-\(\alpha\) is as effective or slightly more effective than SC IFN-\(\alpha\).\textsuperscript{114} Likewise, SC peginterferon-\(\alpha\) may be more effective than lamivudine in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB,\textsuperscript{115-117} and the addition of lamivudine to peginterferon-\(\alpha\) did not significantly enhance efficacy.\textsuperscript{118} Interferon-\(\alpha\) is effective in patients with HBV and hepatitis D virus coinfection,\textsuperscript{119} although they are less responsive than patients infected with HBV alone.\textsuperscript{120} Guidelines for the management of CHB in HIV-infected patients were recently published\textsuperscript{121,122}; for patients not requiring anti-HIV therapy, peginterferon-\(\alpha\) for 12 months is considered a therapeutic option. Lamivudine and the other antiviral nucleos(t)ides are most commonly and aplastic anemia (rarely), cardiovascular disorders (eg, arrhythmias), endocrine disorders (eg, thyroid disorders), and pulmonary disorders (eg, dyspnea and pneumonitis).\textsuperscript{140-142} Patients at risk for developing depression are those with preexisting mood and anxiety dis-

Interferons have multiple overlapping biological activities, including antiviral, antiproliferative, and immunoregulatory functions. After binding to receptors, IFNs initiate a cascade of events that lead to various cellular responses, such as inhibition of virus replication, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Interferons have been used in treating multiple viral infections and are most commonly used for treating chronic viral hepatitis.\textsuperscript{112} Interferon-\(\alpha\) was the first drug approved for treatment of compensated liver disease due to CHB; it is not approved for treating acute hepatitis B. For CHB, IFN-\(\alpha\)-2a or \(\alpha\)-2b is given parenterally, depending on dosing schedule, for 4 to 6 months or up to 48 weeks.\textsuperscript{112,113} Interferon was most effective in patients with recently acquired hepatitis B virus (HBV), high pretreatment levels of alanine aminotransferase (ALT), and low levels of HBV DNA. Subcutaneous peginterferon-\(\alpha\) is as effective or slightly more effective than SC IFN-\(\alpha\).\textsuperscript{114} Likewise, SC peginterferon-\(\alpha\) may be more effective than lamivudine in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB,\textsuperscript{115-117} and the addition of lamivudine to peginterferon-\(\alpha\) did not significantly enhance efficacy.\textsuperscript{118} Interferon-\(\alpha\) is effective in patients with HBV and hepatitis D virus coinfection,\textsuperscript{119} although they are less responsive than patients infected with HBV alone.\textsuperscript{120} Guidelines for the management of CHB in HIV-infected patients were recently published\textsuperscript{121,122}; for patients not requiring anti-HIV therapy, peginterferon-\(\alpha\) for 12 months is considered a therapeutic option. Lamivudine and the other antiviral nucleos(t)ides for the treatment of HBV often have anti-HIV properties and may result in the development of HIV resistance if given as monotherapy in HBV-HIV coinfected patients.

Interferon-\(\alpha\)-2a and -2b are approved for the treatment of chronic hepatitis C (CHC); however, they are not approved for acute hepatitis C. A meta-analysis found that IFN-\(\alpha\) for at least 12 months had the best risk-benefit ratio for patients with CHC.\textsuperscript{123} Once-weekly peginterferon-\(\alpha\) was more effective than IFN-\(\alpha\) given 3 times weekly in patients with CHC.\textsuperscript{124-126} However, combination therapy with IFN-\(\alpha\) and oral ribavirin is more effective than either drug used alone.\textsuperscript{127} Combining oral ribavirin with peginterferon-\(\alpha\) may be more effective than combining it with IFN-\(\alpha\).\textsuperscript{128,129} Therefore, the British Society for Gastroenterology and the American Association for the Study of Liver Diseases\textsuperscript{130} recommends once-weekly SC peginterferon-\(\alpha\) combined with oral ribavirin as the first line of treatment of CHC. The recommended duration of treatment of CHC in patients not infected with HIV is 24 weeks (for hepatitis C virus [HCV] genotype 2 or 3) or 48 weeks (for HCV genotype 1).

For patients coinfected with HIV and HCV, the rate of intolerance to a combination regimen of IFN-\(\alpha\) and ribavirin is higher and the rate of sustained virologic response (SVR) lower than in patients infected with HCV alone.\textsuperscript{131-133} Use of peginterferon-\(\alpha\) resulted in a higher SVR rate than use of IFN-\(\alpha\).\textsuperscript{131,133} The APRICOT study reported an SVR rate of 40% for patients treated with peginterferon-\(\alpha\) plus ribavirin, compared with 20% for those treated with peginterferon-\(\alpha\) monotherapy, and 12% for those treated with IFN-\(\alpha\) plus ribavirin.\textsuperscript{132} A lower SVR rate to combination peginterferon-\(\alpha\) plus ribavirin therapy was observed in patients coinfected with HCV genotype 1 (29%) than with HCV genotypes 2 and 3 (62%).\textsuperscript{132,133} Guidelines for the management of HIV and HCV coinfection have been published recently.\textsuperscript{130} In general, the guidelines recommend combination therapy with peginterferon-\(\alpha\) and ribavirin for 48 weeks.

Interferons are generally not recommended in acute viral hepatitis, but treatment of acute HCV with IFN-\(\alpha\) has resulted in a more rapid resolution of viremia and reduced progression to chronic hepatitis.\textsuperscript{134,135} The American Association for the Study of Liver Diseases recommends either IFN-\(\alpha\) or peginterferon-\(\alpha\) for at least 6 months for acute HCV if infection persists for 2 to 4 months after diagnosis.

Interferons are also approved as intralesional therapy for condyloma acuminatum of genital and perianal areas.\textsuperscript{136} Intralesional injection ensures relatively high concentrations of IFN at the local site of infection, but occurrence of systemic adverse effects suggests its absorption from this site. Currently, HSV is generally treated with acyclovir, but beneficial responses to topical IFN-\(\alpha\) have been reported for genital herpes\textsuperscript{137} and HSV keratitis.\textsuperscript{90} Beneficial responses to IFN-\(\alpha\) have been reported for HIV-associated progressive multifocal leukoencephalopathy\textsuperscript{138}; however, these findings are debatable because IFN-\(\alpha\) may not provide added benefits when used with highly active antiretroviral therapy.\textsuperscript{139} Most patients receiving IFN may develop flulike symptoms, which appear to be dose-related, are more likely to occur at the start of treatment, and typically respond to acetaminophen. Among the more serious adverse effects are neuropsychiatric disorders (eg, depression and homicidal and suicidal ideation), neurologic disturbances (eg, confusion and seizures), myelosuppression (neutropenia [most commonly] and aplastic anemia [rarely]), cardiovascular disorders (eg, arrhythmias), endocrine disorders (eg, thyroid disorders), and pulmonary disorders (eg, dyspnea and pneumonitis).\textsuperscript{140-142} Patients at risk for developing depression are those with preexisting mood and anxiety dis-
orders, those with a history of major depression, and those receiving higher doses of IFN-α or undergoing long-term treatment regimens. Selective serotonin reuptake inhibitors have been used successfully to treat patients with IFN-associated depression, allowing therapy to be continued, and as a pretreatment to prevent its occurrence in high-risk patients. Other adverse effects are altered liver function, renal insufficiency, and gastrointestinal manifestations.

**Ribavirin**

Ribavirin, a synthetic nucleoside analogue of guanine, is available in oral, aerosolized, and IV formulations. Oral ribavirin is absorbed extensively, but its bioavailability is only 65% because of first-pass metabolism. Peak plasma ribavirin concentrations occur within 1 to 2 hours after oral dose. Peak plasma concentrations increase over time and are 6 times higher after 4 weeks of treatment. Administration of aerosolized ribavirin leads to high concentrations in the respiratory tract, with some ribavirin absorbed systemically. Ribavirin is mainly excreted in the urine.

The mechanism of action of ribavirin is known to be diverse but is not completely understood. It may be a competitive inhibitor of cellular enzymes because its antiviral activity is reversed by guanosine. Its triphosphorylated form, ribavirin triphosphate, is a potent competitive inhibitor of inosine monophosphate dehydrogenase, influenza virus RNA polymerase, and mRNA guanylyltransferase. As a result of this competitive inhibition, intracellular guanosine triphosphate pools are markedly reduced and viral nucleic acid and protein synthesis are inhibited. Ribavirin does not alter viral attachment, penetration, or uncoating, nor does it induce IFN production.

Ribavirin inhibits multiple viruses in vitro. Among the susceptible DNA viruses are herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include HCV, Lassa virus, influenza, parainfluenza, measles, mumps, RSV, and HIV. However, no correlation has been found between ribavirin’s in vitro activity and its activity against human infections.

Oral ribavirin is approved for use, in combination with IFN-α or peginterferon-α, for the treatment of CHC. However, it is not effective when given as monotherapy. The duration of treatment, and sometimes its dose, may be dictated by HCV genotype. Treatment for infections with HCV genotype 1, and probably with genotype 4, should generally continue for 48 weeks, whereas those with genotype 2 or 3 may be treated for 24 weeks. Treatment of HCV in patients coinfected with HIV should be for 48 weeks.

Ribavirin is approved for the treatment of RSV in children, including hematopoietic stem cell transplant recipients. When used for the treatment of RSV pneumonia, ribavirin is usually given by the aerosol route, which delivers high concentrations at the site of infection. Oral ribavirin has also been used with good outcomes. Ribavirin has been used, off-label, for the treatment of HSV, influenza, severe acute respiratory syndrome coronavirus, La Crosse encephalitis, Nipah encephalitis, Lassa fever, hemorrhagic fever with renal syndrome, Crimean-Congo hemorrhagic fever, Bolivian hemorrhagic fever, and hantavirus pulmonary syndrome.

Aerosolized ribavirin can cause sudden deterioration of respiratory function and cardiovascular effects. Precipitation of inhaled ribavirin may occur in ventilatory tubings. Hemolytic anemia occurs commonly, and ribavirin should not be given to patients with preexisting medical conditions exacerbated by ribavirin-induced hemolysis, including significant cardiac disease or hemoglobinopathies. Severe depression, suicidal ideation, and relapse of drug abuse may occur, and ribavirin is contraindicated in patients with a history of, or existing, psychiatric disorders. Significant teratogenic and/or embryocidal effects have been observed in animals exposed to ribavirin. Ribavirin is therefore contraindicated in pregnant women and their male partners, and it is recommended that patients use 2 forms of contraception and avoid pregnancy during therapy and for 6 months thereafter.

**Nucleos(t)ide Analogues for CHB**

In addition to IFN, several nucleos(t)ide analogues are available for the treatment of CHB (Table 2). With the exception of telbivudine, these drugs possess anti-HIV properties, serving as inhibitors of the HIV reverse transcriptase inhibitors. The specific mechanism of their anti-HBV property is through competitive inhibition of HBV DNA polymerase. Because of their anti-HIV properties, it is highly recommended that CHB patients considered for treatment with these drugs be tested for HIV infection, and monotherapy with these drugs should be avoided for HIV-infected patients to reduce the risk of HIV resistance. Hepatitis B virus may also develop resistance to these drugs, usually after prolonged exposure, and this risk may be reduced by a strategy of combination antiviral therapies. The exact duration of anti-HBV treatment is not defined, and HBV relapse often occurs after discontinuation of treatment. Severe exacerbation of hepatitis may also occur on discontinuation of these drugs; hence, monitoring for hepatotoxicity should be performed after stopping treatment. Lactic acidosis may occur with nucleos(t)ide analogues, and the drugs should be withdrawn if there is a rapid increase in ALT levels, progressive hepatomegaly or steatosis, or acidosis.

**Adefovir.** Adefovir dipivoxil is an acyclic nucleotide analogue of adenosine monophosphate. Oral adefovir
Adefovir is converted intracellularly by cellular kinases to its active metabolite, adefovir diphosphate, which competitively inhibits HBV DNA polymerase. Although adefovir has the distinction of being the least potent among the currently available anti-HBV drugs, it has been used in combination with tenofovir in HIV/HBV–coinfected patients. Emtricitabine is an analogue of cytidine. Although not currently approved for the treatment of CHB, emtricitabine has been used clinically in combination with tenofovir in HIV/HBV–coinfected patients. Emtricitabine is very similar to lamivudine, and cross-resistance between these drugs is common. Emtricitabine may be more potent than lamivudine; however, it should not be used as monotherapy because of high rates of resistance development. The rate of emtricitabine resistance among patients with HBV monoinfection is 18% at 96 weeks. Adverse effects are reportedly uncommon and include mild to moderate headache, nausea, diarrhea, and rash.

**Entecavir.** Entecavir, a nucleoside guanosine analogue, is considered one of the most potent agents for the treatment of patients with CHB, including those resistant to lamivudine. Oral entecavir is extensively absorbed: peak plasma concentrations occur in 30 to 90 minutes, and oral bioavailability is almost 100%. Despite low plasma concentrations, entecavir maintains its potency by the long intracellular half-life of its active metabolite entecavir triphosphate. Entecavir is mainly excreted by glomerular filtration and active tubular secretion. The mechanism of action of entecavir is somewhat unique because it inhibits 3 specific functions of the HBV DNA polymerase: priming of the HBV DNA polymerase, reverse transcription of the negative strand from the pregenomic mRNA, and synthesis of positive-strand HBV DNA. Entecavir is approved for the treatment of CHB, at a dose of 0.5 mg orally once daily for nucleoside

---

### TABLE 2. Antiviral Nucleos(t)ides for the Treatment of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Suggested dosage</th>
<th>Drug characteristics</th>
<th>Toxicity</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td>10 mg orally once daily</td>
<td>Acyclic nucleotide analogue of adenosine monophosphate</td>
<td>Nephrotoxicity</td>
<td>rtN236T is most common</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg orally once daily</td>
<td>Nucleoside analogue of cytidine</td>
<td>Lactic acidosis</td>
<td>rtM204V/I provides cross-resistance with lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 mg orally once daily for treatment-naive patients; 1 mg orally once daily for treatment-experienced patients and patients with decompensated liver disease</td>
<td>Nucleoside analogue of guanosine</td>
<td>Well tolerated</td>
<td>High barrier to resistance; requires 3 mutations for phenotype: rtM204V/I plus rtL180M plus rtT184S/A/L/L or rtS202G/C or rtM250L</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>100 mg orally once daily</td>
<td>Nucleoside analogue of cytosine</td>
<td>Lactic acidosis</td>
<td>rtM204V/I is most frequent</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg orally once daily</td>
<td>Acyclic nucleoside phosphonate diester analogue of adenosine monophosphate</td>
<td>Lactic acidosis</td>
<td>rtM204I is most frequent</td>
</tr>
</tbody>
</table>

---

* HBV = hepatitis B virus; HIV = human immunodeficiency virus.
* All drugs inhibit hepatitis B replication by acting as a competitive substrate for the HBV DNA polymerase. All drugs except telbivudine have anti-HBV properties, and all patients with chronic hepatitis B who are considered for treatment should be screened for HIV.
* A common toxicity of the nucleos(t)ide analogues is lactic acidosis, with the potential to cause increases in serum alanine aminotransferase levels and hepatomegaly.
Lamivudine. Lamivudine is a nucleoside analogue of cytosine. Oral lamivudine provides bioavailability of about 85%, and peak serum concentrations occur in 1.0 to 1.5 hours. Hepatic metabolism is low, and up to 70% is excreted unchanged by the kidneys. Lamivudine is phosphorylated intracellularly into its active 5′-triphosphate metabolite, lamivudine triphosphate. When the active metabolite is incorporated into viral DNA by HBV polymerase, it results in DNA chain termination.

Lamivudine was the first drug to be used as an alternative to IFN-α for the treatment of CHB. In a double-blind study involving about 350 patients with CHB, lamivudine was associated with substantial histologic improvement, HBeAg antibody seroconversion, and ALT normalization. However, relapses are common once treatment is discontinued.

The adverse effects of lamivudine are mild and include headache, fatigue, nausea, diarrhea, and insomnia. Entecavir has a high barrier to resistance and requires at least 3 mutations for phenotypic resistance. Entecavir resistance requires a baseline rtM204V/I and rtL180M mutation plus either rtT184S/A/I/L, rtS202G/C, or rtM250L. Among nucleoside-naive patients, the rate of entecavir resistance is less than 1% after 5 years, but patients with preexisting rtM204V/I have a higher rate of entecavir resistance (51%) after 5 years.

Telbivudine-triphosphate inhibits HBV by competitive inhibition of viral DNA polymerase. Oral telbivudine is approved for the treatment of CHB in patients with compensated liver disease and evidence of active viral replication, persistently increased serum ALT concentrations, and histologic evidence of active liver inflammation and fibrosis. It is considered more effective than lamivudine and adefovir. Compared with lamivudine, telbivudine was associated with a higher degree of reduction in HBV DNA levels; however, no significant differences were found in ALT level normalization, loss of HBeAg, or anti-HBe seroconversion.

The most common adverse effects reported for telbivudine are dizziness, fatigue, gastrointestinal symptoms, and rash. Unique adverse effects are peripheral neuropathy and myopathy with elevation in creatine kinase levels. Telbivudine treatment should be discontinued if either peripheral neuropathy or myopathy is diagnosed. The rate of resistance to telbivudine is 25% after 96 weeks of treatment.

Tenofovir disoproxil fumarate, an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, is considered one of the most potent anti-HBV drugs. In oral form, it is rapidly absorbed and converted to tenofovir, reaching peak plasma concentrations in 1 to 2 hours. Oral bioavailability, which is only 25% in the fasting state, can be enhanced when taken with a high-fat meal. The terminal elimination half-life of tenofovir is 12 to 18 hours, and it is excreted mainly by active tubular secretion and glomerular filtration.

Tenofovir disoproxil fumarate is a produg that requires diester hydrolysis for conversion to tenofovir. Subsequent phosphorylation by cellular enzymes forms tenofovir diphosphate, which competes with the natural substrate deoxyadenosine 5′-triphosphate for incorporation into the viral DNA strand.

Tenofovir is used for the treatment of CHB. In a randomized trial comparing tenofovir and adefovir, a higher percentage of patients receiving tenofovir achieved HBV DNA level suppression. In HBeAg-positive patients, the biochemical response was higher with tenofovir; however, the anti-HBe seroconversion rates and histologic responses were similar for adefovir and tenofovir.

The adverse effects of tenofovir include gastrointestinal symptoms, dizziness, fatigue, and headache. Renal toxicities, including nephritis, proximal renal tubulopathy (including Fanconi syndrome), and renal failure, have been associated with tenofovir.

Primary tenofovir resistance mutations have not been well defined. Although viruses with rtN236T are not resistant to tenofovir, they have a slower response than do wild-type viruses. One study reported rtA194T as a tenofovir re-
sistance mutation; however, this pattern was not confirmed in other studies.

**Protease Inhibitors for the Treatment of CHC**

The current standard treatment of CHC is peginterferon-α in combination with ribavirin for 24 weeks (for HCV genotype 2 or 3) or 48 weeks (for HCV genotype 1). The major aim of treatment is to achieve SVR, which is defined as undetectable HCV RNA at 24 weeks after completion of treatment. A combination regimen of peginterferon-α and ribavirin results in SVR rates between 38% and 46%, and the rate is even lower among black patients. Hence, major efforts have been made to develop novel therapies for CHC. Recently, 2 serine protease inhibitors were approved as novel therapies for CHC due to genotype 1 infection. The addition of serine protease inhibitors to the backbone therapies of peginterferon-α and ribavirin will emerge as the standard of care for the HCV genotype 1 infection, both in treatment-naive and treatment-experienced patients.

**Boceprevir.** Boceprevir is a linear peptidomimetic ketomamide serine protease inhibitor that was recently approved for the treatment of CHC, particularly for genotype 1. It is available in oral formulation, and the time to peak concentration after oral administration is 2 hours. Food enhances its absorption. Boceprevir is metabolized primarily in the liver. It has an elimination half-life of 3 hours and is excreted mostly in the feces. Boceprevir exerts anti-HCV properties by binding reversibly to the HCV nonstructural 3 protein, ultimately inhibiting viral replication. In a recently conducted phase 3 international randomized placebo-controlled trial that enrolled previously untreated black and nonblack adults with HCV genotype 1 infection (SPRINT-2 [serine protease inhibitor therapy 2] trial), the addition of boceprevir for 22 weeks or 44 weeks to standard therapy (peginterferon-α-2b and ribavirin) resulted in significantly higher SVR rates compared with standard therapy alone for the nonblack cohort (67% and 68% vs 40%, respectively) and the black cohort (42% and 53% vs 23%, respectively). The relative increases in SVR rates for the nonblack cohort were 68% and 70%, respectively, compared with the standard therapy.

The HCV RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2) trial evaluated boceprevir for the treatment of patients who had experienced a relapse or who had not achieved SVR to peginterferon-ribavirin treatment. In this randomized open-label trial that enrolled 403 patients, the SVR rates were significantly higher for patients who received peginterferon-ribavirin plus boceprevir treatment for 32 weeks (59%) or 44 weeks (66%) compared with standard peginterferon-ribavirin treatment alone (21%). In a multivariable stepwise logistic regression analysis, the baseline factors associated with SVR were boceprevir use, previous relapse (compared with previous nonresponder), low viral load at baseline, and absence of cirrhosis.

Boceprevir (800 mg 3 times daily) was approved by the FDA as the first HCV protease inhibitor for the treatment of CHC, specifically for genotype 1; it should be combined with peginterferon and ribavirin. The most common adverse effects of boceprevir are flulike illness, fatigue, nausea, dysgeusia, and anemia. The addition of boceprevir nearly doubled the rate of anemia compared with the use of standard peginterferon and ribavirin therapy, with many patients requiring the use of erythropoietin.

**Telaprevir.** Telaprevir is an orally available inhibitor specific to the HCV nonstructural 3/4A serine protease. It inhibits HCV replication by binding reversibly to nonstructural 3 serine protease. After oral administration, telaprevir achieves peak plasma concentrations in 4 to 5 hours. It is metabolized primarily in the liver and it has an elimination half-life of 4 to 5 hours. Most of the drug is excreted in the feces.

Early-phase studies demonstrated the potent anti-HCV properties of telaprevir. In a recent phase 3 international randomized double-blind placebo-controlled clinical trial, the addition of telaprevir to the standard treatment of peginterferon-ribavirin was associated with significantly higher SVR rates compared with standard peginterferon-ribavirin alone in a cohort of 1088 patients with previously untreated HCV genotype 1 infections. Specifically, the group of patients who received 12 weeks of telaprevir combined with peginterferon-ribavirin, followed by peginterferon-ribavirin for 12 weeks (if HCV RNA was undetectable at weeks 4 and 12) or 36 weeks (if HCV RNA was still detectable at weeks 4 and 12), had SVR rates of 75% vs 44% with standard therapy. The SVR rates were also significantly higher compared with standard therapy among patients who received only 8 weeks of telaprevir combined with peginterferon-ribavirin (69% vs 44%). In the second randomized phase 3 trial that evaluated telaprevir in treatment-experienced patients with HCV genotype 1 infection, the addition of telaprevir to the standard treatment regimen of peginterferon-α and ribavirin was associated with significantly higher SVR rates compared with the standard regimen of peginterferon-ribavirin alone.

Collectively, these studies indicate that the addition of telaprevir to standard peginterferon-ribavirin therapy can significantly improve SVR rates in treatment-naive patients infected with HCV genotype 1 and in those who did not benefit from initial treatment with peginterferon-α-2a and ribavirin. As a result of these findings, the FDA approved telaprevir (750 mg 3 times daily) for this treatment.
indication. The most common adverse effects are anemia, neutropenia, leukopenia, and rash.201 In one study, 41% to 60% of patients reported some kind of rash.199 Rash es can be mild to severe, and Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms have been reported. Telaprevir therapy should be discontinued if these dermatologic complications occur, especially in cases of severe rash or even mild to moderate rash if accompanied by systemic symptoms. The mechanism underlying rash development is unknown.199 Fatigue, pruritus, and gastrointestinal symptoms (eg, nausea, diarrhea, and taste disturbance) may also be observed.199

CONCLUSION

This review has highlighted the pharmacokinetics, mechanisms of action, clinical indications, and adverse effects of clinically available drugs for the management of viruses other than HIV. The currently available antiviral drugs target 3 main groups of viruses: herpes, hepatitis, and influenza viruses. The antiviral therapeutic armamentarium has evolved over the years and is rapidly expanding. Some of the “old” antiviral drugs retain their clinical utility for most infections, such as acyclovir for herpes simplex virus and ganciclovir for CMV. However, other of these “old” antiviral drugs (eg, amantadine and rimantadine for influenza virus infections) have lost their clinical utility because of the rapid and widespread development of resistance. This serves as a catalyst for the development of novel therapies and, more importantly, should urge the medical community to use these drugs optimally in the clinical setting. Indeed, increased resistance has been observed to the neuraminidase inhibitors for the treatment of influenza viruses and the nucleos(t)ide analogues for the treatment of CHB. As novel therapies develop (eg, the serine protease inhibitors for the treatment of CHC), care must be taken to optimize their use so that the clinical life span of these drugs is not abbreviated by the development of resistance.

REFERENCES


87. Snidy DR. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood.* 2006;107:3002-3008.


ANTIVIRAL THERAPIES


The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
Antimicrobial Stewardship

SHIRA DORON, MD, AND LISA E. DAVIDSON, MD

On completion of this article, readers should be able to: (1) describe the goals of antimicrobial stewardship and discuss why there is an increasing need for antimicrobial stewardship programs; (2) identify stewardship techniques that can be used in a variety of hospital settings by different health care practitioners; and (3) list steps for starting a stewardship program and identify potential barriers to implementation.

Antimicrobial resistance is increasing; however, antimicrobial drug development is slowing. Now more than ever before, antimicrobial stewardship is of the utmost importance as a way to optimize the use of antimicrobials to prevent the development of resistance and improve patient outcomes. This review describes the why, what, who, how, when, and where of antimicrobial stewardship. Techniques of stewardship are summarized, and a plan for implementation of a stewardship program is outlined.


WHY DO WE NEED ANTIMICROBIAL STEWARDSHIP?

In the early days of antibiotics, booming drug development meant that even when resistance developed, a new drug was always available to treat the increasingly resistant bacteria. Fourteen new classes of antibiotics were introduced between 1935 and 2003. However, rapid antimicrobial development came with a cost—antimicrobial resistance. In the hospital, resistance to antibiotics and antifungals poses the greatest concern. In 2003, US intensive care units (ICUs) reported to the Centers for Disease Control and Prevention that nearly 60% of Staphylococcus aureus isolates were resistant to methicillin. Although the rate of invasive methicillin-resistant S aureus infections in health care settings was shown to be decreasing in a 2010 Centers for Disease Control and Prevention study, isolates immediately or overtly resistant to vancomycin are becoming less rare. Perhaps even more difficult to manage has been the increase in gram-negative resistance. Programs such as the international SMART (Study for Monitoring Antimicrobial Resistance Trend) and the SENTRY Antimicrobial Surveillance Program have shown substantial increases in the rate of Klebsiella resistance to third-generation cephalosporins, extended-spectrum β-lactamase–producing Klebsiella pneumoniae and Escherichia coli, and Pseudomonas resistant to fluoroquinolones. During the past 30 years, antibiotic development has slowed considerably, and our options for treating increasingly resistant infections are becoming more and more limited. This review aims to describe the why, what, who, how, when, and where of antimicrobial stewardship.

Tens of thousands of Americans die of infections caused by antibiotic-resistant pathogens every year. Every day, patients die of bacterial infections for which no active agents are available. Yet since 1998 only 10 new antibiotics have been approved, only 2 of which (linezolid and daptomycin) actually have new targets of action. The reasons for this are simple: drug development is risky and expensive, and drugs to treat infections are not as profitable as those that treat chronic disease. Antibiotics currently in development are in existing classes and are broad spectrum in nature, which means they are likely to further promote the development of resistance if approved and used. In the hospital, an estimated 50% of antibiotic orders are unnecessary. It is in this setting that the broadest-spectrum antibiotics are being used, and rampantly. It is also in this setting that the most dangerous and extreme drug resistance has been seen. All of this has led the Infectious Diseases Society of America’s Bad Bugs, No Drugs task force to call for a global commitment from stakeholders to support the development of 10 new drugs in novel classes by the year 2020. This so-called 10 × 20 initiative has been likened to John F. Kennedy’s dream of walking on the moon.

WHAT IS ANTIMICROBIAL STEWARDSHIP?

Until this next giant step is achieved, those of us not developing new drugs have another job: conserve the antibiotics

From the Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, MA. The authors have no conflict of interest to disclose.

Address correspondence to Shira Doron, MD, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, 800 Washington St, Boston, MA 02111 (sdoron@tuftsmedicalcenter.org). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

© 2011 Mayo Foundation for Medical Education and Research


For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
we have. In the hospital, antimicrobial stewardship teams are charged with this important initiative. Antimicrobial stewardship has been defined as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.” The goal of antimicrobial stewardship is 3-fold.

The first goal is to work with health care practitioners to help each patient receive the most appropriate antimicrobial with the correct dose and duration. Joseph and Rodvold10 wrote about the “4 D’s of optimal antimicrobial therapy”: right Drug, right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy. The optimal care of an infected patient means treating with the correct, properly dosed antibiotic and one that has the least likelihood of causing collateral damage (ie, leading to resistance in the patient or his or her contacts). An added benefit of programs that aim to optimize antibiotic use is that they generally experience cost savings because fewer doses of antibiotic are used and less expensive antibiotics are chosen. Comprehensive programs have demonstrated annual savings of $200,000 to $900,000.11-17

The second goal is to prevent antimicrobial overuse, misuse, and abuse. In both the hospital and the outpatient setting, physicians use antibiotics when they are not necessary. Antibiotics are given to patients with viral infections, noninfectious processes (a classic example is the febrile patient with pancreatitis), bacterial infections that do not require antibiotics (such as small skin abscesses that will resolve with incision and drainage), and bacterial colonization (as in the case of a positive urine culture result in a patient with a bladder catheter). Antibiotics are also frequently misused, such as in the very common scenario of the use of broad-spectrum antibiotics that cover multidrug-resistant organisms in a patient whose infection was acquired in the community or the failure to adjust antibiotics according to culture data, thus maintaining the patient on a regimen to which the organism is not susceptible. Abuse of antibiotics is more difficult to define, but the term might be used to describe the use of one particular antibiotic preferentially over others by a physician as a result of aggressive detailing by the pharmaceutical representative or worse because of financial interest.

The third goal is to minimize the development of resistance. Both at the individual patient level and at the community level, antibiotic use changes susceptibility patterns. Patients exposed to antibiotics are at higher risk of becoming colonized or infected by resistant organisms.18-20 The most common cause of the development of Clostridium difficile diarrhea is exposure to antibiotics.21 Gram-negative resistance to carbapenems and cephalosporins has been shown to increase 10- to 20-fold with exposure to these broad-spectrum antimicrobials.22-24 In a recent systematic review and meta-analyses of outpatient prescribing practices, the use of common antibiotics was associated with significant increased risk of development of antibiotic resistance, up to 12 months after antimicrobial exposure (pooled odds ratio [OR], 1.33; 95% confidence interval [CI], 1.2-1.5).25 More importantly, antimicrobial resistance is associated with increased morbidity and mortality. Carbapenem-resistant K pneumoniae is associated with an increased attributable mortality compared with sensitive Klebsiella (OR, 4.69; 95% CI, 1.9-11.58; \( P = .001 \))22 and methicillin-resistant S aureus bacteremia, relative to methicillin-sensitive S aureus bacteremia, has a significantly greater mortality risk as well (OR, 1.93; 95% CI, 1.54-2.42; \( P = .001 \)).26 These resistant organisms can become transmitted to other individuals within the hospital or in the patient’s community. Antimicrobial resistance also has significant hospital and societal costs. A recent study by Roberts et al27 estimated that the cost of an antimicrobial-resistant infection is $18,588 to $29,069 per patient, with an excess duration of hospital stay of 6.4 to 12.7 days and attributable mortality of 6.5%.27

**WHO: BUILDING THE STEWARDSHIP TEAM**

Every hospital should work within its resources to create an effective team given its budget and personnel constraints. The stewardship team does not have to fit a particular mold, and it would be a mistake to delay implementation of a stewardship program because of a lack of availability of one or more of the typical team participants listed subsequently. Most stewardship teams include either an infectious disease physician or a pharmacist (with or without specialized training in infectious disease) or both. Sometimes a hospitalist with an interest in infectious disease serves in this role. Often the infection preventionsist is an active member of the team. Close collaboration with the staff in the microbiology laboratory, hospital epidemiology, and administration is essential to a well-functioning program. A working relationship with the information specialist can be especially helpful. Engaging hospital leadership will open doors to good relationships with other physician groups. Therefore, early involvement of thought leaders from hospital administration and the various practitioner groups will improve acceptance and implementation.

**HOW: STEWARDSHIP STRATEGIES**

**Approaches**

There are 2 major approaches to antimicrobial stewardship, with the most successful programs generally implementing...
ANTIMICROBIAL STEWARDSHIP

In addition to using one or both of these common approaches, comprehensive antimicrobial stewardship programs (ASPs) use a variety of other strategies and techniques to optimize antimicrobial use in the hospital.

TECHNIQUES

Formulary Restriction. Most hospitals have a formulary that is somewhat selective and does not include every available antimicrobial. The realities of the process of negotiating with pharmaceutical companies make this necessary because the price of the drug depends not only on how much of it the hospital uses but also on how little it uses of the competitor drug. As an example, most hospitals carry only one echinocandin antifungal. Formulary restriction is also a first step toward stewardship because, very simply, making only certain drugs available is a way to steer clinicians toward the use of those drugs. Formulary restriction can be a challenge for long-term acute care facilities that accept patients from multiple acute care hospitals with different formularies because they may feel an obligation to be able to offer the referring hospital continuation of the same antimicrobial the patient was receiving on transfer.

Order Sets and Treatment Algorithms. Order sets, whether on paper or as part of a computerized physician order entry system, can be an important tool in the stewardship team’s efforts to ensure guideline-based appropriate empiric antibiotic ordering. Depending on the level of sophistication of the paper or electronic order set, the system can prompt the prescriber to make guideline-based antibiotic choices based on relevant clinical factors, to think about allergies, to remember to adjust for renal function, to consider the cost of therapy, and to order the appropriate tests, monitoring, and consultations. Hermsen et al used a surgical prophylaxis order form to improve antibiotic choices. This study demonstrated a significant increase in appropriate antimicrobial use, appropriate weight-based dosing, and appropriate duration of prophylaxis, as well as a decrease in the mean cost of antimicrobial prophylaxis. Treatment algorithms are similar decision tools but lack a direct interface with the ordering process. Some stewardship teams have even created pocket or online guidebooks for clinicians, which contain empiric antibiotic recommendations for common infections, dosing guidelines, and other helpful information.

Clinical Guidelines. One of the advantages of guideline development as part of an ASP is that it provides the opportunity to incorporate many thought leaders within a hospital to develop hospital- or network-specific algorithms. Guidelines can use national recommendations but should incorporate local trends in antimicrobial resistance and hospital-specific targets for decreased use. Ibrahim et al demonstrated that implementation of ventilator-

a combination of both. The front-end or preprescription approach to stewardship uses restrictive prescriptive authority. Certain antimicrobials are considered restricted and require prior authorization for use by all except a select group of clinicians. Clinicians without authority to prescribe the drug in question must contact the designated antimicrobial steward and obtain approval to order the antimicrobial. The front-end approach has the advantage of targeting specific antimicrobials for specific indications based on local resistance patterns and the hospital formulary. Antimicrobials can be approved for a specific duration, thereby prompting review after culture data have been obtained. Data suggest that programs that use this approach have been able to demonstrate significant reductions in expenditures of the targeted drug but also result in increased use of antimicrobials that are not restricted, which may or may not be the desired effect.

The back-end or postprescription approach to stewardship uses prospective review and feedback. The antimicrobial steward reviews current antibiotic orders and provides clinicians with recommendations to continue, adjust, change, or discontinue the therapy based on the available microbiology results and clinical features of the case. Studies of programs that use this approach have shown decreased antimicrobial use, decreased number of new prescriptions of antimicrobials, and improved clinician satisfaction. The back-end approach has the advantage of being able to focus on de-escalation, a critical aspect of appropriate antimicrobial use. De-escalation is modification of the initial empiric antimicrobial regimen based on culture data, other laboratory tests, and the clinical status of the patient. De-escalation includes changing a broad-spectrum antibiotic to one with narrower coverage, changing from combination therapy to monotherapy, or stopping antibiotic therapy altogether as it becomes more apparent that these drugs are not needed.

The newer rapid molecular diagnostic tests are designed to help clinicians de-escalate earlier in the antibiotic course. Peptide nucleic acid technology is widely available in the United States and allows for identification of common organisms from a positive blood culture within 90 minutes. Matrix-assisted laser desorption/ionization technology is gaining popularity in Europe and can be used to identify an increasing number of organisms from positive culture within 60 minutes. In one recent study, rapid polymerase chain reaction was used to differentiate methicillin-resistant S aureus bacteremia from methicillin-sensitive S aureus in blood culture and the results provided immediately to an infectious disease pharmacist. During the period when this technology was being used, mean length of stay was 6.2 days shorter and mean hospital costs $21,387 less for patients with S aureus bacteremia. Other technologies are available and in development.

Clinical Guidelines. One of the advantages of guideline development as part of an ASP is that it provides the opportunity to incorporate many thought leaders within a hospital to develop hospital- or network-specific algorithms. Guidelines can use national recommendations but should incorporate local trends in antimicrobial resistance and hospital-specific targets for decreased use. Ibrahim et al demonstrated that implementation of ventilator-
associated pneumonia treatment guidelines during a 2-year period doubled the rate of appropriate initial therapy, while decreasing length of therapy and ventilator-associated pneumonia recurrence. Other studies of guidelines for ventilator-associated pneumonia, including at our own institution, have shown similar results.\textsuperscript{36-38} After an increase in \textit{C difficile} infections, the province of Quebec, Canada, initiated a global education program to reduce unnecessary antimicrobial use.\textsuperscript{39} Eleven guidelines were produced by a group of experts, sent to all physicians and pharmacists in Quebec, and posted on a dedicated Web site. Importantly, these guidelines were widely promoted throughout the province. After the guideline campaign, there were 4.1 fewer prescriptions per 1000 inhabitants (95% CI, −6.6 to −1.6; \textit{P}<.002) and a decrease in prescription costs of $134.50 per 1000 inhabitants (95% CI, −270.5 to 1.6; \textit{P}=0.054) in Quebec compared with the rest of Canada. These trends persisted 36 months later.

One of the advantages of using guidelines and clinical pathways for ASPs is the ability to reach out to frontline professionals who are not specialists in infectious disease. Jenkins et al\textsuperscript{40} recently published a study on the introduction of empiric therapy guidelines for uncomplicated cellulitis. The program targeted emergency department and general medicine physicians. Using this institutional guideline to standardize and streamline the evaluation of inpatient cellulitis resulted in a significant decrease in the use of microbiological and radiologic tests, a decrease in duration of antimicrobial therapy, and significant decreases in the use of broad-spectrum antimicrobials.

\textbf{Education.} All successful ASPs include an educational component. Clinicians are educated about the use of antimicrobials during the process of reading the order sets and treatment algorithms, during telephone conversations with the antimicrobial steward for the purpose of obtaining authorization for use of a restricted antimicrobial, during interaction with the antimicrobial steward conducting current review and feedback, and through formal didactic sessions or Grand Rounds–type lectures. At our institution, an Antimicrobial Management Team Question of the Week is sent by e-mail to all clinicians and has been very well received. In a recent study of pediatricians in Israel, the primary hypothesis was that a multifaceted intervention based on physicians’ engagement with an education process that involved physician, parents, and child would result in long-standing reduction in antimicrobial resistance rates.\textsuperscript{41} Using a cluster randomized controlled design, the intervention group engaged physicians by conducting activities focused on self-developed guidelines, improving parent and physician knowledge, diagnostic skills, and parent-physician communication skills that promoted awareness of antibiotic resistance. Compared with the control group, a significantly greater decrease occurred in annual prescription rates in the intervention vs control group (relative risk, 0.89; 95% CI, 0.81–0.98), and the effect was sustained during the 4 following years.

\textbf{Pharmacodynamic Dose Optimization.} One stewardship technique that is being used with increasing frequency is pharmacodynamic dose optimization. Concepts, such as the pharmacodynamic parameter that is correlated with efficacy and knowledge of achievable tissue concentrations, guide the use of specific antimicrobials in previously unconventional and often off-label ways to optimize microbial killing and thus minimize the risk of promoting resistance. For β-lactam antibiotics, these dosing strategies maximize the percentage of time that the concentration of the unbound drug is above the minimum inhibitory concentration of the organism. Some of these dosing regimens are suggested by studies that use Monte Carlo simulation. Examples are given in Table 1.

\textbf{Computer-Assisted Decision Support Programs.} The rapidly increasing use of electronic medical records and computerized physician order entry systems provides a critical opportunity for both electronic surveillance of

### TABLE 1. \textit{Novel Approaches to Antimicrobial Dosing to Combat Resistance}

<table>
<thead>
<tr>
<th>Strategy and drug</th>
<th>Pharmacodynamically optimized dose</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged infusion of β-lactams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>3.375 g IV every 8 h for 4 h (prolonged infusion)</td>
<td>42</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g IV for 360 min every 6 h (continuous infusion)</td>
<td>43</td>
</tr>
<tr>
<td>Doripenem</td>
<td>500 mg IV every 8 h for 4 h (prolonged infusion)</td>
<td>44</td>
</tr>
<tr>
<td>Increased frequency dosing of quinolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg IV every 8 h</td>
<td>45</td>
</tr>
<tr>
<td>Adjusting antimicrobial dosage to achieve specific recommended blood level Vancomycin</td>
<td>Maintain trough above 10 mg/L to prevent development of resistance</td>
<td>46-48</td>
</tr>
<tr>
<td>Use of high-dose therapy to overcome high MICs Cefepime</td>
<td>2 g IV every 8 h (3-h infusion)</td>
<td>49</td>
</tr>
</tbody>
</table>

\textit{IV} = intravenous; \textit{MIC} = minimum inhibitory concentration.
antimicrobial-prescribing practices and use of electronic systems to provide guidance to clinicians. Many decision support programs have been developed during the past few years to assist the antimicrobial stewardship team. These programs can identify allergies, inappropriate dosages, and, with the appropriate software and information technology systems, mismatches between drug and susceptibility. Evans et al demonstrated that one such model was able to provide physician feedback in a timely manner and resulted in significant reductions in the use of antimicrobials and length of stay. In a study conducted in Australia, a Web-based monitoring and approval system was used for cephalosporins. This system provided feedback on prescribing patterns to staff. Cephalosporin use decreased from 38.3 to 21.2 defined daily doses (DDDs) per 1000 patient-days after intervention. At the same time, concordance with national antibiotic guidelines increased. In a pediatric study, a Web-based automated clinical decision support tool provided real-time communication with prescribers of antibiotics. This system resulted in an 11.6% reduction in doses of antibiotics prescribed during 1 year and an increase in satisfaction of prescribers and pharmacists. The cost savings using this system was estimated at $370,069.

Pharmacist-Driven Intravenous to Oral Switch Programs. Most clinicians cannot remember which medications are highly bioavailable, meaning that the oral formulation of these medications will achieve nearly the same blood level as the intravenous. For this reason many hospitals empower pharmacists to write orders to switch highly bioavailable antimicrobials (and other medications) from the intravenous to the oral formulation provided the patient meets certain criteria. Patients who are clinically stable and consuming a normal diet and other oral medications are automatically switched by pharmacy to oral drugs, saving money without detriment to the patient. Antimicrobials that are candidates for switch programs are summarized in Table 2.

Pharmacy Dosing Programs. In some hospitals, pharmacists are responsible for the dosing and monitoring of vancomycin and/or aminoglycosides. Often using electronic dose calculators, pharmacists are able to choose initial doses and adjust dosing based on levels with more accuracy to achieve appropriate subsequent blood levels compared with physicians who often base dose adjustments on techniques of estimation or at best use dosing nomograms. Bond and Raehl conducted a study evaluating outcomes in Medicare patients in hospitals with or without pharmacist-managed vancomycin or aminoglycoside dosing protocols. Those hospitals without pharmacist-managed protocols had higher mortality ($P<.0001$), longer length of stay ($P<.0001$), increased adverse events ($P<.001$), and higher hospital costs ($P<.0001$). One criticism of this type of program has been that clinicians, particularly resident physicians, will fail to learn or will forget how to dose these antibiotics if not practiced on a regular basis.

Antibiotic Cycling. Antibiotic cycling is the scheduled removal and substitution of specific antimicrobials or antimicrobial classes in a given patient care unit. The hypothesis is that by removing specific classes of antimicrobials on a regular basis, the development of resistance can be avoided. For example, all patients with suspected ventilator-associated pneumonia in a certain ICU might be treated with a fourth-generation cephalosporin in January, an anti-pseudomonal β-lactam/β-lactamase inhibitor in February, and an antipseudomonal carbapenem in March; then the cycle is repeated. Studies of antimicrobial cycling are limited and heterogeneous. Several studies in ICU populations have demonstrated a decrease in ventilator-associated pneumonia due to multidrug-resistant infection with cycling. However, these studies also noted that cycling occurred in conjunction with de-escalation and an overall decrease in antimicrobial use. Therefore, it is difficult to ascertain whether the results were attributable to cycling or decreased use. Unfortunately, many trials of antimicrobial cycling are hampered by heterogeneous study populations and large percentages of patients receiving “off-cycle” antimicrobials. A recent systematic review was not able to conclude that cycling was beneficial. Because of insufficient data, the current Infectious Diseases Society of America guidelines on antimicrobial stewardship do not recommend antibiotic cycling.

Table 3 lists the most common antimicrobial stewardship approaches and techniques with their benefits and drawbacks and examples from the literature.

**Table 2. Highly Bioavailable Antimicrobials That Are Good Candidates for Intravenous to Oral Switch Programs**

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>Macrolides (azithromycin, erythromycin)</td>
</tr>
<tr>
<td>Doxycycline</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Rifampin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Fluconazole</td>
</tr>
</tbody>
</table>

**Steps to Take When Implementing an ASP**

**Understand Problem Pathogens and Antimicrobial Use at Your Institution**

An important first step in building an ASP should be to identify current institutional resistance patterns and an-
ANTIMICROBIAL STEWARDSHIP

TABLE 3. Summary of Antimicrobial Stewardship Techniques

<table>
<thead>
<tr>
<th>Stewardship approaches and strategies</th>
<th>Description</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Front-end or preprescription authorization</td>
<td>The antimicrobial steward reviews the order for appropriateness at the time it is written. Specific antimicrobials are restricted to use by certain prescribers or units, whereas others must obtain authorization. Antimicrobial order forms or order sets can help prompt clinicians to obtain approval</td>
<td>Target antimicrobials that are overused, misused, or abused</td>
<td>Unclear impact on antimicrobial resistance</td>
<td>57-59</td>
</tr>
<tr>
<td>Back-end or postprescription review and feedback</td>
<td>The antimicrobial steward reviews existing antibiotic orders and provides clinicians with direct recommendations to continue, adjust, change, or discontinue the therapy based on the available microbiology results and clinical features of the case</td>
<td>Direct interaction and feedback with prescriber</td>
<td>Requires active surveillance by an ASP, which is time-consuming</td>
<td>12, 31, 32, 60, 61</td>
</tr>
<tr>
<td>Clinical guidelines, order sets, and treatment algorithms</td>
<td>Prompt the prescriber to make evidence-based antibiotic choices based on local antimicrobial resistance patterns, national guidelines, and relevant clinical factors</td>
<td>Can incorporate feedback from multidisciplinary team</td>
<td>May be difficult to perform frequently in settings with fewer resources</td>
<td>35-38, 40, 62</td>
</tr>
<tr>
<td>Education</td>
<td>Grand Rounds, departmental conferences, house staff teaching, e-mail alerts, guidebooks</td>
<td>Direct ASP to practitioner interaction</td>
<td>Need to educate clinicians to identify patients who are not appropriate for specific guidelines (eg, history of MDR infection, immunocompromised)</td>
<td>39, 41</td>
</tr>
<tr>
<td>Pharmacodynamic dose optimization</td>
<td>Use of PK/PD properties of antimicrobial agents to optimize drug efficacy based on organism, site of infection, and patient characteristics</td>
<td>Optimal use of currently available antimicrobials may improve outcomes without increased risk of toxic effects</td>
<td>Education of nursing staff regarding prolonged or atypical administration</td>
<td>42-45</td>
</tr>
<tr>
<td>Computer-assisted decision support programs</td>
<td>Computer-based algorithm that guides a practitioner and makes recommendations for antimicrobial regimens based on suspected infection, patient characteristics, local microbiology, and optimal drug dosing</td>
<td>Can be incorporated into existing CPOE based on drug or suspected infection</td>
<td>Requires significant time and effort from information technology services</td>
<td>50-52, 63, 64</td>
</tr>
<tr>
<td>Pharmacy-based dosing programs</td>
<td>Algorithms empower pharmacists to transition bioequivalent drugs from IV to PO formulation; dosing and monitoring of vancomycin and aminoglycosides</td>
<td>Decreased length of stay and early transition to oral antimicrobials</td>
<td>Prescribers may quickly lose comfort with appropriate dosing and monitoring of these potentially nephrotoxic and ototoxic agents</td>
<td>53</td>
</tr>
</tbody>
</table>

ASP = antimicrobial stewardship program; CAP = community-acquired pneumonia; CPOE = computerized physician order entry; IV = intravenous; MDR = multidrug resistant; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; SCIP = surgical care improvement program; SSI = skin and soft tissue infection; UTI = urinary tract infection; VAP = ventilator-acquired pneumonia.

ASSESS YOUR CURRENT RESOURCE
Before funding can be secured for your ASP, it is crucial to understand what systems are in place that may be accessed to promote stewardship. First and foremost, many institutions have or are building electronic medical records and

Antimicrobial use. Not all hospitals need the same level of interventions. Antimicrobial stewardship programs should be tailored to institutional problem pathogens and overuse of particular classes of drugs. Engage your microbiology laboratory, infection control, and pharmacy colleagues.
computerized physician order entry systems. These systems may be ideal places to begin development of guidelines and order sets. Many pharmacy purchasing systems may have the ability to track antimicrobial use and/or to record interventions. Educational forums, such as Grand Rounds or Lunch and Learns, may present opportunities for focus groups to discuss people’s misconceptions and concerns about the idea of restricting antimicrobials. In addition, many national and international resources for stewardship have become available in recent months. The Centers for Disease Control and Prevention recently launched the Get Smart for Healthcare Web site and has many excellent resources for developing ASPs. The Infectious Diseases Society of America has guidelines on ASPs and support for clinical physicians developing a business plan.

Many centers that have ASPs have made their resources available online.

Resources may also include current staffs that have an interest in developing a stewardship program. As noted, there is no set formula to determine who needs to be part of a stewardship program. Support and interest can be found from a wide range of practitioners at your institution.

**Determine Priority Areas and Plan for Interventions**

Once you have determined the current state of resistance and antimicrobial use in your institution and your current resources, you can begin to prioritize what areas need to be addressed. You can also begin to determine the most effective way of implementing change, for example, guidelines, order forms, guidebooks, electronic monitoring, and educational detailing. Identify what resources will be needed to fund these endeavors; can existing staff and technology be used or does a business plan need to be developed for funding of this program?

**Engage Hospital Leaders**

A key to establishing successful stewardship is the engagement of hospital leadership. Determining whether antimicrobial resistance and stewardship is important to hospital administration is a critical first step. If it is not, then you have ample opportunity to demonstrate why stewardship can improve safety and clinical outcomes and decrease antibiotic expenditures. If stewardship has not been a high priority, identifying an administrative “champion” who will support your case in discussion with the administration is extremely important. Antimicrobial resistance should be viewed as a quality and safety issue and can tie into many current safety campaigns and bundles, such as those focusing on community-acquired pneumonia, antimicrobial prophylaxis for surgery, and asymptomatic bacteriuria.

**Develop a Business Plan**

Developing a business plan might seem to be the most daunting part of developing an ASP. Start by determining your baseline expenditures. Then examine the attributable cost savings associated with the proposed interventions based on the literature and your own hospital data. For instance, if use of antibiotics targeting gram-negative bacteria for patients with uncomplicated skin and soft tissue infections is a problem at your institution, you can calculate the amount of drug saved if you were to implement an algorithm approach similar to that of Jenkins et al and assuming similar results. Overall, antimicrobial programs have been shown to be cost-effective.

Determine the costs associated with the infectious disease diagnosis of interest. Costs may include not only the price of the antimicrobials but also those associated with laboratory tests and with adverse events from using the incorrect dose or type of antimicrobial. As an example, a simple and straightforward goal of any stewardship program can be implementation of a program for conversion of intravenous drugs to oral drugs. Oral drugs are usually less expensive and do not require placement of long-term intravenous catheters, minimizing complications from vascular access and enabling earlier discharge from the hospital.

Perhaps the biggest barrier to developing a stewardship program is the personnel cost. Many administrators see stewardship as part of the infectious disease consultant’s job, and yet consultants are unable to bill for stewardship. There is currently no mechanism for direct reimbursement of stewardship programs, and therefore costs must be justified by demonstrating savings to the institution. Also, a widely held perception is that stewardship will result in a decreased number of consultations. In fact, stewardship programs should be aimed at augmenting and supporting the consultative service and may even result in an increased number of referrals.

**Put Your Plan Into Action**

Determine how you would like to roll out your ASP. Remember that the most successful plans incorporate educational outreach and physician feedback. If possible, survey hospital staff before and after each step of the program is implemented to determine practitioner satisfaction and room for improvement. Before implementation, identify what outcome data you would like to prospectively collect, such as practitioner satisfaction, antimicrobial use, expenditures, and clinical outcome variables, including readmission for specific conditions (eg, cellulitis and community-acquired pneumonia). Pharmacy purchasing systems usually track DDDs or days of therapy (DOTs), which are extremely useful measures of the success of the program.
ANTIMICROBIAL STEWARDSHIP

Measure your outcomes and incorporate feedback. It is important to have a predetermined timeline for assessment of goals and launching of each step of your ASP. Feedback on success and failure should be incorporated into the program on a regular basis. For each process implemented, there should be an outcome goal and measure. Antimicrobial consumption and expenditures are common outcome measurements, as discussed subsequently, but may not reflect other important goals, such as improved practitioner satisfaction, decrease in adverse drug events, improvement in adherence to Medicare or other quality measures, or changes in antimicrobial resistance.

The 2 most common methods used to evaluate drug consumption are DDD or DOTs. The DDD is calculated as the total number of grams of antimicrobial agent used divided by the number of grams in an average daily dose. The DDD is defined by the World Health Organization.69 The advantage of the DDD is the ability to compare standardized doses among hospitals. The disadvantage is that the DDD does not account for alternative dosing regimens due to renal dysfunction, age, or regimens that optimized pharmacokinetic or pharmacodynamic dosing. Therefore, in many cases the administered dose is different from the DDD recommended by the World Health Organization. This can result in either overestimation or underestimation of drug consumption. An alternative measurement is the number of DOTs. 68 DOTs are expressed as the administration of a single agent on a given day regardless of the number of doses administered or dosage strength. The advantage is that DOTs are not affected by changes in dosing regimens. DOTs will not reflect actual doses and may not adequately represent antimicrobials that are administered multiple times daily. The DDD may be more helpful when benchmarking institutions or in large studies, whereas DOTs may be more helpful in comparing use of different classes of antimicrobials within an institution.

Many institutions begin implementing stewardship as a tiered program to improve practitioner comfort and acceptance. Philmon et al57 used a 3-tiered approach to introduce stewardship in a community teaching hospital in Dallas, TX: conversion from intravenous to oral administration for selected highly bioavailable antimicrobials, cessation of perioperative prophylaxis within 24 hours for patients undergoing clean and clean-contaminated surgery, and consultation with an infectious disease physician before continuing administration of selected drugs beyond 48 hours. From April 2001 through December 2003, a total of 1426 requests for antimicrobial therapy met criteria for intervention. Antimicrobial costs per patient-day decreased by 31%, and total savings in acquisition costs were $1,841,203. Significant decreases were found in Klebsiella resistance.

Soliciting practitioner feedback is a crucial step in the establishment of a successful stewardship program. We showed that house officer satisfaction with the stewardship program increased significantly between 2008 and 2010 after conducting a survey requesting feedback on the program and addressing their concerns by making programmatic changes.70

WHERE CAN THINGS GO WRONG: BARRIERS AND PITFALLS

One of the greatest challenges of antimicrobial stewardship research is demonstrating a clear causal association between implementation of ASPs and decreased rates of antimicrobial resistance. Early studies that achieved decreased cephalosporin use were successful in controlling the incidence of resistant gram-negative infections to cephalosporins but resulted in an increase in carbapenem use and resistance to carbapenems.71 This is an example of the “squeezing the balloon” phenomenon, in which decreasing use of one antimicrobial or class results in increasing use of another, often with associated resistance. Studies of outbreaks of C difficile infections have shown improvement in infection rates with decreased use of cephalosporins and fluoroquinolones.72,73 These studies are encouraging in that they suggest that ASPs can impact the rate of C difficile infections in hospitals. However, when such interventions come at the cost of increased use of extended-spectrum β-lactam/β-lactamase inhibitors72 and carbapenems, other consequences may be experienced.

Studies of the implementation of antimicrobial stewardship and its effects on resistance are extremely difficult to control and are usually observational. One systematic review of the literature attempted to identify “rigorous evaluations” of interventions to improve hospital prescribing of antimicrobial drugs. Of the 16 studies that met criteria for inclusion, only 4 provided strong evidence that changes in prescribing antimicrobial drugs to hospital inpatients can decrease antimicrobial resistance.74 Four studies were negative, and the 8 remaining studies were cited as having flawed designs, allowing for alternative explanations for the outcome. Most studies of antimicrobial stewardship compare individual patient-level data points, such as antibiotic use and rates of colonization or infection with resistant organisms. Correlating the relationship between antimicrobial use and resistance over time may be more appropriate. Time-series analyses rely on aggregated, ecologic-level data and attempt to account for such variables as the introduction of infection control measures, the variation in use of broad-spectrum classes of drugs, colonization rates, and the lag time between implementation of interventions and development of resistance. In particular, time-series
analysis is useful in study designs in which infection rates have been ascertained before and after an intervention, but controlling with a nonintervention group may not be practical or ethical. Several time-series analyses of methicillin-resistant *S. aureus* and *C. difficile* have shown that variations in rates of multidrug-resistant infection may be attributed not only to changes in drug use but also to implementation of infection control practices and rates of colonization with multidrug-resistant bacteria.75-77

From a practical standpoint, implementing a stewardship program can seem like a monumental task. In a nationwide survey of hospitals, of 406 respondents, we found that 51% had what they would consider formal ASPs. Of those who did not, the most commonly cited barriers to implementation were staffing constraints, funding, and lack of time.78

**CONCLUSION**

As hospitalized patients become more complex to treat, the increasing prevalence of antimicrobial resistance in both health care and community settings represents a daunting challenge. With the increasing complexity of infections and a paucity of new antimicrobials in development, the future of successful antimicrobial therapy looks bleak. Antimicrobial stewardship can provide all practitioners with tools to prevent the overuse of valuable resources and help control the increase in antimicrobial resistance. Although often underappreciated, the increase of antimicrobial resistance has finally caught the attention of influential international health care organizations. The Institute of Medicine has identified antibiotic resistance79 as one of the key microbial threats to health in the United States and has listed decreasing the inappropriate use of antimicrobials as a primary solution to address this threat. The Get Smart campaign, initiated by the Centers for Disease Control and Prevention in 1995, focused on reducing the use of inappropriate antimicrobials in the outpatient setting. In 2010, the Centers for Disease Control and Prevention launched Get Smart for Healthcare, a campaign focused on improving antibiotic use in inpatient health care facilities to prevent overuse of antimicrobials and promote the use of antimicrobial stewardship. The 2011 World Health Organization World Health Day focused on international antimicrobial resistance. This World Health Organization campaign has drawn together agencies from all over the world to focus resources and combat the increase in antimicrobial resistance.

These organizations are drawing attention to the battles that practitioners face on a daily basis. This attention should be a call to action for insurance providers, national and state governments, and hospital administrators to provide much needed resources to practitioners who incorporate stewardship practices into everyday patient care. The California Department of Public Health Antimicrobial Stewardship Initiative is an example of how government resources can be used to promote proper antibiotic use in health care facilities. California Department of Public Health staff assess existing stewardship practices at health care facilities to identify barriers to success and methods to overcome those barriers. They also provide consultative services to help facilities, including long-term care hospitals, where inappropriate antibiotic use is known to be especially common,80 to assist in implementation of stewardship activities and development of formal programs. By making antimicrobial stewardship part of our daily practice, we can improve patient safety and care, reduce the unnecessary use of valuable resources, and reduce resistance.

**REFERENCES**


ANTIMICROBIAL STEWARDSHIP


The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.

Ana Maria Rivera, MD, and Helen W. Boucher, MD

On completion of this article, the reader should be able to (1) compare current antibiotic options to treat infections caused by resistant gram-positive bacteria, differentiating them on the basis of adverse effect profile and evidence supporting their use in a clinical setting; (2) recognize the activity profile of each antibiotic against the resistant gram-positive organisms discussed in the article: methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci; and (3) use knowledge on current antibiotics to treat the infections caused by these organisms, considering potential to induce resistance.

Gram-positive bacteria cause a broad spectrum of disease in immunocompetent and immunocompromised hosts. Despite increasing knowledge about resistance transmission patterns and new antibiotics, these organisms continue to cause significant morbidity and mortality, especially in the health care setting. Methicillin-resistant *Staphylococcus aureus* poses major problems worldwide as a cause of nosocomial infection and has emerged as a cause of community-acquired infections. This change in epidemiology affects choices of empirical antibiotics for skin and skin-structure infections and community-acquired pneumonia in many settings. Throughout the world, the treatment of community-acquired pneumonia and other respiratory tract infections caused by penicillin-resistant *Streptococcus pneumoniae* has been complicated by resistance to β-lactam and macrolide antibiotic drugs. Vancomycin-resistant enterococci are a major cause of infection in the hospital setting and remain resistant to most standard antibiotics. Treatment of diseases caused by resistant gram-positive bacteria requires appropriate use of available antibiotics and stewardship to prolong their effectiveness. In addition, appropriate and aggressive infection control efforts are vital to help prevent the spread of resistant pathogens.


**BSI** = bloodstream infection; **CA-MRSA** = community-associated methicillin-resistant *Staphylococcus aureus*; **CAP** = community-acquired pneumonia; **CLSI** = Clinical Laboratory Standards Institute; **CNS** = central nervous system; **FDA** = Food and Drug Administration; **MIC** = minimum inhibitory concentration; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **MSSA** = methicillin-sensitive *Staphylococcus aureus*; **PBP** = penicillin-binding protein; **PCV7** = pneumococcal conjugate vaccine 7; **SSSI** = skin and skin-structure infection; **UTI** = urinary tract infection; **VAP** = ventilator-associated pneumonia; **VRE** = vancomycin-resistant enterococci; **VISA** = vancomycin-intermediate *Staphylococcus aureus*

*Staphylococcus aureus* causes a broad spectrum of disease. Humans are colonized by this organism mainly in the nasopharynx and on the skin.1 *S aureus* has the unique propensity to infect and destroy normal healthy tissue, causing skin and wound infections, bloodstream infection (BSI), pneumonia, osteomyelitis, endocarditis, lung abscess, and pyomyositis. Manifestations of *S aureus* central venous catheter–related infection include local infection at the site, thrombophlebitis and tunnel infections, and central venous catheter–related BSI.2 These well-described health care–associated infections continue to challenge physicians globally.

Community-associated methicillin-resistant *S aureus* (CA-MRSA) has been described in patients with no previous contact with the health care environment. Unlike hospital-associated MRSA, many CA-MRSA strains are susceptible to gentamicin, tetracyclines, lincosamides, and trimethoprim-sulfamethoxazole.1,3 Many of these infections are limited to superficial skin and skin-structure infections (SSSIs). However, CA-MRSA can cause severe systemic infections, including pneumonia and BSI.4 In the United States, the first cases of severe CA-MRSA disease were 4 cases of fatal pneumonia reported to the Centers for Disease Control and Prevention in 1997-1999, all associated with a particular strain of CA-MRSA.5 Several subsequent studies reported *S aureus* community-acquired pneumonia (CAP) with high mortality rates.6,7 In a study of 3 different communities, more than two-thirds had SSSIs, followed by wound infection, urinary tract infection (UTI), sinus infection, and pneumonia as the most common manifestations of their CA-MRSA infection.8 New challenges in treating...
infections caused by more resistant *S aureus* organisms include *S aureus* with heteroresistant vancomycin-intermediate *S aureus* (VISA), vancomycin-resistant *S aureus*, and MRSA resistant to linezolid and daptomycin. In this article, we provide an overview on MRSA treatment.

**METHICILLIN-RESISTANT S AUREUS SSSIs**

The spectrum of MRSA SSSIs includes impetigo, folliculitis, cellulitis, erysipelas, staphylococcal scalded skin syndrome, toxic shock syndrome, furuncles, carbuncles, and deep skin abscesses. In a study examining bacterial syndrome, toxic shock syndrome, furuncles, carbuncles, ulitis, cellulitis, erysipelas, staphylococcal scalded skin infections caused by more resistant *S aureus* organisms include *S aureus* with heteroresistant vancomycin-intermediate *S aureus* (VISA), vancomycin-resistant *S aureus*, and MRSA resistant to linezolid and daptomycin. In this article, we provide an overview on MRSA treatment.

**METHICILLIN-RESISTANT S AUREUS SSSIs**

The spectrum of MRSA SSSIs includes impetigo, folliculitis, cellulitis, erysipelas, staphylococcal scalded skin syndrome, toxic shock syndrome, furuncles, carbuncles, and deep skin abscesses. In a study examining bacterial causes of SSSIs in 11 US emergency departments in 2004, CA-MRSA was the No. 1 cause of endemic SSSIs.

No clear predictors of CA-MRSA exist, and local trends should be considered when selecting empirical therapy. However, some risk factors include a positive history of contact with CA-MRSA, crowding, contaminated personal objects, compromised skin integrity, and absence of cleanliness. Person to person transmission, among men who have sex with men and as the result of heterosexual contact, has been implicated in CA-MRSA epidemiologic trends.

Although there are several strains of CA-MRSA in the United States, the predominant US strains include the USA300 and USA400 clones. The most common throughout the United States is the USA300 clone, except in Alaska. In Europe the epidemiology is heterogeneous, but overall the most common clone is the *luskF-PV*-positive European ST80-MRSA-IV clone. Community-acquired MRSA has unique virulence factors, including Panton-Valentin leukocidin, and is frequently associated with inadequate antibiotic therapy.

**AGENTS CURRENTLY AVAILABLE TO TREAT MRSA INFECTION**

Some uncomplicated CA-MRSA SSSIs in immunocompetent hosts can be treated with incision and drainage, local debridement, and abscess drainage alone. However, in patients with signs of systemic illness or comorbidities, empirical treatment of SSSIs should include antibacterial therapy. Unfortunately, clinical predictors of drug resistance are limited, so local rates of CA-MRSA must be considered when treating SSSIs. No large randomized controlled trials have compared oral antibiotics to treat SSSIs, although several ongoing National Institutes of Health studies should help address these questions.

Observational studies demonstrate successful clinical outcomes with oral antibiotics, including trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Isolates that test resistant to erythromycin and are susceptible to clindamycin should be tested for inducible clindamycin resistance (via the D-test) because treatment failures have been reported. Linezolid is not recommended to treat uncomplicated SSSIs because of the associated toxicity and cost.

Treatment of SSSIs in patients with comorbidities or signs of systemic disease includes monotherapy with intravenous antibiotics in addition to prompt and thorough incision and drainage of abscesses, as well as debridement of wounds. Table 1 lists the systemically available gram-positive antibiotics. Vancomycin may be used at a dosage of 10 to 15 mg/kg intravenously every 12 hours adjusted for renal function. Other options include linezolid, 600 mg intravenously every 12 hours, with the limitations mentioned herein, including cost and toxicity. Daptomycin is another agent effective for therapy of SSSIs at a dosage of 4 mg/kg daily. New agents for SSSIs include telavancin, approved by the US Food and Drug Administration (FDA) in 2009 at the dosage of 10 mg/kg daily in patients with normal renal function, and ceftaroline, which was FDA approved in 2010 for treatment of acute bacterial SSSIs at the dosage of 600 mg intravenously every 12 hours in patients with normal renal function. High cost and risk of toxic effects limit use of these new drugs. The mechanisms of resistance for MRSA are presented in Table 2.

**THERAPY FOR INVASIVE MRSA INFECTIONS**

**Vancomycin**

Vancomycin remains first-line antimicrobial therapy for serious infections caused by MRSA, including complicated SSSIs, pneumonia, and BSI. Available in multiple generic formulations, vancomycin is reasonably well tolerated, associated with a low incidence of adverse effects, and relatively inexpensive. However, despite being the criterion standard therapy, the susceptibility of MRSA to this antibiotic may be decreasing, and reports of clinical failure are increasing.

Changes in MRSA vancomycin susceptibility have been observed over time. Increasing minimum inhibitory concentrations (MICs) seem to be related to vancomycin use. As the MIC increases, the frequency of heteroresistant VISA also has been observed to increase. Although most MRSA strains appear susceptible, subpopulations of strains may have VISA selected by vancomycin treatment. Furthermore, increased vancomycin MIC has correlated with adverse clinical outcomes in some studies. However, these data are limited in that they derive from retrospective studies, subset analyses, and variations among MIC testing methods. In 2006, on the basis of clinical evidence suggesting reduced efficacy in the treatment of isolates with borderline susceptible MICs, the vanco-
CURRENT CONCEPTS IN ANTIMICROBIAL THERAPY AGAINST SELECT GRAM-POSITIVE ORGANISMS

mycin breakpoints were lowered by the Clinical Laboratory Standards Institute (CLSI). The MRSA vancomycin MIC decreased from 4 μg/mL or less to 2 μg/mL or less for “susceptible,” from 8 to 16 μg/mL to 4 to 8 μg/mL for “intermediate,” and from 32 μg/mL or more to 16 μg/mL or more for the “resistant” designation.32 Despite concerns about evolving resistance, most cases of invasive or severe infections caused by MRSA remain highly susceptible to vancomycin.28,33,34 Nonetheless, recent guidelines suggest treating with higher doses of vancomycin with goal trough values of 15 to 20 μg/mL.23 In patients who do not respond, follow-up cultures should be obtained and, when results are positive, repeat susceptibility testing performed to assess for increasing vancomycin MICs. Alternative antibiotics should be considered when the clinical response is suboptimal.11

Studies evaluating MRSA infections with reduced susceptibility to vancomycin (including VISA and heterogeneous VISA) suggest that prospective identification of these isolates may have limited value, but the importance of identifying these strains is critical in the context of clinical failure of vancomycin therapy.35

In a prospective, multinational cohort study evaluating the outcome of severe S aureus infections, higher MIC was associated with an increased mortality at 30 days. The remarkable finding of this study was that high vancomycin MIC was associated with worse outcomes in patients with methicillin-sensitive Staphylococcus aureus (MSSA) infections not treated with vancomycin. This finding suggests that other factors, presumably related to the bacteria or the host, may be implicated in the worse outcomes. This finding is aligned with current recommendations to consider changing from vancomycin therapy in light of clinical response, not MIC alone.36,37

The predictability of vancomycin nephrotoxicity has been demonstrated in a number of studies and is associated with higher vancomycin trough concentrations.38 It has also been associated with underlying renal disease, longer duration of therapy, and use of other nephrotoxic medications.39,40

TEICOPLANIN
Teicoplanin is an antibiotic widely used outside the United States for the treatment of infections caused by gram-positive bacteria. It is chemically related to the group of glycopeptides, which also includes vancomycin.41 This antibiotic demonstrates bactericidal activity against a broad spectrum of gram-positive organisms, including MRSA and methicillin-resistant coagulase-negative Staphylococcus epidermidis. It has a longer half-life, higher protein binding, higher bone uptake, and less potential for nephrotoxicity compared with vancomycin.42

In the United Kingdom, the most recent guidelines for the treatment of MRSA infections include teicoplanin as one of the glycopeptides of choice. Local epidemiology and the clinical setting would influence the choice of vancomycin vs teicoplanin. The pharmacokinetics of teicopla-
Linezolid

Linezolid is a bacteriostatic, gram-positive antibiotic that inhibits protein synthesis at the 50S ribosome. A synthetic oxazolidinone active against MRSA, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE), linezolid is currently FDA approved for the treatment of complicated SSSIs and nosocomial pneumonia. Linezolid is administered at a dosage of 600 mg every 12 hours orally or intravenously, and dose adjustment is not necessary. Studies have shown higher clinical cure rates and reduced lengths of hospitalization in patients with complicated SSSIs treated with linezolid compared with vancomycin. Higher survival rates were found in subset analyses of clinical trials comparing linezolid to vancomycin in the treatment of MRSA pneumonia. One potential explanation for this effect is that linezolid achieves higher concentration levels in lung tissue.

The role of linezolid in the treatment of MRSA BSI is unclear. Successful treatment of cases of BSI associated with pneumonia or SSSIs have been reported with linezolid. However, on the basis of the results of a more recent open-label study of catheter-related BSI, linezolid is not recommended for the treatment of BSI. An imbalance in deaths among linezolid-treated patients led to early termination of this European study. However, in the published analysis, this imbalance appears to have been driven by deaths among patients with gram-negative BSI or in whom no bacterial cause was elucidated.

Linezolid is generally well tolerated. Bone marrow suppression is generally reversible with discontinuation of linezolid therapy. The association with serotonin toxicity and thrombocytopenia may limit its use. Linezolid should be administered to patients receiving serotonin reuptake inhibitors with caution, and linezolid therapy should be discontinued if serotonin syndrome is suspected. Patients with renal insufficiency have been found to be at a higher risk of developing thrombocytopenia. The most common gastrointestinal adverse effects include nausea, vomiting, and diarrhea. Sporadic cases of lactic acidosis, peripheral neuropathy, and optic neuritis have been reported. Patients who receive therapy for more than 2 weeks should be monitored closely for myelosuppression and other less common toxic effects.

**Linezolid-Resistant S. aureus**

Most strains of *S. aureus* are susceptible to linezolid. Resistance surveillance data demonstrate that more than 99% of isolates are susceptible. The first MRSA isolate resistant to linezolid was reported in 2001 in a patient treated for dialysis-associated peritonitis. Since then, the emergence of linezolid-resistant *S. aureus* has been reported in recent studies. Appropriate monitoring for resistance should be considered during long courses of therapy. As in the case of vancomycin and daptomycin, clinical failure should prompt submission of specimens for culture, susceptibility testing, and MIC determination.

**Daptomycin**

Daptomycin is a cyclic lipopeptide active in vitro against most resistant gram-positive bacteria. This bactericidal agent is thought to cause depolarization of the bacteria via calcium-dependent insertion to the cell membrane. Daptomycin susceptibility may depend on its ability to penetrate through the cell wall to reach its target. Heteroresistant VISA may have an increased daptomycin MIC, probably related to increased cell wall thickness. Daptomycin was approved by the FDA for the treatment of serious MRSA infections, including SSSIs, MRSA, and MSSA BSI and right-sided endocarditis, on the basis of the results of prospective randomized clinical trials. The daptomycin dosage is 4 mg/kg intravenously once daily for complicated SSSIs and 6 mg/kg intravenously once daily for *S. aureus* BSIs, including right-sided endocarditis, in patients with normal renal function. Daptomycin should not be used to treat pneumonia because it failed in clinical trials.
and was subsequently found to be inhibited by pulmonary surfactant. Resistance developed in several daptomycin-treated patients in the *S. aureus* BSI trial. In these cases, clinical failure while receiving daptomycin was related to increased daptomycin MIC from 0.25 or 0.5 μg/mL to 2 or 4 μg/mL. The mechanism is not well understood.

Daptomycin therapy is associated with myopathy. Creatine kinase levels should be monitored at baseline and weekly while the patient is undergoing therapy, more often in patients with symptoms of muscle pain or weakness and renal insufficiency or those who receive concomitant statin therapy. Daptomycin therapy should be discontinued for muscle pain or weakness or elevations in creatine kinase levels if the level is 5 to 10 times or more the upper normal limit. Acute eosinophilic pneumonia has been reported with daptomycin therapy. Although the mechanism of toxicity has not been proven, the release of inflammatory mediators after antigen presentation by macrophages or accumulation in the epithelium after daptomycin binding with surfactant has been implicated. It is a diagnosis of exclusion, but physicians should have a low threshold for stopping therapy if daptomycin-induced acute eosinophilic pneumonia is suspected.

**Tigecycline**

Tigecycline is a derivative of minocycline and the first drug approved in the class of glycylcyclines. A modified side chain binds to the 30S ribosomal subunit, inhibiting protein translation in bacteria. Tigecycline is active against various drug-resistant pathogens, including MRSA, VRE, and many extended β-lactamase, gram-negative bacteria. Tigecycline has a large volume of distribution and produces high concentrations in tissue. However, serum concentrations decrease rapidly after intravenous administration.

On the basis of these pharmacokinetic and pharmacodynamic properties, tigecycline should be used with caution in patients with suspected or proven BSI. In the United States, this drug is approved for the treatment of complicated SSSIs due to MRSA and the treatment of complicated intra-abdominal infections caused by MSSA. The approved tigecycline dosage is a 100-mg intravenous loading dose followed by a 50-mg dose given every 12 hours. Common adverse effects include nausea and vomiting.

In a large, randomized, double-blind clinical study of patients with hospital-acquired pneumonia comparing tigecycline with an imipenem-cilastatin regimen, cure rates were lower in the tigecycline ventilator-associated pneumonia (VAP) group (67.9%) compared with imipenem (78.2%), whereas in the non-VAP patients tigecycline was noninferior to imipenem. Mortality rates were also higher in the tigecycline group. These results may be related to decreased tigecycline concentrations in these critically ill patients. On the basis of these trends and subsequent observations, the FDA recommends seeking alternatives to tigecycline to treat patients with severe infections. A study is under way to evaluate the role of tigecycline at 2 higher dosages (75 or 100 mg every 12 hours) compared with imipenem-cilastatin in parallel in the treatment of hospital-acquired pneumonia.

**Quinupristin-Dalfopristin**

Quinupristin-dalfopristin is a combination streptogramin agent that is FDA approved for the treatment of SSSIs due to MSSA, streptococci, and the treatment of VRE BSI. This combination antibiotic is bactericidal against *S. aureus* via inhibition of protein synthesis. It was studied in patients with MRSA infections who were intolerant of other antibiotics. In an open-label, emergency use program, quinupristin-dalfopristin was successful in treatment of 66.7% of patients, most of whom had SSSIs and osteoarticular infections. Therapy failed in patients with endocarditis. Dose-limiting adverse effects include joint pain, muscle pain, and severe pain at the site of infusion.

**Telavancin**

Telavancin is a semisynthetic lipoglycopeptide that produces inhibition of cell wall synthesis and disruption of membrane barrier function. It has a long half-life of 7 to 9 hours, allowing once-daily administration using 7.5 to 10 mg/kg daily. It is a rapidly bactericidal agent, active against MRSA. Telavancin was approved by the FDA in 2009 for the treatment of complicated SSSIs caused by gram-positive bacteria, including MRSA. In clinical trials, telavancin was found to be noninferior to vancomycin, with cure rates of 88.3% and 87.1% in the treatment of complicated SSSIs. Telavancin was compared with vancomycin in large randomized studies in the treatment of hospital-acquired pneumonia due to gram-positive bacteria, particularly MRSA, and found to be noninferior to vancomycin based on clinical response. The most common adverse effects include taste disturbances, nausea, headache, vomiting, constipation, insomnia, and foamy urine. Telavancin therapy was associated with adverse fetal outcomes in animal studies, and the United States package insert includes a warning concerning the potential risk of abnormal fetal development. Nephrotoxicity has been reported with elevation in the serum creatinine levels, which was more likely to occur in patients with underlying diseases that predisposed the patient to kidney dysfunction.

**Ceftaroline**

Ceftaroline is a cephalosporin antibiotic with MRSA activity. Ceftaroline has high affinity for penicillin-binding protein (PBP) 2a, an MRSA-specific PBP, which correlates...
to its low MIC for MRSA. It demonstrates bactericidal, time-dependent killing in vitro and in vivo.\textsuperscript{85,86} On the basis of randomized clinical trials, ceftaroline was approved by the FDA for SSSIs and CAP in 2010. The drug is dosed according to renal function and associated with toxic effects similar to other β-lactam antibiotics.\textsuperscript{70,87} Recommended dosing is 600 mg intravenously every 12 hours or 400 mg intravenously every 12 hours for patients with moderate renal dysfunction.\textsuperscript{88}

Activity against other pathogens, including coagulase-negative staphylococci, enterococci, β-hemolytic and viridans group streptococci, and some Enterobacteriaceae (\textit{Escherichia coli}, \textit{Klebsiella} spp, and \textit{Proteus mirabilis}), makes ceftaroline a reasonable empirical antibiotic option in the treatment of SSSIs and CAP.\textsuperscript{89}

Ceftaroline was compared with ceftriaxone for the treatment of CAP in 2 large randomized, double-blind multicenter studies. Of the patients treated with ceftaroline, 84.3% achieved clinical cure compared with 77.7% in the ceftriaxone group. Ceftaroline demonstrated a safety profile similar to ceftriaxone. \textit{Staphylococcus aureus} was isolated in 55 (16.5%) of 333 patients treated with ceftaroline in these studies.\textsuperscript{90}

**PENICILLIN-RESISTANT PNEUMOCOCCI**

\textit{Streptococcus pneumoniae} is one of the most common pathogens that causes CAP, otitis media, and meningitis.\textsuperscript{91} Antimicrobial resistance among \textit{S pneumoniae} has increased significantly in past decades. Penicillin susceptibility breakpoints were established in the late 1970s. Over time, studies in children and adults demonstrated more treatment failures in penicillin-treated patients found to have pneumococcal isolates from meningitis with higher penicillin MICs.\textsuperscript{92} This observation was not seen among penicillin-treated patients with \textit{S pneumoniae} infecting other areas of the body, including pneumonia and otitis media. However, the clinical impact of antimicrobial resistance remains unclear because of the lack of complete correlation between drug susceptibility data and treatment failure.\textsuperscript{93} The CLSI recently reviewed the breakpoints of \textit{S pneumoniae}.\textsuperscript{94} Using the new meningitis penicillin breakpoint criteria (≥0.12 µg/mL), resistance prevalence was 34.8% in 2008, but it was found to be 12.3% using the old criteria (≥2 µg/mL) for cerebrospinal fluid isolates.\textsuperscript{95}

Risk factors associated with \textit{S pneumoniae} resistance to penicillin include the presence of underlying immunosuppression and receipt of antibiotics within 3 months.\textsuperscript{92} Resistance to β-lactam antibiotic drugs is mediated by alterations in PBPs, decreasing the affinity of the antibiotic to the \textit{S pneumoniae}. Alterations in PBPs occur by transformation of genes that can be transferred not only by \textit{S pneumoniae} species but also by other groups of streptococci.\textsuperscript{96} Macrolide resistance occurs when there is a change in the ribosomal RNA though \textit{erm} (B) or \textit{mef} (A). \textit{Erm} (B) alters the site of macrolide binding through methylation, causing lack of recognition, whereas \textit{mef} (A) encodes an efflux pump. Resistance to quinolones occurs by alteration of topoisomerases.\textsuperscript{97} Multidrug resistance is usually spread through resistant genetic material with a small number of predominant clones.\textsuperscript{98}

The impact of the pneumococcal conjugate vaccine 7 (PCV7) was evaluated using data from isolates collected in 2008 as part of the SENTRY surveillance program. The seroprevalence of PCV7 serotypes decreased from 68.5% before the vaccine to 29.3%. Most isolates with drug resistance before the vaccine were PCV7 serotypes; however, postvaccine noninvasive, nonvaccine serotypes were found to be increased and are more likely to acquire resistance over time.\textsuperscript{99} The introduction of the 13-valent pneumococcal conjugate vaccine, licensed by the FDA for prevention of invasive pneumococcal disease caused by 13 pneumococcal serotypes, could further change the prevalence of isolates in the future.

**AGENTS CURRENTLY AVAILABLE FOR TREATMENT OF RESISTANT \textit{S PNEUMONIAE} INFECTION**

Treatment of non–central nervous system (CNS) infection caused by antibacterial-resistant pneumococcal infection still relies on penicillins, aminopenicillins, and third-generation cephalosporins.\textsuperscript{100} Some of the common mechanisms of resistance are listed in Table 2.\textsuperscript{23} Meningitis is the exception because a combination of vancomycin and a third-generation cephalosporin is recommended due to concerns about emergence of penicillin or cefotaxime nonsusceptible pneumococcal isolates.\textsuperscript{101}

There is no consensus on the use of combination therapy for resistant \textit{S pneumoniae} pneumonia and associated BSI.\textsuperscript{92} Macrolide monotherapy is not recommended as empirical treatment of CAP, especially in geographic areas with high rates of resistant \textit{S pneumoniae} strains.\textsuperscript{102} Treatment failure with fluoroquinolones has been reported.\textsuperscript{103} Fluoroquinolones should be used only when local epidemiology suggests high rates of nonsusceptible \textit{S pneumoniae} strains or in cases of allergy or intolerance to first-line antimicrobial therapy for CAP.\textsuperscript{104} Although fluoroquinolones allow easy switch from parenteral to oral regimens and have excellent bioavailability, this class of drugs has several drawbacks, including broad-spectrum activity associated with “collateral damage,” including disturbance of gastrointestinal flora, selection of resistance for multiple bacteria (eg, MRSA), drug interactions, and risk of \textit{Clostridium difficile} infection.\textsuperscript{105}

Resistance among pneumococci to fluoroquinolones is caused by quinolone resistance–determining regions in...
genes that encode subunits of topoisomerases. During 2001-2002, S pneumoniae isolates were collected in the United States to determine susceptibility. Testing was performed on 1902 isolates. Although the rates of fluoroquinolone resistance remains low in the United States, 40% were found to have quinolone resistance–determining region mutations, and 35% of levofloxacin-nonsusceptible pneumococci were closely related to widespread pneumococcal clones that have spread antibiotic resistance among pneumococci strains in past decades. The authors suggest potential for a rapid increase in resistance associated with clonal dissemination and the wide use of quinolones worldwide.

In a European study evaluating the outcome of patients treated for severe pneumococcal CAP, excluding penicillin-resistant pneumococci, the combination of levofloxacin with a β-lactam was associated with lower mortality rates than ofloxacin or ciprofloxacin. This study had many limitations, including recruitment over a long period and changes in standard antibiotic therapy in the intensive care unit during the study period.

**NEW OPTIONS FOR TREATMENT OF RESISTANT S PNEUMONIAE INFECTION**

**Ceftaroline**

Ceftaroline binds to PBPs in S pneumoniae, interfering with cell wall synthesis. In the international, multicenter, randomized, double-blind clinical trials comparing ceftaroline to ceftriaxone in the treatment of CAP, the cure rate for the ceftaroline group was 85.5% compared with 68.6% for ceftriaxone. However, few pneumococci with high MICs were isolated. In the treatment of patients with multidrug-resistant S pneumoniae pneumonia, ceftaroline cure rates were numerically higher compared with ceftriaxone. However, the numbers were small, with cure rates of 4 of 4 patients in the ceftaroline group compared with 2 of 9 patients in the ceftriaxone group.

**Linezolid**

In animal models, linezolid has shown efficacy in the treatment of pneumococcal pneumonia. The most important predictor of efficacy is the interval during which drug concentration exceeds the MIC. The role of linezolid in the setting of CAP has been evaluated in several trials. In an open-label trial of 1700 patients comparing intravenous linezolid followed by oral linezolid with ceftriaxone followed by oral cefpodoxime, the linezolid-treated patients (n=272) had a cure rate of 91% compared with a clinical cure rate of 89% (n=225/254) in patients in the ceftriaxone-cefpodoxime group. In a subgroup analysis examining the eradication of S pneumoniae and S aureus, a subset of 53 patients with blood cultures positive for S pneumoniae had a clinical cure rate of 93% (30 patients) in the linezolid group compared with 70% (23 patients) in the ceftriaxone-cefpodoxime group.

**Telavancin**

Telavancin demonstrates in vitro activity against penicillin-nonsusceptible S pneumoniae. In an animal model of meningitis, telavancin was found to be more efficacious than vancomycin plus ceftriaxone against a penicillin-resistant pneumococcal strain. We hope that data from future clinical studies will define the role of telavancin in the treatment of clinical infections caused by penicillin-nonsusceptible S pneumoniae.

**Tigecycline**

Although not registered for the treatment of infections with penicillin-nonsusceptible S pneumoniae, tigecycline is active in vitro and might be considered as salvage therapy for these infections. A study is currently under way to evaluate the role of tigecycline in the treatment of hospital-acquired pneumonia.

**Vancomycin-Resistant Enterococci**

Enterococci are part of normal gastrointestinal tract flora and have relatively low virulence. Most clinical isolates are Enterococcus faecalis and Enterococcus faecium and are less commonly other enterococcal species. The CLSI defines vancomycin-susceptible enterococci as having a vancomycin MIC of 4 μg/mL or less and vancomycin-resistant enterococci as having an MIC of 32 μg/mL or more. The first cluster of infections due to vancomycin-resistant enterococci was reported in 22 patients with end-stage renal disease. Enterococcal BSIs continue to pose a problem in the hospital setting, causing nosocomial BSIs and postsurgical UTIs. E faecium, which was much less common clinically than E faecalis, emerged as an important nosocomial infectious pathogen, with rates of vancomycin resistance of up to 60%. Despite this problem there is a paucity of clinical data with the newer antibacterial agents, including linezolid, daptomycin, and tigecycline, in the treatment of this disease. Moreover, even in the era of these newer agents, patients infected with VRE still need better tolerated alternatives.

Antibiotic resistance among enterococci is conferred through mutation and acquisition of genetic material from other species. E faecium often has acquired resistance to penicillin by increased expression of low-affinity PBP5 of mutations at this site. E faecalis can have penicillin resistance, although it is less common, through a β-lactamase similar to the one found in S aureus. One mechanism involves plasmid transfer among E faecalis isolates. Although there are 6 phenotypes of vancomycin resistance,
2 can be harbored on plasmids (VanA and VanB).\textsuperscript{42} The VanA phenotype is encoded by a gene located in a plasmid transferred to other isolates through conjugation. The VanA phenotype has a vancomycin MIC greater than 256 μg/mL and is teicoplanin resistant. The VanB phenotype codes for resistance to vancomycin and is also transferable to other enterococci; however, these isolates remain susceptible to teicoplanin.\textsuperscript{122,123} The most common mechanisms of resistance in VRE are described in Table 2.\textsuperscript{25}

In a large VRE surveillance program, most resistant isolates were \textit{E. faecium} (91\%) and \textit{E. faecalis} (7.8\%). These rates vary geographically, with a higher prevalence of the VanA phenotype in North America (76\%) compared with Europe (40\%).\textsuperscript{124} In the health care setting, multiple factors drive the transmission of VRE, including selective pressure due to antibiotic use, the proportion of patients colonized with VRE vs susceptible enterococci, and adherence to prevention measures.\textsuperscript{125-127}

Infection with VRE affects patients in intensive care units and those with intravascular or bladder catheter devices. Immunosuppressed patients, particularly recipients of liver and other solid organ transplants and hematopoietic stem cell transplants, remain vulnerable to VRE infections. Prolonged hospitalization, residence in long-term care facilities, and exposure to antibiotics are also implicated in VRE infections.\textsuperscript{128}

Clinical outcome is worse and mortality rates higher in patients with VRE infections compared with those with infections caused by vancomycin-susceptible enterococci. One of the main challenges for physicians treating VRE is the intrinsic resistance to many antibiotics, including β-lactams, aminoglycosides, lincosamides, and trimethoprime-sulfamethoxazole.\textsuperscript{129} Vancomycin-resistant \textit{E. faecalis} is usually susceptible to β-lactams.\textsuperscript{130}

One of the most important decisions to make when presented with a positive microbiological report of VRE is to identify whether the isolate represents infection or colonization. Commonly, VRE isolates can be reported from superficial wounds, removed catheters, urine cultures, and abdominal drains. Positive blood cultures, as well as cultures of normally sterile sites, represent VRE infection. Catheters should be removed in the setting of VRE infection. Management and debridement of wounds and surgical management for source control should be performed as a first rule in the management of localized infections.\textsuperscript{131}

### AGENTS CURRENTLY AVAILABLE FOR TREATMENT OF VRE INFECTION

Infections due to VRE include urinary tract, wound infections, BSI, endocarditis, and meningitis. Efficacy data for agents used in the management of VRE infections are limited. Often based on anecdotal report, most of these drugs are not approved by the FDA for the treatment of VRE infections.\textsuperscript{132} Tetracycline, doxycycline, oral novobiocin with ciprofloxacin, and doxycycline have been reported as effective in treating VRE infections. However, there are no clinical studies to support these therapies.\textsuperscript{133}

For treatment of lower UTIs, nitrofurantoin may be effective because this agent is excreted into the urine.\textsuperscript{134} Fosfomycin can be used for treatment of uncomplicated UTIs.\textsuperscript{135} Invasive VRE infection, including BSI, endocarditis, and meningitis, warrants therapy with a bactericidal agent. Synergistic activity of a cell wall–active agent and aminoglycoside is used in the setting of endocarditis and/or critical illness. For serious enterococcal infections, including meningitis and endocarditis, treatment includes a cell wall–active agent and an aminoglycoside to produce a synergistic effect.\textsuperscript{130,136}

### FOSFOMYCIN

Fosfomycin is a phosphonic acid derivative that was first isolated from cultures of \textit{Streptomyces} species in 1969.\textsuperscript{137} In the United States it is approved for the treatment of uncomplicated UTIs caused by \textit{E. coli} and \textit{E. faecalis}, but it is used widely intravenously, particularly in Europe. Fosfomycin has activity against gram-positive and gram-negative bacteria. Fosfomycin is active in vitro against \textit{S. aureus}, \textit{S. epidermidis}, \textit{S. pneumoniae}, and \textit{E. faecalis},\textsuperscript{138} as well as against a number of gram-negative organisms.\textsuperscript{139} In a review of 1311 potentially relevant trials, 63 studies of fosfomycin for the treatment of infections caused by gram-positive and gram-negative bacteria were reviewed. The most common gram-positive organism was \textit{S. aureus}. Most patients received fosfomycin in combination with other antibiotics. The diversity and heterogeneity of the studies make it difficult to draw conclusions, but fosfomycin may be considered an antibiotic option for the treatment of infections caused by multidrug-resistant pathogens. Further studies should be performed to assess a possible role for intravenous fosfomycin.\textsuperscript{140}

### QUINUPRISTIN-DALFOPRISTIN

Quinupristin-dalfopristin is a protein synthesis–inhibiting antibiotic that has potent in vitro activity against \textit{E. faecium} but poor activity against \textit{E. faecalis}.\textsuperscript{141} In a large study of 396 patients with vancomycin-resistant \textit{E. faecium} infection, the overall efficacy of quinupristin-dalfopristin was 66\%.\textsuperscript{142} The most common sites of infection were intra-abdominal, BSI, UTI, catheter-related BSI, and SSSI.\textsuperscript{142} Severe myalgias, arthralgias, and gastrointestinal adverse effects limit its use.\textsuperscript{78}

### LINEZOLID

Linezolid has potent in vitro and in vivo activity against vancomycin-resistant strains of \textit{E. faecium} and \textit{E. faecalis}. Initial data, obtained through compassionate use stud-
ies, demonstrated resolution of infection in 63% to 81% of cases and led to FDA approval of linezolid in 2000. Although linezolid has not been approved specifically for the treatment of enterococcal endocarditis, it has been used in this setting. In a large study of 796 patients who were treated for endocarditis, linezolid was used in patients who were intolerant to vancomycin or did not respond to it or were intolerant to quinupristin-dalfopristin therapy. Among these patients, 32 were re-treated, 59.9% had infection caused by VRE, and 19.4% had infection caused by MRSA. Overall, patients with vancomycin-resistant *E. faecium* had a clinical cure rate of 81.4%, those with MRSA infection had a cure rate of 66.1%, and therapy failed in 12.8%.

**Daptomycin**

Daptomycin is bactericidal in vitro against most gram-positive organisms, including VRE. Although daptomycin has not been approved for *E. faecium* infections, it has been recommended for treatment based on in vitro data and few clinical studies. Daptomycin MICs for *E. faecium* are higher than for *E. faecalis*. There are no FDA-approved daptomycin MIC breakpoints for *E. faecium*, but the CLSI suggests that a daptomycin MIC greater than 4 μg/mL is nonsusceptible. The approved dosing is 4 mg/kg intravenously once daily for complicated SSSIs. For *S. aureus* BSI, the approved dosage is 6 mg/kg intravenously daily. Some experts favor higher dosages of 8 mg/kg intravenously once daily. Patients receiving daptomycin therapy should be monitored regularly for the development of myopathy with serum creatine kinase values measured at least weekly and careful monitoring for development of muscle pain or weakness.

**Tigecycline**

Tigecycline is approved for the treatment of complicated SSSIs and intra-abdominal infections, including those caused by vancomycin-susceptible *E. faecalis*. On the basis of in vitro and animal data, VRE appears susceptible to tigecycline. Further studies are needed to define the role of tigecycline in the treatment of VRE infections.

Published studies of antibacterial therapy for deep eye infections and CNS infections caused by resistant gram-positive bacteria are limited. Animal models suggest that daptomycin may have some advantages compared with vancomycin due to its bactericidal activity. There are also some data examining linezolid in animal infection models. In a clinical study evaluating the possible role of linezolid in the treatment of acute postoperative endophthalmitis, 21 patients undergoing cataract surgery were included. Linezolid concentration intraocularly was measured after intravenous administration of 600 mg of linezolid. This study demonstrated acceptable aqueous humor concentrations of linezolid. We hope that further studies will help elucidate its role in acute postoperative endophthalmitis.

In an open-label, prospective study evaluating linezolid in the management of neurosurgical infections, eradication of causative bacteria was documented in 2 patients with CNS infections and in 1 patient with staphylococcal bacteremia. The outcome for these 2 patients was favorable after 14 days of therapy. Twelve patients were treated prophylactically with linezolid, 1 of whom had a positive blood culture with *S. epidermidis*.

A study in Germany with 10 patients with poor response to other treatments demonstrated improvement in 6 patients with linezolid; however, some patients had abscesses and there were multiple organisms, including atypical mycobacteria. Another study evaluated the use of linezolid for the management of nosocomial CNS infections; however, the study was limited because it was retrospective and the group was heterogenous, including differences in indwelling devices and intracranial collections in some patients.

Although the data seem to be limited to case reports and small reports of CNS infections treated with linezolid, this antibiotic should be considered for the management of serious CNS infections that may not be responsive to other first-line antibiotics or in cases of failure to other antibiotics, but further clinical randomized prospective studies should be performed to clarify its role.

**CONCLUSION**

Resistant gram-positive bacteria cause significant morbidity and mortality. Methicillin-resistant *S. aureus* continues to cause a variety of clinical syndromes worldwide. Vancomycin remains the mainstay treatment, but with the emergence of less susceptible strains other therapeutic options should be considered, depending on the clinical setting. Both MRSA BSI and endocarditis may be treated with daptomycin, but daptomycin should not be used for pneumonia. Linezolid is recommended for MRSA pneumonia and skin infection but not as first-line therapy for BSI. Tigecycline provides an alternative for MRSA SSSIs. Quinupristin-dalfopristin should be reserved for refractory cases of invasive MRSA because its use is limited by its adverse effects. Telavancin was approved for the treatment of SSSIs, but concerns of toxicity preclude its use in this indication; we hope to learn more about its potential role in VAP in the near term. Ceftaroline is the newest agent approved for MRSA SSSIs and CAP.

Penicillin-resistant pneumococcal strains vary in different countries and regions. Linezolid and telavancin have shown in vitro activity, but further studies are needed to clarify their role. These agents may be considered in the
context of intolerance or resistance to β-lactams. β-Lactam antibiotics remain first-line therapy. However, knowledge of local epidemiology and resistance patterns may help inform empirical management of infections caused by these bacteria. Vancomycin plus a third-generation cephalosporin is recommended in the treatment of *S pneumoniae* CNS infection because of the concern of emergence of resistance. Cefaroline represents a novel class of cephalosporins and may be a new option for treatment of penicillin-resistant *S pneumoniae*.

Vancomycin-resistant enterococci have emerged as concerning pathogens in the hospital setting with a high rate of BSI and other nosocomial infection. Nitrofurantoin and fosfomycin are options for the management of uncomplicated VRE UTI. Other agents, including tetracycline, novobiocin, and doxycycline, have been used to treat VRE infections, but supportive clinical trial data are lacking. Newer VRE therapies include quinupristin-dalfopristin, linezolid, and daptomycin. Quinupristin-dalfopristin and linezolid therapy are limited by tolerability and toxicity concerns; a paucity of efficacy data and uncertainty regarding optimal dose limit daptomycin use. We hope that new agents will be developed to address these challenges.

Improved knowledge of mechanisms of resistance continues to inform development of new antimicrobial therapies. These medicines are but one part of a comprehensive approach to the problem of antimicrobial resistance. Physicians must use existing antimicrobial drugs prudently and practice impeccable infection control in health care facilities if we are to control the spread of resistant bacteria.

REFERENCES

2. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin-thera-
17. Deleo FR, Otto M, Kreiswirth BN, Chambers HF. Community-asso-
18. Kleven RM, Morrison MA, Nadle J, et al. Active Bacterial Core Sur-
veillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylo-
21. Silberman RK, Tekle T, Carroll K, Dick J. Failure of clindamycin treat-
ment of methicillin-resistant *Staphylococcus aureus* expressing inducible clinda-
23. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin thera-
mum inhibitory concentration on the treatment of methicillin-resistant *Staphylo-
27. Lodise TP, Graves J, Evans A, et al. Relationship between vancomy-


CURRENT CONCEPTS IN ANTIMICROBIAL THERAPY AGAINST SELECT GRAM-POSITIVE ORGANISMS


CURRENT CONCEPTS IN ANTIMICROBIAL THERAPY AGAINST SELECT GRAM-POSITIVE ORGANISMS


The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

The contributions to the Symposium on Antimicrobial Therapy are a CME activity. For CME credit, see the link on our Web site at mayoclinicproceedings.com.
Questions About Current Concepts in Antimicrobial Therapy Against Select Gram-Positive Organisms

1. A 60-year-old man recently underwent hemodialysis for end-stage kidney disease associated with poorly controlled diabetes mellitus. He is evaluated in the hospital after development of fever during dialysis. The patient was hospitalized 3 months ago for placement of an atrioventricular fistula and receives dialysis through a Hickman catheter. On physical examination, his temperature is 39.3°C, blood pressure is 100/70 mm Hg, pulse rate is 100/min, and respiratory rate is 22/min. There is tenderness at the catheter insertion site and a new grade 3/6 holosystolic murmur that increases with inspiration, heard at the left lower sternal border. Multiple blood cultures reveal growth of methicillin-resistant Staphylococcus aureus. Transthoracic echocardiography reveals a 0.5-cm vegetation on the tricuspid valve and moderate tricuspid insufficiency. The patient has a history of documented urticaria, bronchospasm, and hypotension associated with vancomycin use.

In addition to removal of the catheter, which one of the following is the most appropriate treatment?

a. Vancomycin
b. Daptomycin
c. Linezolid
d. Ceftaroline
e. Tigecycline

2. A 55-year-old woman developed a fever during her third week of hospitalization in the cardiac care unit after she had a myocardial infarction and experienced cardiogenic shock. Initially, broad-spectrum antibiotics were prescribed, including vancomycin and cefepime; use of these agents was discontinued after 72 hours, when it was clear that her hypotension and shock were related to her cardiac status. The patient has been in acute renal failure, with a creatinine level ranging from 5.0 to 8.0 mg/dL in the past week. Soon after admission, her glomerular filtration rate was less than 10 mL/min. She is now febrile, with a temperature of 39.1°C. You are called by the microbiologist after blood cultures from the patient’s central catheter yielded vancomycin-resistant Enterococcus faecalis.

Which one of the following would be the most appropriate treatment to initiate in this patient?

a. Start antibiotics only if cultures remain positive after removal of the catheter
b. Quinupristin-dalfopristin
c. Daptomycin
d. Linezolid
e. Ciprofloxacin

3. A 24-year-old male athlete is hospitalized after fever developed associated with an infected turf burn. He noticed some redness in the area 2 days ago but now has some purulent drainage and swelling. Cultures obtained from the drainage yielded S aureus, which is resistant to oxacillin but susceptible to vancomycin and linezolid.

Susceptibility testing of this strain will most likely show susceptibility to other antibiotics except for which one of the following?

a. Dicloxacillin
b. Linezolid
c. Trimethoprim-sulfamethoxazole
d. Tetracycline
e. Clindamycin

4. A 65-year-old woman with a medical history notable for diabetes mellitus and chronic obstructive pulmonary disease is admitted for symptoms consistent with possible exacerbation of chronic obstructive pulmonary disease and pneumonia. She has received azithromycin treatment many times in the past as an outpatient and again recently before this hospitalization. The patient is seeking treatment now because she is not improving with azithromycin therapy.

If the cause of her symptoms is Streptococcus pneumoniae, resistance to macrolides is most likely caused by which one of the following?

a. Alteration of topoisomerases
b. Presence of the ermB or mefA genes
c. Decreased permeability of the outer cell envelope
d. Plasmid acquisition
e. Presence of the meca gene

5. Which one of the following antibiotics is approved by the Food and Drug Administration for the management of methicillin-resistant S aureus nosocomial pneumonia?

a. Linezolid
b. Daptomycin
c. Ceftarolin
d. Tigecycline
e. Telavancin

Correct answers: 1. b, 2. d, 3. a, 4. b, 5. a
Mechanisms of Resistance and Clinical Relevance of Resistance to β-Lactams, Glycopeptides, and Fluoroquinolones

Louis B. Rice, MD

Abstract

The widespread use of antibiotics has resulted in a growing problem of antimicrobial resistance in the community and hospital settings. Antimicrobial classes for which resistance has become a major problem include the β-lactams, the glycopeptides, and the fluoroquinolones. In gram-positive bacteria, β-lactam resistance most commonly results from expression of intrinsic low-affinity penicillin-binding proteins. In gram-negative bacteria, expression of acquired β-lactamases presents a particular challenge owing to some natural spectra that include virtually all β-lactam classes. Glycopeptide resistance has been largely restricted to nosocomial Enterococcus faecium strains, the spread of which is promoted by ineffective infection control mechanisms for fecal organisms and the widespread use of colonization-promoting antimicrobials (especially cephalosporins and antianaerobic antibiotics). Fluoroquinolone resistance in community-associated strains of Escherichia coli, many of which also express β-lactamases that confer cephalosporin resistance, is increasingly prevalent. Economic and regulatory forces have served to discourage large pharmaceutical companies from developing new antibiotics, suggesting that the antibiotics currently on the market may be all that will be available for the coming decade. As such, it is critical that we devise, test, and implement antimicrobial stewardship strategies that are effective at constraining and, ideally, reducing resistance in human pathogenic bacteria.
specialized units, resistance is becoming increasingly common in the community setting, leading to substantial changes in our typical prescribing practices. The use of β-lactam antibiotics to empirically treat soft tissue infections in many regions of the world has been compromised by the widespread isolation of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA). Similarly, the emergence and spread of Escherichia coli strains resistant to both fluoroquinolones and extended-spectrum cephalosporins has driven the greater use of carbapenems for the treatment of urinary tract infections. Perhaps as a consequence, the emergence of carbapenem resistance in previously susceptible species has been identified around the world.

For most of the antibiotic era (roughly from the mid-1940s forward), concerns about resistance were tempered by the knowledge that newer, more potent agents were being developed by the dozens of companies in the business of making antibiotics. We no longer have the luxury of anticipating the imminent introduction of the solution to our resistance problems. The number of large pharmaceutical corporations actively engaged in antibiotic discovery has dwindled to the single digits, and the number of new antimicrobial agents introduced has been reduced to a trickle over the past decade. Numerous explanations for the retreat from antimicrobial discovery have been proffered. Concern has been raised that the criteria for clinical development promoted by the US Food and Drug Administration is increasing the cost of drug development. Along the same lines, pharmaceutical companies preferentially develop drug classes with greater potential for profit (net asset value) than that obtained with antibiotics. These concerns can be addressed by public policy modifications. Perhaps the most problematic challenge to developing new antibiotics that are active against currently resistant pathogens is that, given the multiresistant nature of modern pathogens and the varied (sometimes nonspecific) mechanisms of resistance, identifying and developing safe new agents with broad activity is extremely difficult. As such, it has never been more important for practitioners to develop better strategies for using antibiotics to minimize the emergence and spread of resistance. This review focuses on resistance to 3 classes of antibiotics (β-lactams, glycopeptides, and fluoroquinolones), reviewing mechanisms and pointing out some of the challenges in employing antimicrobial usage strategies to curb growing resistance.

DEFINING RESISTANCE

Antimicrobial resistance and susceptibility in the clinical setting take many forms that are not predictable by in vitro susceptibility testing. For example, susceptible bacteria deep inside an abscess may not be accessible to antibiotics and therefore behave as if they are resistant. A fully susceptible organism may also act resistant if present in a biofilm attached to a foreign body. Conversely, species often considered resistant to specific antibiotics (eg, Pseudomonas aeruginosa and tetracycline) may be treated successfully if the infection occurs in the lower urinary tract, where the antibiotic can be concentrated heavily and the density of bacteria is generally low. Thus, the advisability of using an antimicrobial agent in a particular situation depends on a careful consideration of the in vitro susceptibility of the bacterial strain, the drug concentrations achievable at the site of infection, and the metabolic state of the infecting bacteria. Standard-setting organizations (the US Food and Drug Administration, the European Committee on Antimicrobial Susceptibility Testing, the Clinical and Laboratory Standards Institute) establish susceptible, intermediate, and resistance standards based on a careful analysis of achievable serum levels, susceptibilities of bacteria, results of animal experiments, and human clinical trials. Given the variability of individual clinical circumstances, it is clear that these designations must be considered educated guides rather than firm pronouncements.

Resistance can be achieved either through gene mutation or through the acquisition of exogenous resistance determinants. Mechanisms by which resistance genes are acquired vary. Transferable plasmids may be very large (>150 kb) and contain a variety of resistance gene. Plasmids may form cointegrates with transposons that incorporate one or more resistance genes. Some plasmids encode their own transfer machinery, whereas others can be mobilized by a coresident transferable plasmid. Chromosomal elements may also transfer on their own or be mobilized by transferable plasmids. Excellent work by Manson et al has shown that large chromosomal transfers among Enterococcus faecalis result from mobilization of segments of the chromosome by conjugative plasmids through cointegration across identical insertion sequences located on both replicons. These findings suggest that virtually any part of the genome can be mobilized, emphasizing the fluidity of many bacterial genomes.

RESISTANCE TO SPECIFIC ANTIMICROBIAL CLASSES

Resistance to β-Lactams

β-Lactam antibiotics act by binding to cell wall synthesis enzymes known as penicillin-binding proteins (PBPs), thereby inhibiting peptidoglycan syn-
thesis. Inhibition of PBPs weakens the cell wall, resulting in inhibition of cell growth and frequently in cell death. The 3 mechanisms of β-lactam resistance are reduced access to the PBPs, reduced PBP binding affinity, and destruction of the antibiotic through the expression of β-lactamases (enzymes that bind and hydrolyze β-lactams) (Table). In gram-positive bacteria, antibiotics have free access to the bacterial cytoplasmic membrane, where the PBPs are located. In gram-negative bacteria, the bacterial outer membrane (absent in gram-positive bacteria) can both restrict β-lactam entry and concentrate β-lactamase molecules. If β-lactam molecules are sufficiently excluded from this periplasmic space by either reduced entry or increased efflux, and if β-lactam molecules are heavily concentrated, even a relatively weak β-lactamase can confer high levels of resistance.

### Resistance to β-Lactams in Gram-Positive Bacteria

With the exception of staphylococci (which produce a narrow-spectrum penicillinase), clinically important β-lactam resistance in gram-positive species occurs almost exclusively through the expression of PBPs that bind β-lactams with low affinity. In *S. aureus*, resistance to methicillin results from the expression of low-affinity PBP2a. Penicillin-binding protein 2a is encoded by the mec determinant, which is found exclusively in mobile chromosomal elements referred to as staphylococcal chromosomal cassette mec (SCCmec). It is presumed that the transfer of these elements between staphylococcal strains has contributed to the spread of MRSA, although such transfer has not been documented in vitro. The sizes of the SCCmec elements vary, with recent CA-MRSA isolates demonstrating a smaller, more compact element devoid of other resistance determinants (partially explaining the greater susceptibility of the community-acquired strains than their nosocomial counterparts). Genotyping data suggest that relatively few CA-MRSA clones are circulating around the world, although more recent data using genome-wide single nucleotide polymorphisms suggest that there may have been multiple transfers of the element into clinical strains with similar genotypes.

Expression of methicillin resistance in *S. aureus* is complex, involving the participation of several other loci that have become known as *fem* (factors essential for methicillin resistance) or *aux* (auxiliary) factors. Many of these loci encode functions involved in the development of precursors of the cell wall. Their inactivation generally results in reduced levels of resistance, suggesting that PBP2a is limited in its ability to process cell wall precursors differing from the norm. As a class B PBP, PBP2 does not have a functional glycosyltransferase region, so it must work in concert with the glycosyltransferase of PBP2 to make peptidoglycan. Consequently, deletion of PBP2 renders PBP2a unable to confer resistance to β-lactam antibiotics.

The chromosomal location of the SCCmec determinants and the small size of the more recently identified regions suggest that the metabolic costs of retaining these determinants may be insignificant. Moreover, β-lactam antibiotics do not achieve sufficient concentrations at sites of *S. aureus* colonization to convincingly select for colonization by resistant strains. As such, strategies to limit MRSA by reducing consumption of β-lactam antibiotics have had, at best, mixed results. Strategies designed to limit the spread of MRSA through infection control interventions have been more effective.

Compelling data suggest that β-lactam antibiotics are superior to vancomycin for the treatment of methicillin-susceptible *S. aureus*. Until the recent introduction of cefsulodin and celtaroline, expression of PBP2a was considered to confer resistance to all β-lactam antibiotics. Whether the superiority of β-lactams will extend to MRSA now that these agents are available remains to be determined.

The widespread resistance of *Enterococcus faecium* to ampicillin is attributable to the expression of low-affinity PBP5, which though apparently intrinsic to the species, is transferable between *E. faecium* strains. The spread of ampicillin-resistant *E. fae-

### TABLE. Named β-Lactamases From Clinical Isolates, by Ambler Class

<table>
<thead>
<tr>
<th>Ambler classb (No.)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM (190)</td>
<td>IMP (30)</td>
<td>CMY (73)</td>
<td>OXA (224)</td>
<td></td>
</tr>
<tr>
<td>SHV (141)</td>
<td>VIM (3)</td>
<td>FOX (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTX-M (120)</td>
<td>INH (8)</td>
<td>ACT (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GES (17)</td>
<td>NDM (6)</td>
<td>DHA (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPC (11)</td>
<td>MOX (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PER (7)</td>
<td>MIR (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEB (7)</td>
<td>ACC (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SME (3)</td>
<td>CFE (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC1 (1)</td>
<td>LAT (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on information obtained from Lahey Clinic Web site (http://www.lahey.org/studies/) on July 25, 2011.  
*Ambler classification is based on DNA sequence similarity and does not directly correlate with function or spectrum.  
*PC1 is the only β-lactamase of clinical importance found in gram-positive bacteria. At this time, it is virtually uniformly present in pathogenic staphylococcal species and has never been shown to extend its spectrum to include broad-spectrum cephalosporins.
Antimicrobial Resistance: Colonization by Ampicillin-Resistant Strains

Colonization by ampicillin-resistant strains has been attributed to clonal complex 17, a loosely associated group of strains that have undergone significant gene acquisition. Recent work suggests that E. faecium of this clonal complex has acquired lower-affinity PBP5 on several occasions.

The extent to which genetic exchange and recombination occur in E. faecium strains seriously complicates attempts to establish specific genetic lineages.

Clinical studies and a series of animal experiments suggest that cephalosporins, especially those that enter the gastrointestinal tract in high concentrations, are powerful selectors for high-level gut colonization by ampicillin-resistant E. faecium. The second wave of resistance in this species is associated with reductions in ampicillin-resistant E. faecium colonization.

Streptococcus pneumoniae takes advantage of its capacity to take up DNA to become resistant to β-lactams. Resistant strains exhibit a variety of “mosaic” genes derived from recombination between native pneumococcal PBP genes and those from less susceptible viridans streptococci. Resistance achievable by this mechanism is limited by the levels of resistance expressed by the native PBPs that contribute to the mosaic and generally remains at low levels that affect the efficacy of intravenous antibiotics only in the cerebrospinal fluid. Other naturally transformable species, such as Neisseria gonorrhoeae, also exhibit mosaic PBP genes. Recently, the first gonococcal strain exhibiting high-level resistance to extended-spectrum cephalosporins was shown to mediate resistance through a mosaic PBP gene.

It stands to reason that a mosaic gene would be less “efficient” at performing its function than the native gene and that therefore reductions in the selective pressure favoring persistence of these genes (ie, reduction in use of β-lactam antibiotics) would result in reduced prevalence of resistance. Systematic attempts to reduce use of antibiotics in the community have been associated with reductions in S. pneumoniae resistance, however, specific correlations between reductions in use of β-lactams (as opposed to erythromycin or trimethoprim-sulfamethoxazole) and penicillin resistance have been difficult to demonstrate. Moreover, antimicrobial usage analyses have been complicated by the widespread use of the 7-valent pneumococcal conjugate vaccine, which has played a major role in reducing rates of penicillin resistance in S. pneumoniae by targeting serotypes with a high prevalence of resistance.

Resistances to β-Lactams in Gram-Negative Bacteria

Resistance to β-lactams in gram-negative bacteria occurs overwhelmingly by expression of β-lactama
tes. The combination of proliferation of β-lactam antibiotics and the widespread access to molecular biological techniques has led to an explosion in the number of named β-lactamases in the past decade. As of July 25, 2011, the number of named β-lactamases listed on the authoritative Web site managed by George Jacoby at Lahey Clinic was 927 from 24 different β-lactamase classes.

The first wave included a few different narrow-spectrum penicillinases that emerged in association with the use of ampicillin to treat gram-negative infections. The growing prevalence of strains elaborating these enzymes, such as TEM-1 of E. coli and SHV-1 of Klebsiella pneumoniae, prompted the development of newer β-lactam classes (such as the cephaplorins, carbapenems, and aztreonam) that were resistant to hydrolysis. The second wave of clinical importance occurred in the 1980s and involved the emergence of resistance to extended-spectrum cephalosporins. This resistance was focused primarily in K. pneumoniae and resulted from the accumulation of point mutations within TEM or SHV-type enzymes. The accumulation of enough point mutations, usually in combination with increased expression due to promoter changes and reduced β-lactam access to the periplasmic space from reductions in porin expression, resulted in expression of high-level resistance to extended-spectrum cephalosporins.

There are 3 important points to make about this second wave of β-lactamases. The first is that most of the mutations resulted in an “opening up” of the enzyme-active site. This opening up allowed the accommodation of the bulky extended-spectrum cephalosporins, but at the cost of weakening activity against ampicillin. The second is that, with few exceptions, the mutations resulted in increased susceptibility to clinically available β-lactam inhibitors (although the clinical strains were generally resistant to the β-lactam–β-lactamase inhibitor combinations because they made multiple enzymes in high quantity). Finally, these extended-spectrum β-lactamases were inactive against carbapenems, resulting in carbapenems being used more frequently in settings in which they were prevalent. The weakening of the β-lactamases against penicillins, their hypersusceptibility to inhibition, and their universal susceptibility to carbapenems suggested that reductions of cephalosporin use in favor of either in-
hibitor combinations or carbapenems would result in reductions in their prevalence. Several institutions reported reductions in extended-spectrum \(\beta\)-lactamase prevalence in association with reduced cephalosporin use during this period.\(^3\)\(^7\)-\(^3\)\(^9\) The third wave overlapped with the second and involved the emergence and spread of the CTX-M family of \(\beta\)-lactamases.\(^4\)\(^0\) Derived from the chromosomal enzyme of *Kluyvera* spp, these enzymes are natural cephalosporinases. They have penetrated widely into many different species, including *K. pneumoniae*. In contrast to the first wave, CTX-M enzymes are also widely prevalent in pathogenic *E. coli*.\(^4\)\(^1\) Worldwide spread of sequence type ST131 *E. coli* expressing both CTX-M–type enzymes and fluoroquinolone resistance has seriously complicated the empirical treatment of community-acquired urinary tract infections in many regions.\(^4\)\(^2\)-\(^4\)\(^3\) Whether reductions in cephalosporin use will lead to reduced prevalence of these strains is unclear, as they are cephalosporinases by nature (ie, they will not likely be overtaken by narrow-spectrum variants). Moreover, the nearly universal association with fluoroquinolone resistance makes coselection a significant problem.

The fourth wave of \(\beta\)-lactamase–mediated resistance is the emergence and spread of carbapenemases.\(^4\)\(^4\) The carbapenemases are broadly active precisely because they resist hydrolysis by a wide range of \(\beta\)-lactamases and are often a “last line” of effective therapy for serious infections caused by gram-negative bacteria. There are 3 broad categories of carbapenemases. The first is the KPC (*K. pneumoniae* carbapenemase) class, which is found primarily, but not exclusively, in *K. pneumoniae*.\(^4\)\(^5\) Strains expressing these enzymes have spread worldwide and are characteristically resistant to all \(\beta\)-lactam antibiotics as well as resistant to inhibition by currently available \(\beta\)-lactamase inhibitors. In vitro expression of resistance to carbapenemases is variable and may be dependent on difficult-to-detect factors like plasmid copy number or porin reduction,\(^4\)\(^6\) making these strains difficult to detect at times. The KPC enzymes are often encoded on a mobile transposon designated Tn\(4401\)\(^4\)\(^7\) and can be transferred to different species on transferable plasmids. Originally concentrated in *K. pneumoniae* in the United States, KPC genes have now been identified in a wide variety of different gram-negative species and have been found throughout the world.\(^4\)\(^5\)

The second major class of carbapenemases are the metalloenzymes, so-named because they require the presence of a metal (usually zinc) as a
cofactor for activity. A number of different “groups” of metalloenzymes have been described. Originally concentrated in Japan (where the number of carbapenems and their use was greatest in the 1980s and 1990s), they have now been identified worldwide. The mechanism by which they hydrolyze β-lactams differs in important ways from the other types of β-lactamases, and therefore they are not subject to inhibition by any of the clinically available β-lactamase inhibitors. Although metalloenzymes in general hydrolyze aztreonam poorly, and therefore their presence can be suggested by carbapenem resistance in the setting of aztreonam susceptibility, the frequent co-drolyze aztreonam poorly, and therefore their presence can be suggested by carbapenem resistance in the setting of aztreonam susceptibility, the frequent co-expression of more common extended-spectrum β-lactamases in conjunction with metalloenzymes results in clinical strains that express resistance to both classes. Although a number of different types of metalloenzymes have been described, enzymes designated VIM-1 and NDM-1 have been implicated in recent international outbreaks and in rising endemicity in different regions.

The third major class of carbapenemases are the OXA-type enzymes. More than 100 such enzymes have been described in a number of gram-negative species. Only a few are associated with carbapenem resistance. These enzymes are responsible for most of the carbapenem resistance observed in Acinetobacter species. Like the other carbapenemases, they are not susceptible to inhibition by currently available β-lactamase inhibitors.

In many instances, in vitro analysis of carbapenem hydrolysis by carbapenemases demonstrates relatively weak activity. Clinical resistance results from the frequent presence of auxiliary mechanisms that augment β-lactamase-mediated resistance, such as increased expression of β-lactamase (generally through the acquisition of stronger promoters) and reduced β-lactam access to the periplasmic space through porin mutations or pump activations.

The broad activity of carbapenemases compromises both therapy for individual patients and strategies designed to modify antimicrobial selective pressures. There are no classes of β-lactams that have predictable activity against strains producing carbapenemases, and many carbapenem-resistant strains also express resistance to fluoroquinolones and aminoglycosides. Thus, clinicians must frequently turn to second-line agents such as colistin or tigecycline. Given concerns about toxicity, efficacy, and spectrum that accompany use of these agents, it is hard to envision circumstances in which their use as empirical agents would be welcomed.

Resistance to Glycopeptides

Glycopeptides (vancomycin is the only glycopeptide licensed for use in the United States) are of sufficient size to preclude their passage through the porins that allow entry into the periplasmic space of gram-negative bacteria, so they are active only against gram-positive bacteria. Glycopeptides act by binding to the terminal D-alanine present on the peptidoglycan stem of peptidoglycan precursors, thereby inhibiting the transpeptidation step required for peptidoglycan cross-linking. High-level resistance to glycopeptides results from the acquisition and expression of operons that substitute a terminal D-lactate or D-serine for the D-alanine, thereby reducing the vancomycin binding affinity.

Expression of these operons is regulated by response regulators encoded by the same transposons that encode resistance, so the cost of having them is minimized. Vancomycin-resistant enterococci (VRE) (predominantly E. faecium) emerged in the 1980s, most likely in response to the widespread use of orally administered (and nonabsorbed) glycopeptides in humans with gastrointestinal infection due to Clostridium difficile (in the United States) and to the use of orally administered glycopeptides to animals as a feed additive (in Europe). Although a large number of different glycopeptide resistance operons have now been described (VanA, B, C, D, E, F, G, L, M), VanA and VanB remain the most clinically relevant. Both have been identified on transposons that are presumed to be the mechanisms that facilitate their dissemination. For reasons that remain unexplained, the acquired glycopeptide resistance determinants have remained concentrated in E. faecium. Vancomycin-resistant E. faecalis generally represents a minority of isolates but may be particularly important in the rare transfer of these operons to S. aureus.

Of great concern more than a decade ago was the possibility that the glycopeptide resistance determinants prevalent in E. faecium would become widespread in MRSA, many strains of which were susceptible only to glycopeptides. The level of concern over this possibility has diminished in the intervening years for 2 reasons. The first is that several new agents (quinupristin-dalfopristin, linezolid, daptomycin, tigecycline, telavancin, cefaroline) have been introduced that have activity against MRSA. The second reason is the S. aureus strains expressing the known vancomycin resistance determinants have been exceedingly rare. To date, roughly a dozen such strains have been reported, and there is no compelling evidence for any clonal spread.

A more common type of reduced vancomycin susceptibility observed in S. aureus is a stepwise, intermediate resistance that raises the minimum inhibitory concentration (MIC) marginally (to 4-8 µg/mL) but enough to compromise treatment of clinical staphylococcal infection by vancomycin. This type of intermediate resistance (vancomycin-intermediate S. aureus, or VISA) appears to be an intrinsic adapta-
tion of certain \textit{S aureus} strains that occurs under circumstances of persistent vancomycin selective pressure.\textsuperscript{57} Although the mechanisms underlying the intermediate phenotype remain unclear, most appear to involve a thickening of the cell wall in a way that contains increased numbers of unlinked peptidoglycan precursors.\textsuperscript{57} These unlinked precursors are thought to bind the glycopeptides before they can interact with peptidoglycan precursors at the cytoplasmic membrane, essentially soaking up the antibiotic before it can bind to the cell wall precursors. The intermediate phenotype is often unstable in the absence of persistent glycopeptide selective pressure, and clonal spread of these strains has not been observed.

A potentially more troublesome development in \textit{S aureus} has been what some have noted as “MIC creep.” Clinical failures have been observed more commonly with \textit{S aureus} strains having MICs of 2 \(\mu\text{g/mL}\) or higher. Consequently, the most recent recommendation from the Infectious Diseases Society of America for treatment of serious \textit{S aureus} infections is that alternative therapeutic agents should be used for patients whose isolate MICs are equal to or greater than 2 \(\mu\text{g/mL} \).\textsuperscript{58} The extent to which \textit{S aureus} MIC creep truly exists is debatable. One recent study indicated that the creep identified over a 10-year period was methodology dependent and most pronounced with the use of E-test strips.\textsuperscript{59} It remains good advice to follow up patients closely and, if the clinical progress dictates, switch to a non-glycopeptide for the treatment of serious \textit{S aureus} infections. Some experts recommend targeting higher trough concentrations in dosing regimens. However, a recent multicenter study concluded that a 3-fold increased risk of renal dysfunction was associated with vancomycin regimens in which the trough concentration exceeded 15 \(\mu\text{g/mL} \).\textsuperscript{60}

The mutational evolution to vancomycin resistance in \textit{S aureus} appears to be a phenomenon that is only advantageous in the setting of continued vancomycin selective pressure, probably because thick-walled \textit{S aureus} cocci are not favored in the natural environment. But what of the vancomycin resistance operons? Is it likely that reduced vancomycin use will reduce their prevalence in \textit{E faecium}? Probably not. Associations between vancomycin use in the clinical setting and VRE colonization have often been tenuous. The potential connection between oral vancomycin use and VRE colonization was recognized early, leading to recommendations that metronidazole, rather than oral vancomycin, be used to treat \textit{C difficile} colitis. Unfortunately, it was soon recognized that exposure to potent anti-anaerobic antibiotics, including metronidazole, was a significant risk factor for VRE colonization.\textsuperscript{61} Recent data indicate that reductions of use of oral glycopeptides in European feed animals have dramatically decreased animal colonization with VRE.\textsuperscript{62} However, reduction of parenteral vancomycin use in humans is unlikely to have a major impact on hospital prevalence, since little vancomycin enters the gastrointestinal tract when it is administered parenterally. The strongest selective pressure for VRE colonization and infection most likely comes from the use of extended-spectrum cephalosporins,\textsuperscript{63} which select for ampicillin-resistant \textit{E faecium} (the vast majority of VRE are ampicillin-resistant \textit{E faecium}). Whether systematic efforts to reduce cephalosporin use will reduce VRE prevalence remains to be determined.

### Resistance to Fluoroquinolones

High levels of resistance to fluoroquinolones in both gram-positive and gram-negative bacteria are attributable to the accumulation of point mutations in genes encoding cellular topoisomerases (enzymes that act to coil and uncoil complementary DNA strands) along with acquisition of auxiliary mechanisms that serve to augment the level of resistance expressed.\textsuperscript{64} These point mutations occur primarily in the quinolone resistance–determining regions, the areas of the topoisomerases involved in quinolone binding. The level of resistance to a specific fluoroquinolone associated with a mutation depends on the nature of the mutation and whether it is located in the gene encoding the primary target for that fluoroquinolone (gyrA or parC, for example). In general, single point mutations confer only modest levels of resistance. This observation has led to the idea that a “mutant prevention concentration”\textsuperscript{65} (MPC) can be identified that prevents the clinical emergence of resistant strains from susceptible populations. In other words, keeping the concentration of a fluoroquinolone persistently above the level of resistance expressed by a first-order mutant effectively suppresses that mutant from emerging. In vitro and some animal studies support the effectiveness of this strategy.\textsuperscript{66-69}

Unfortunately, in the clinical environment, the relationship between antimicrobial administration and the emergence of resistance is not simple. There are several mechanisms by which bacteria, especially gram-negative bacteria, can move closer to the breakpoint for resistance without actually becoming clinically resistant. Mechanisms facilitating such increases include the increased expression or acquisition of a number of efflux pumps, the acquisition of plasmids that encode “protection enzymes” (Qnr), or the acquisition of plasmids encoding enzymes that inactivate the fluoroquinolone [aac(6\(^\prime\))]-Ib-cr] (Figure 2). In one study, the presence of qnrA in an \textit{E coli} strain increased the MPC 8-fold, from 1 to 8 \(\mu\text{g/mL}\), pushing it beyond clinically achievable
concentrations. Moreover, the concentrations of fluoroquinolone achieved throughout the body are not uniform. The concentration in the lung may be considerably higher than in the bowel (where many mutants are waiting to emerge). Finally, the MPC for moxifloxacin against *S pneumoniae* is considerably different than the moxifloxacin MPC against *P aeruginosa*. Consequently, concentrations that suppress the emergence of fluoroquinolone-resistant mutants in *S pneumoniae* may promote their emergence in *P aeruginosa* in the same patient. In the current environment, in which fluoroquinolone-resistant variants of common pathogens are commonplace, use of these agents invites colonization by resistant strains. It is therefore unlikely that any strategies designed to try to suppress the emergence of resistance by using higher concentrations of fluoroquinolones will be successful in the clinical setting.

**CONCLUSION**

Although the emergence of antimicrobial resistance is invariably associated with antimicrobial use, the multiple mechanisms of resistance, the frequency of gene exchange in the natural environment, and the nonspecific nature of many resistance mechanisms make developing resistance-specific strategies to reduce individual resistance phenotypes complicated and fraught with potential deleterious unintended consequences. Efforts to reduce overall antimicrobial exposure, for example, through organized efforts to identify appropriate minimal lengths of therapy, hold greater promise for reducing the burden of

---

**FIGURE 2.** Representative graph (not based on actual data) of the individual and combined contributions of various fluoroquinolone resistance mechanisms to clinical resistance to fluoroquinolones. In this case, the baseline susceptible species (*Escherichia coli*, for example) would have a minimum inhibitory concentration (MIC) in the absence of any resistance mechanism of 0.06 μg/mL. In vitro experiments performed during the development of a fluoroquinolone, for example, would determine the mutant prevention concentration (MPC) (the concentration of antimicrobial agent that will suppress the emergence of single-step mutants) to be 1 μg/mL, or one doubling dilution above the MIC that would result from a single *gyrA* amino acid substitution (which confers a 3-fold increase in resistance). With clinical use of the agent, auxiliary mechanisms of resistance, such as activation of intrinsic efflux pumps or acquisition of *qnr* genes or modifying enzyme gene *aac(6')-Ib-cr*, are acquired by strains and increase the MIC but not to a level that would be considered clinically resistant. With one or more of these auxiliary genes present, the 8-fold increase in MIC associated with a single amino acid change in *gyrA* results in a strain that has an MIC above the previously defined MPC (ie, 1 μg/mL is no longer the MPC). Under these circumstances, a previously defined MPC is inaccurate and misleading and may result in selection of resistant mutants.
resistance. Reductions in the use of antibiotics (eg, the fluoroquinolones) that promote the emergence of broad-spectrum mechanisms of resistance may have greater benefits in reducing the prevalence of resistance to a variety of troublesome nosocomial pathogens.

Correspondence: Address to Louis B. Rice, MD, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903 (rice@lifespan.org). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.org.

The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

REFERENCES


Current Concepts in Laboratory Testing to Guide Antimicrobial Therapy

Stephen G. Jenkins, PhD, and Audrey N. Schuetz, MD, MPH

CME Activity

Target Audience: The target audience for Mayo Clinic Proceedings is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine; and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care providers must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. Mayo Clinic Proceedings aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: College of Medicine, Mayo Clinic is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: College of Medicine, Mayo Clinic designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit(s). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives: Educational objectives. On completion of this article, readers should be able to: (1) interpret the results generated by the various standardized methods of antimicrobial susceptibility testing commonly employed by clinical microbiology laboratories; (2) evaluate findings generated from phenotypic methods used for detection of antimicrobial resistance; and (3) explain the rationale for use of molecular methods for detection and characterization of antimicrobial resistance determinants.

Disclosures: As a provider accredited by ACCME, College of Medicine, Mayo Clinic (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity and scientific rigor in its educational activities. Course Director(s), Planning Committee Members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so those participants in the activity may formulate their own judgments regarding the presentation. In their editorial and administrative roles, William L. Lanier, Jr., MD, Scott C. Litin, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry. Drs Jenkins and Schuetz have no financial disclosures relevant to this manuscript. Two drugs mentioned in the article are off-label use for antimicrobial therapy.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.
3. Review and complete the CME Test Evaluation and Evaluation of Learning Style. Upon successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 3/1/2012

Expiration date: 2/28/2014 (Credit can no longer be offered after it has passed the expiration date.)


Questions? Contact dletsupport@mayo.edu.

Abstract

Antimicrobial susceptibility testing (AST) is indicated for pathogens contributing to an infectious process that warrants antimicrobial therapy if susceptibility to antimicrobials cannot be predicted reliably based on knowledge of their identity. Such tests are most frequently used when the etiologic agents are members of species capable of demonstrating resistance to commonly prescribed antibiotics. Some organisms have predictable susceptibility to antimicrobial agents (ie, Streptococcus pyogenes to penicillin), and empirical therapy for these organisms is typically used. Therefore, AST for such pathogens is seldom required or performed. In addition, AST is valuable in evaluating the activity of new and experimental compounds and investigating the epidemiology of antimicrobial resistant pathogens. Several laboratory methods are available to characterize the in vitro susceptibility of bacteria to antimicrobial agents. When the nature of the infection is unclear and the culture yields mixed growth or usual microbiota (wherein the isolates usually bear little relationship to the actual infectious process), AST is usually unnecessary and results may, in fact, be dangerously misleading. Phenotypic methods for detection of specific antimicrobial resistance mechanisms are increasingly being used to complement AST (ie, inducible clindamycin resistance among several gram-positive bacteria) and to provide clinicians with preliminary direction for antibiotic selection pending results generated from standardized AST (ie, β-lactamase tests). In addition, molecular methods are being developed and incorporated by microbiology laboratories into resistance detection algorithms for rapid, sensitive assessment of carriage states of epidemiologically and clinically important pathogens, often directly from clinical specimens (ie, presence of vancomycin-resistant enterococci in fecal specimens).
Laboratory testing to guide antimicrobial therapy

such as Enterobacteriaceae, staphylococci, enterococci, countered pathogens (eg, members of the family Enterobacteriaceae, staphylococci, enterococci, and some nonfermentative gram-negative bacilli, such as Pseudomonas aeruginosa), and resistant) of the antimicrobial agent and the pathogen under study, and the infection site. Ranges tested vary with the antimicrobial agent, the organism used for the testing of frequently encountered pathogens (eg, members of the family Enterobacteriaceae, staphylococci, enterococci, and some nonfermentative gram-negative bacilli, such as Acinetobacter baumannii and Pseudomonas aeruginosa) may be supplemented or, in some cases, replaced by another medium, allowing for accurate testing of many fastidious organisms for which standardized methods are not available for reliable disk diffusion testing. Dilution methods are also amenable for use in automated antibiotic susceptibility testing systems.

Breakpoints derived by regulatory bodies and professional groups are frequently similar. For example, there are relatively small numbers of discordant breakpoints between the US Food and Drug Administration (FDA) and the Clinical and Laboratory Standards Institute (CLSI), and those discrepancies are under active review by both organizations. By comparison, there are sometimes sizable differences in the interpretive criteria used in different countries or regions of the world for the same antibiotics. Such disparities are sometimes a function of the fact that different dosages and/or administration intervals are used for the same antimicrobial agents. In addition, some breakpoint-setting organizations are more conservative than others in assessing susceptibility to anti-infectives, placing more emphasis on detection of emerging resistance based on examination of microorganism population distributions. Technical factors, including incubation temperature and atmosphere, inoculum size, and test medium formulation, can also affect zone diameters and MICs, justifying different breakpoints.

**Agar Dilution Method**

Mueller-Hinton agar is the medium recommended for routine testing of most rapidly growing aerobic and facultatively anaerobic bacterial pathogens. The solvents and diluents that are required to prepare stock solutions of antibiotics and the methods used to perform such testing are defined in the CLSI standard on dilution AST. The agar dilution approach to susceptibility testing is both well standardized and reproducible and may be used as a reference method in the evaluation of other dilution assays. This method facilitates the concomitant and efficient testing of large numbers of organisms. In addition, population heterogeneity (ie, resistant subpopulations of organisms) and inoculum contamination (ie, “mixed” cultures) are more easily detected by agar than by broth testing. The primary disadvantages of this testing approach are the labor-intensive, time-consuming steps required to prepare testing plates, particularly when the number of compounds to be tested is high or when only a limited number of bacteria are to be studied, or both. For these reasons, most clinical microbiology laboratories do not use this approach for routine AST.

**Broth Dilution Methods**

General approaches to broth dilution testing include both macrodilution, wherein volumes of broth in test tubes for each dilution typically equal or exceed 1 mL, and broth microdilution (BMD), in which antimicrobial concentrations are most frequently of smaller volumes in 96-well microtiter plates. The broth macrodilution approach is both reliable and well standardized and is of particular utility in research studies and in testing of a single antimicrobial agent for 1 bacterial isolate. The method is, however, both laborious and time intensive and, because of the ready commercial availability of convenient microdilution systems, is not generally considered practical for routine use in clinical microbiology laboratories.

The convenience afforded by BMD has led to its widespread use in both clinical and reference laboratories. This approach is, in fact, now considered the reference international testing method. Plastic, disposable plates containing a panel of several antibiotics to be tested concomitantly may be prepared.
within the laboratory or, alternatively, purchased from commercial vendors either as freeze-dried or frozen trays. The BMD technique is also well standardized and reliable. The inoculation and reading procedures readily lend themselves to the simultaneous testing of several antibiotics with single bacterial isolates. Although most commercially available systems use multipoint inoculating devices or automated inoculation instruments, plates may also be inoculated with multichannel pipetors. Testing results may be determined either visually or through the use of semiautomated or automated instruments. An example of a commercially available manual BMD is Sensititre (TREK Diagnostic Systems, Cleveland, OH). Examples of automated BMD platforms include the BD Phoenix (Becton Dickinson, Franklin Lakes, NJ), Microscan (Siemens Healthcare Diagnostics, Deerfield, IL), and Vitek (bioMérieux, Marcy l’Etoile, France).

AGAR DISK DIFFUSION TESTING

In many clinical microbiology laboratories an agar disk diffusion method is routinely used for the testing of common, rapidly growing, and some fastidious bacterial pathogens, allowing categorization of most such isolates as susceptible, intermediate, or resistant to a wide range of antimicrobial agents. This approach is particularly common in resource-limited settings and when performed according to standardized methods, such as those published by the CLSI, provides accurate direction to clinicians making therapeutic antibiotic decisions. With this testing approach, commercially prepared filter paper disks impregnated with specified predetermined concentrations of the antibiotics to be assessed are applied to the surface of a defined agar medium previously inoculated with the challenge bacterial pathogen. The antimicrobial agents then diffuse from the disks through the agar, and as the distance from the disks increases, the drug concentrations decrease in a logarithmic fashion, creating gradients of drug concentrations in the medium around the disks. Simultaneously with the diffusion of the drugs, the bacteria inoculated to the agar surface not inhibited by the concentrations of the antibiotics in the agar multiply, creating a visible lawn of growth. In areas where the test organism is inhibited by the antimicrobial agents, growth fails to occur, resulting in zones of inhibition around each active drug. The inhibitory zone diameters are influenced by the diffusion rates of the various antimicrobial agents through the agar, a function of the molecular sizes and hydrophilicities of the compounds. The zone sizes are inversely proportional to the logarithms of the antibiotic MICs. After incubation at recommended temperatures, atmospheric conditions, and times, depending on the pathogen under study, the diameters of the zones of inhibition are measured in millimeters and interpreted based on published standards. The most recent criteria for interpreting zone diameters of inhibition for antibiotics approved for use by the FDA are listed in Table 3 of a document updated annually by the CLSI.

Such disk diffusion interpretive criteria (breakpoints) are chosen after the establishment of MIC breakpoints, which is accomplished by plotting the inhibition zone diameters against the MICs derived from the testing of a large number of strains of various species. A statistical approach using a linear regression formula may be used to calculate the appropriate zone diameter intercepts for previously determined MIC breakpoints. An alternative, practical approach to deriving disk diffusion interpretive criteria is the use of the error rate–bounded method by which the zone diameter breakpoints are selected based on the minimization of disk interpretive errors, particularly very major errors. This most recent CLSI approach focuses on the rate of interpretive errors near the proposed breakpoint vs error rates for MICs greater than a single log_{10} dilution from the MIC breakpoints. The concept of this approach is that errors occurring with organisms for which MICs closely approximate the MIC breakpoints are less of a clinical concern than errors for more highly susceptible or resistant isolates.

The disk diffusion approach for AST has been standardized primarily for commonly encountered, rapidly growing bacterial pathogens and is applicable to neither anaerobes nor fastidious species that demonstrate marked variability in growth rate from strain to strain. The disk diffusion test approach has been modified, though, to allow for reliable testing of several species of fastidious bacteria, including Haemophilus influenzae and Neisseria gonorrhoeae. There are several advantages to the disk diffusion approach to AST, including the following: (1) it is technically easy to perform and results are reproducible, (2) the reagents and supplies are inexpensive, (3) it does not require the use of expensive equipment, (4) it generates categorical interpretive results well understood by clinicians, and (5) it allows for considerable flexibility in the selection of antibiotics for testing. However, this method also has a number of drawbacks. For example, only a limited number of bacterial species can be tested using this approach. In addition, the disk diffusion test is inadequate for detection of vancomycin-intermediate Staphylococcus aureus. Of importance, it provides only a qualitative result, whereas a quantitative MIC result that indicates the degree of susceptibility may in some cases be required (eg, when prolonged or continuous infusion of specific antimicrobial agents is being considered for treatment of infections caused by relatively resistant bacteria).
METHODS FOR FASTIDIOUS BACTERIA

Many fastidious bacterial species do not grow satisfactorily using standard in vitro susceptibility testing approaches with unsupplemented media. For several of the more frequently encountered pathogens (eg, *Streptococcus pneumoniae* and *Streptococcus* spp other than *S pneumoniae*, *N gonorrhoeae*, and *Neisseria meningitidis*, and *H influenzae* and *Haemophilus parainfluenzae*), modifications have been made to the standard CLSI MIC and disk diffusion methods to allow laboratories to perform reliable AST. Such modifications typically involve the use of test media with supplemental nutrients, prolonged incubation times, and/or incubation in an atmosphere with an increased concentration of carbon dioxide. Specific MIC and zone diameter breakpoints have been established by the CLSI for such organisms, as have recommended acceptable ranges for the testing of applicable quality control strains. The CLSI has also published guidelines for AST of the fastidious and/or infrequently recovered bacteria listed in the Table.13 Methods for the standardized testing of potential agents of bioterrorism (eg, *Bacillus anthracis*, *Francisella tularensis*, *Brucella* spp, *Yersinia pestis*, and *Burkholderia pseudomallei*) have also been developed, and specific conditions for their testing are defined in Table 2 of the CLSI M45-A2 document.13 Currently, specific recommendations for several other fastidious bacteria, including *Legionella* and *Bordetella* spp, do not exist, partially because infections caused by these species typically respond well to the recommended drugs of choice, they are relatively uncommon isolates in clinical laboratories, and they require special complex media for recovery in vitro, presenting unique problems in the development of AST assays.

For the most part, breakpoints for these bacteria were predicated on interpretive criteria established for other organisms as published in CLSI standards and adapted based on published literature and the experience of the authors of the document. This is in sharp contrast to the extensive body of clinical microbiologic, pharmacokinetic, and pharmacodynamic information typically used for the establishment of breakpoints as published in other CLSI standards. Because of the limited testing and nature of the potential agents of bioterrorism and *Helicobacter pylori*, the interpretive recommendations and testing approaches for these organisms were recently transferred from the standard CLSI M100 documents to the M45 guideline.13

As mentioned, in addition to standard disk and MIC methods, many species of fastidious bacteria...
may be tested by a gradient agar technique. The Etest method permits placement of strips on media optimal for the growth of the organism being tested and allows the use of various incubation conditions. A major limitation, however, to such an approach is lack of approval for such testing by the FDA. When FDA clearance has not been awarded, the results of such testing should be interpreted with caution, and an applicable qualifying comment should be an integral component of any resultant patient report.

SUSCEPTIBILITY TESTING OF ANAEROBIC BACTERIA

The importance of anaerobic bacteria as participants in and causes of significant infections and the need for specific antibiotic therapy for bacteremia and surgical prophylaxis against anaerobes are well documented.14-19 As a rule, AST is considered a necessity for effective guidance of antibiotic therapy, but how and when susceptibility testing of anaerobic bacteria should be performed have been topics of debate, in part owing to a number of misconceptions and confounding factors.20-24 Specimens collected from infections in which anaerobes are involved are typically polymicrobial, rendering isolation and identification of individual organisms slow and the results of AST too delayed to have a consistent positive effect on individual patient outcomes. For clinicians, the combination of surgical intervention and broad-spectrum antibiotics has limited the correlation of potential antibacterial resistance with outcome, directing many clinical microbiology laboratories away from the routine performance of anaerobic susceptibility testing. There is considerable evidence, though, that antibiotic resistance is common among many anaerobic species and that patient treatment with inactive agents results in poor clinical responses and increased rates of mortality.14,16,19,25,26 Results of AST have also indicated that substantial differences exist in resistance patterns among hospitals on a local, regional, and national basis, suggesting that one medical center’s patterns may not be applicable to those of other facilities.27-30 Therefore, the need for anaerobic AST is of far more importance today than in the past.

If practical, individual hospitals should establish antibiograms for the more frequently recovered anaerobes on a periodic basis and test individual patient isolates as needed to assist in patient care. For purposes of presenting cumulative antimicrobial susceptibility data, an attempt should be made to include the results from 80 to 100 anaerobic isolates with recognized important resistance mechanisms (eg, clindamycin resistance among members of the Bacteroides fragilis group). Ideally, following CLSI guidelines for preparation of antibiograms, 30 isolates for each genus or species should be included.31 When this is not possible, an effort should be made to present data for 30 isolates from the B fragilis group and at least 10 strains for other genera. Antibiotics in the report should reflect the hospital formulary. A recent CLSI document included an antibiogram for members of the B fragilis group generated from the results of testing of isolates collected at many health care facilities across the United States by 3 reference laboratories.32 Clinicians

<table>
<thead>
<tr>
<th>TABLE. Clinical and Standards Laboratory Institute Published Guidelines for Antimicrobial Susceptibility Testing of Fastidious and/or Infrequently Recovered Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiotrophia and Granulicatella spp (once referred to as thiol-dependent, pyridoxal-dependent, or nutritionally variant streptococci)</td>
</tr>
<tr>
<td>Aeromonas spp</td>
</tr>
<tr>
<td>Bacillus spp other than Bacillus anthracis</td>
</tr>
<tr>
<td>Campylobacter coli and Campylobacter jejuni</td>
</tr>
<tr>
<td>Corynebacterium spp</td>
</tr>
<tr>
<td>Erysipelothrix rhitiopathiae</td>
</tr>
<tr>
<td>The group of bacteria previously referred to as the HACEK organisms (Aggregatibacter actinomycetemcomitans, Aggregatibacter aphrophilus, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae)</td>
</tr>
<tr>
<td>Facultatively anaerobic Lactobacillus spp</td>
</tr>
<tr>
<td>Leuconostoc spp</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Pasteurella spp</td>
</tr>
<tr>
<td>Peptococcus spp</td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
</tr>
</tbody>
</table>
may refer to this document when prescribing empirical therapy for suspected or proven *B. fragilis* group infections in settings in which anaerobic AST is not available.

To assist in management, anaerobic susceptibility testing should be performed when (1) the selection of an antibiotic to which the isolate is susceptible is critical for treatment of the patient, (2) long-term therapy is under consideration, (3) anaerobes are recovered from specific, usually sterile, body sites (e.g., bone, blood, joint, or brain), or (4) treatment with an antimicrobial agent typically active against the organism has failed.

The agar dilution susceptibility testing approach, which uses *Brucella* blood agar as the medium, has been designated the reference method by the CLSI anaerobe working group.33 Because of the time-consuming, labor-intensive nature of this method, it is not generally considered practical for routine use in most clinical microbiology laboratories but serves as the reference method to which other more practical testing approaches can be compared. Alternative testing methods currently used include BMD (only standardized for members of the *B. fragilis* group), limited agar dilution, and gradient strip diffusion assays, such as Etest. Disk diffusion and broth disk elution testing should not be used because the results generated from such methods do not correlate with the CLSI reference agar dilution method.33 Although of limited use, β-lactamase testing may be of value for some organisms if therapy with ampicillin or penicillin is being considered.

**METHODS FOR SUSCEPTIBILITY TESTING OF NOCARDIA SPP AND OTHER AEROBIC ACTINOMYCETES**

Susceptibility testing of *Nocardia* spp and other aerobic actinomycetes (*Rhodococcus* spp, *Streptomyces* spp, *Gordonia* spp, and *Tsukamurella* spp) should be performed on clinically significant isolates. Susceptibility testing results serve to guide initial therapeuitic choices and may document emergence of drug resistance. No commercially available broth systems have yet been cleared by the FDA for *Nocardia* spp or other aerobic actinomycetes. The CLSI BMD is the reference method for testing.34 Recommended drugs for primary testing are amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, minocycline, moxifloxacin, trimethoprim-sulfamethoxazole, and tobramycin. Second-line drugs for testing include cefepime, cefotaxime, and doxycycline. Vancomycin and nitroprin results should also be reported on isolates of *Rhodococcus equi* because these drugs are particularly useful therapeutically. Microbiological breakpoints were established in 2003 and are available for *Nocardia* spp only.34 When aerobic actinomycetes other than *Nocardia* spp are tested, the susceptibility categories should be listed as tentative. The breakpoints for *S. aureus* should be adapted as provided in the current CLSI M100 document (M100-S21) for *R. equi*, but they should also be reported as tentative. Susceptibility testing results for most aerobic actinomycetes are available within 3 to 5 days, whereas results for *R. equi* and some isolates of *Tsukamurella* spp may be read at 24 or 48 hours.

Challenges in the identification and AST of *Nocardia* spp have become apparent within the past 10 years. Before the year 2000, conventional phenotypic methods were largely used to identify *Nocardia* spp; however, molecular identification is now the preferred means of reliable identification to the species level.35 Both 16S ribosomal RNA sequencing and matrix-assisted laser desorption/ionization-time of flight are among the techniques currently used, but limitations exist.36 Because routine molecular testing is difficult to implement in many clinical microbiology laboratories, isolates typically must be sent to a reference laboratory for identification. To address this issue, Wallace et al37 proposed a series of various susceptibility patterns that could predict placement of *Nocardia* spp within particular groups, but, as new strains are identified, these groupings have not proved to be valid, particularly for the *Nocardia nova* complex.

The method for susceptibility testing of *Nocardia* spp also presents a challenge to many clinical microbiology laboratories because BMD is somewhat impractical owing to cost, availability of supplies, and expertise needed to perform and interpret the results. Moreover, false resistance with BMD has been noted for ceftriaxone when testing *Nocardia brasiliensis* and imipenem when testing *Nocardia farcinica*.34 In addition, sulfonamide results are inconsistent when using BMD; for this compound, disk diffusion testing with sulfisoxazole may be performed concurrently. Investigators have evaluated use of the Etest method compared with BMD, with varying results.38 However, both lack of agreement with BMD and the absence of standardized methods have restricted routine use of the Etest. The CLSI has proposed that the agar proportion method be used to confirm questionable results from commercial broth systems and to test additional antibiotics or concentrations of drugs.

The major taxonomic revisions within the last 10 years have further complicated testing because clinical and epidemiological differences exist among species. Furthermore, resistance to trimethoprim-sulfamethoxazole and other antimicrobials is increasing among various species; thus,
identification of isolates to the species level remains imperative.39

**METHODS FOR SUSCEPTIBILITY TESTING OF MYCOBACTERIA**

According to the most recent Centers for Disease Control and Prevention mycobacterial susceptibility testing guidelines, initial isolates from patients with tuberculosis should be tested for susceptibility to isoniazid, rifampin, ethambutol, and pyrazinamide.40 This guidance overrides the prior practice of performing susceptibility testing for only 3 drugs (isoniazid, rifampin, and ethambutol) and then only when a pulmonary or infectious disease clinician requested it. Current guidelines also state that susceptibility testing should be repeated after 3 months if the patient remains culture-positive despite appropriate therapy. However, susceptibility testing may be performed earlier if the patient appears to be failing to respond to therapy or if intolerance to the drug regimen is evident. First-line susceptibility test results should be available for isolates of the *Mycobacterium tuberculosis* complex within 15 to 30 days of original receipt of the specimen in the laboratory.41 However, ideally, susceptibility results should be available within 7 to 14 days of specimen receipt.34 If resistance to any of the 4 initially tested agents is discovered, testing of secondary drugs should be performed as soon as possible. If the isolate is resistant only to pyrazinamide, *Mycobacterium bovis* should be ruled out because most *M tuberculosis* isolates are susceptible to pyrazinamide. Further specific guidelines regarding secondary drug testing and follow-up are outlined in CLSI M24-A2.34

The agar proportion approach has traditionally been considered the standard method for antimycobacterial susceptibility testing, but as an agar-based system, the time to result reporting is lengthy (approximately 3 weeks).42 Both the agar proportion method and the radiometric method define resistance as growth of more than 1% of the inoculum of bacterial cells in the presence of an antitubercular drug. The antitubercular drugs are inoculated at specific in vitro concentrations, the values of which correlate to clinical responsiveness. If more than 1% of the bacterial population grows in the presence of a drug, that particular drug will not be of therapeutic utility.32 The agar proportion method is used primarily to confirm results from commercial liquid broth systems and to test additional drugs that may not be available for testing using other systems. The FDA-cleared broth systems for *M tuberculosis* testing have shorter incubation times than the agar proportion method; however, these commercial testing systems are only cleared for certain drugs.13

There are several molecular assays that have been developed for the detection of mutations associated with drug resistance in *M tuberculosis*, including both real-time polymerase chain reaction (PCR) methods and line probe assays.34 Molecular-based methods for detection of *M tuberculosis* drug resistance are more rapid than traditional methods of susceptibility testing. Mutations associated with resistance to isoniazid or rifampin are typically detected by such methods. These tests may be run using growth from positive cultures but may also be performed directly on acid-fast smear-positive specimens if the patient is highly suspected of having drug-resistant tuberculosis. It is currently suggested that molecular testing of drug susceptibility be backed up by culture, with performance of phenotypic culture-based drug susceptibility testing when the isolate is retrieved from culture.34

Susceptibility testing of nontuberculous mycobacteria (NTM) should be performed on isolates considered clinically significant. The American Thoracic Society criteria for clinical significance of NTM are positive cultures from at least 2 sputum specimens or 1 bronchial wash or bronchial lavage specimen. Alternatively, a transbronchial or lung biopsy with histopathologic findings consistent with mycobacteria and positive on culture for NTM is sufficient to be interpreted as clinically significant. In addition, NTM isolates from usually sterile body sites, such as cerebrospinal fluid, are considered clinically significant. However, routine susceptibility testing need not be performed on *Mycobacterium marinum* because acquired resistance is uncommon with this organism.34 Initial susceptibility testing of *Mycobacterium kansasi* to isoniazid, rifampin, and ethambutol need not be performed but can be offered if treatment has failed.

The standard susceptibility testing method for NTM is BMD. The American Thoracic Society and CLSI guidelines exist for susceptibility testing of members of the *Mycobacterium avium* complex, *M kansasi*, *M marinum*, and the rapidly growing mycobacteria.34 However, accurate susceptibility predictions for other slowly growing mycobacteria cannot be made. The macrolides are the only antimicrobial agents that should be tested against *M avium* complex because they are the only agents for which correlations have been demonstrated between in vitro susceptibility tests and clinical response.35 Because the mutation leading to resistance is the same for clarithromycin and azithromycin, only 1 drug need be tested. Generally, clarithromycin is tested because azithromycin demonstrates poor solubility. If the isolate is macrolide resistant, testing for susceptibility to the secondary agents moxifloxacin and linezolid may be considered. Susceptibility testing of *M avium* complex may also be performed if the patient
relapsed while undergoing macrolide therapy. In addition, susceptibility testing should be repeated after 3 months of therapy for patients with disseminated *M avium* complex disease and after 6 months of therapy for patients with chronic pulmonary disease caused by *M avium* complex. Commercially available broth systems have not yet been cleared by the FDA for slowly growing NTM.

**PHENOTYPIC AND GENOTYPIC METHODS FOR DETECTION OF ANTIMICROBIAL RESISTANCE**

A number of phenotypic tests are available to the clinical microbiology laboratory to characterize a pathogen’s susceptibility to an antibiotic by screening for a specific resistance mechanism or phenotype. Although such screening tests do not result in determination of an MIC, some have sufficient specificity and sensitivity that confirmatory testing is not required and the screening test result can be reported without further testing. Other assays require additional or confirmatory testing. For example, tests for inducible clindamycin resistance among staphylococci and screening tests for high-level gentamicin and streptomycin resistance in enterococci are generally considered to be comparable to standard methods for the detection of clinically significant resistance, and they do not require confirmatory testing. By comparison, laboratories that use ertapenem resistance as a surrogate marker for carbapenemase production among certain species of Enterobacteriaceae must confirm resistance to meropenem, imipenem, or doripenem by another more standardized approach because ertapenem-resistant strains are not always resistant to these other agents.

In addition, methods for the direct detection of antibiotic-resistant bacteria in clinical samples have progressed rapidly in recent years, largely because of the continued evolution and spread of multidrug-resistant pathogens, such as methicillin-resistant *S aureus* (MRSA). The development of commercial assays that facilitate rapid detection of such pathogens directly from clinical specimens, often generating results in a few hours or less, has positively enhanced surveillance efforts and patient management. Other genotypic assays for detection of specific antimicrobial resistance genes in gram-negative bacteria (eg, *bla*<sub>TEM</sub>-containing *Klebsiella pneumoniae*) have the potential to improve therapeutic patient decisions and assist in epidemiological investigations of resistance gene dissemination in the hospital and community setting.

**β-LACTAMASE TESTS**

A positive β-lactamase test result indicates that the organism is resistant to applicable β-lactam agents, but a negative reaction is inconclusive because other mechanisms of resistance to the β-lactams may exist. For example, a positive β-lactamase test result for a strain of *N gonorrhoeae* means that the isolate is resistant to penicillin, ampicillin, and amoxicillin and that these drugs would not be appropriate therapeutic choices. However, a β-lactamase test only detects one form of penicillin resistance in *N gonorrhoeae*. Strains with chromosomally mediated resistance with penicillin-binding protein modifications can only be detected by the disk diffusion or the agar dilution MIC method.

Three direct β-lactamase tests—the acidometric, iodometric, and chromogenic methods—have been widely used. All 3 methods involve the testing of isolates grown on nonselective media, and results are typically available within 1 to 60 minutes. Although some bacteria (eg, *N gonorrhoeae* and *H influenzae*) produce β-lactamase constitutively, others (eg, staphylococci) may produce detectable levels of enzyme only after exposure to an inducing agent, typically a β-lactam. Even after induction, though, direct β-lactamase tests may not be sufficiently sensitive to detect β-lactamase production in all staphylococci. Therefore, for serious infections that require penicillin therapy, clinical microbiology laboratories should perform both MIC and induced β-lactamase tests on all subsequent isolates from the same patient. In addition, PCR testing of the isolate for the presence of the *blaZ* β-lactamase gene may also be an option.

**DETECTION OF METHICILLIN RESISTANCE IN STAPHYLOCOCCUS SPP**

The most common currently used method for the detection of MRSA is culture. Traditional MRSA detection methods consist of culture from a selective liquid or solid medium. Recently, chromogenic agars have shown improved sensitivity and specificity over nonchromogenic media for detection of MRSA. Chromogenic agars contain selective antibiotic(s) and various chromogenic substrates, which provide easy visual identification of colonies. An additional advantage of chromogenic agar is the faster time to detection of the organism. MRSA is often detected within 20 to 48 hours on chromogenic media, with a high percentage of cases identified within 24 hours. Several chromogenic media are available from different manufacturers.

The use of an overnight preenrichment step with selective broth medium before inoculation of the agar has been shown to increase sensitivity of the testing by 15% to 30%. However, the delay in detection of an additional 18 to 24 hours and the cost of the selective broth medium represent disadvantages.
Early diagnosis of MRSA in the laboratory is crucial in guiding appropriate antimicrobial therapy. Rapid molecular methods of MRSA detection are increasingly used and are available for testing from a variety of sources. Traditional detection of MRSA from automated blood culture instruments is time-consuming because 24 to 72 hours are required for subculture, biochemical identification, and AST of the isolate once the result turns positive. Several techniques are available for identification of MRSA directly from blood culture bottles that have flagged as positive for growth when gram-positive cocci in clusters are seen on Gram stain. Several commercial molecular methods are available, including nucleic acid amplification and hybridization assays. A commercial penicillin-binding protein 2a latex agglutination kit, which facilitates the detection of the protein product expressed by the mecA gene, is available for detection of MRSA directly from blood culture. Other systems are currently under investigation.

**HIGH-LEVEL AMINOGLYCOSIDE RESISTANCE IN ENTEROCOCCI**

Successful treatment of enterococcal endocarditis and other serious enterococcal infections requires the use of an aminoglycoside with a cell wall–active agent, such as ampicillin, penicillin, or vancomycin. All enterococci demonstrate innate low-level resistance to aminoglycosides because of their facultative anaerobic metabolism, which reduces transmembrane potential, thereby limiting drug uptake. However, the bactericidal combination of an aminoglycoside and a cell wall–active antimicrobial, which allows for markedly enhanced uptake of the aminoglycoside, leads to enhanced killing of the organism in the absence of high-level aminoglycoside resistance (HLAR).

The CLSI recommends HLAR screening of enterococci with both gentamicin and streptomycin from blood cultures or other specimens submitted for the evaluation of endocarditis, such as heart valve tissue. The BMD may be performed by assessing growth of the organism in the presence of 1000 µg/mL of streptomycin or 500 µg/mL of gentamicin in brain heart infusion broth. The recommended screening concentrations for streptomycin and gentamicin using other methods are also covered. Performance data of commercially available media and systems for HLAR screening have been reviewed.

In enterococci, HLAR is mediated by aminoglycoside-modifying enzymes (AMEs), which modify the aminoglycoside by acetylation, adenylation, or phosphorylation. The most prevalent AME gene among enterococci with HLAR to gentamicin is \(\text{aac}(6')-\text{Ie}-\text{aph}(2')-\text{Ia}\), which has both acetyltransferase and phosphotransferase activity. This common AME confers resistance to all available aminoglycosides, except streptomycin. Commonly, HLAR to streptomycin is mediated by either \(\text{ant}(6')-\text{Ia}\) or \(\text{ant}(3')-\text{Ia}\); in such cases, streptomycin should not be used in combination with a β-lactam agent. Detection of HLAR to both gentamicin and streptomycin precludes the use of aminoglycosides for synergism in any clinical situation.

**Enterococcus faecium** possesses a naturally occurring AME, resulting in moderate resistance to tobramycin (MICs, 64-1000 µg/mL). The presence of the \(\text{aac}(6')-\text{Ia}\) gene precludes synergistic treatment with tobramycin, kanamycin, netilmicin, or sisomicin. In addition, many enterococci possess the \(\text{aph}(3')-\text{IIa}\) gene, which confers high-level resistance to kanamycin and abolishes any synergistic effect with amikacin. Thus, gentamicin and streptomycin are the only 2 aminoglycosides to test and consider for synergistic therapy. Novel genes carrying AMEs mediating resistance to gentamicin, such as \(\text{aph}(2')-\text{Ib}, \text{aph}(2')-\text{Ic}, \text{aph}(2')-\text{Id},\) and \(\text{aph}(2')-\text{Ie}\), have been discovered and may further complicate HLAR testing because the susceptibilities to various aminoglycosides differ. Because of the large numbers of AME-encoding genes, molecular HLAR screening in enterococci remains investigational and has not yet been widely available in clinical microbiology laboratories.

Issues that continue to challenge HLAR screening in enterococci include the isolation of multiple AMEs within single enterococcal isolates, isolates that harbor infrequent AMEs but do not demonstrate the HLAR phenotype, and the increasing prevalence of various HLAR enzymes in enterococci.

**DETECTION OF VANCOMYCIN-RESISTANT ENTEROCOCCI**

The vancomycin-resistant enterococci (VRE) are important opportunistic pathogens in many health care facilities and common colonizers of the gastrointestinal tract. The VRE are among the most common causes of hospital-acquired infections in the United States, and patients colonized with VRE in the gastrointestinal tract may serve as reservoirs for nosocomial transmission.

Two common patterns of enterococcal resistance exist, both of which result in elevated vancomycin MICs. The first, and most clinically important, is vancomycin resistance due to acquisition of genetic information, usually on a plasmid or other transmissible genetic element. This acquired trait is most commonly observed in strains of *E. faecium* and *Enterococcus faecalis* harboring the vanA or vanB genes that encode for high-level vancomycin resistance. Expression of the vanA gene results in elevated vancomycin MICs (>128 µg/mL) and is the
dominant resistance factor in enterococci. By comparison, expression of the vanB gene results in lower vancomycin MICs, typically in the range of 16 to 64 μg/mL. The second pattern of resistance, intrinsic (inherent) in nature, is characterized seen in Enterococcus gallinarum and Enterococcus casseliflavus. Most frequently encoded by vanC, this pattern of resistance may also be due to the expression of genes other than vanC (eg, vanE, vanG, and vanL) and results in either low-level resistant or intermediate MICs, typically in the 2- to 16-μg/mL range. Contact precautions are generally only required for patients harboring enterococci with acquired resistance, such as E faecium or E faecalis. Guidelines for susceptibility testing of enterococcal pathogens when grown in culture from blood or other sites have remained fairly standard over time. However, there have been several recent advances in both culture-based and molecular-based screening of stool for VRE, facilitating identification of patients who are potential reservoirs for infection and transmission.

The CLSI guidelines for vancomycin susceptibility testing of enterococci isolated from various sites suggest the use of standard BMD or disk diffusion testing. If disk diffusion or Etest is performed, the susceptibility plates must be held for a total of 24 hours to obtain accurate readings. Organisms for which vancomycin MICs are in the range of 8 to 16 μg/mL should be further identified by biochemical testing because infection control precautions will differ based on identification of the organism as an Enterococcus sp other than E faecalis or E faecium. Accordingly, isolates with intermediate zones on disk testing should be tested by an MIC method and/or further identified by biochemical and other identification tests to guide appropriate infection control practices.

A variety of culture-based and molecular methods have been studied to support active surveillance efforts to identify VRE from the gastrointestinal tract. Although culture-based methods are not as rapid as molecular-based screening methods, isolates obtained from culture can be stored for further study or identification. Molecular-based VRE screening methods decrease the time to identification but are costly. Culture remains the screening method of choice for VRE stool screening, but molecular methods are becoming increasingly recognized and used. Some investigators advocate the use of a broth enrichment step before inoculation of a culture plate or a molecular assay to increase sensitivity.

Traditional screening agars for VRE from stool specimens include Campylobacter medium with 5 antibiotics, including 10 μg/mL of vancomycin, and various types of bile esculin azide agar with vancomycin. The traditional VRE screening agars require 24 to 48 hours to identify colonies preliminarily, with additional time required for confirmatory identification and susceptibility testing and up to 5 days to final identification. Various chromogenic VRE media demonstrate adequate sensitivity and specificity, with reduced turnaround time to results through early visual colony identification. There are many selective and differential chromogenic VRE agars that appear promising for use in VRE stool screening. However, performance data vary according to whether prior overnight broth enrichment of the specimen in liquid media was performed.

Real-time PCR is a sensitive and rapid approach to the identification of VRE from gastrointestinal tract specimens. Recently, the BD GeneOhm VanR (BD Diagnostics, Spark, MD) and Xpert vanA/vanB (Cepheid, Sunnydale, CA) assays, which detect isolates carrying vanA and vanB genes within 2 to 4 hours, have been introduced. Most FDA-cleared assays have been marketed for direct detection of VRE from rectal or perianal swabs, although detection from stool specimens has shown comparable results. Some studies have demonstrated improved performance of molecular assays after overnight aerobic or anaerobic preenrichment of stool in broth media; however, the preenrichment step increases the turnaround time to results. Occasionally, lower specificity has been shown with the use of perianal sampling due to the presence of anaerobes that carry the vanB gene.

In summary, there are a variety of VRE screening methods available, the most promising of which appear to be chromogenic media and molecular assays, due to rapid result reporting. However, some assays require an overnight preenrichment step to maximize sensitivity.

CLINDAMYCIN RESISTANCE IN STREPTOCOCCI AND STAPHYLOCOCCI

Clindamycin and erythromycin resistance in streptococci may either be due to erm genes, which lead to the production of macrolide ribosomal methylases, or to expression of the mef gene, which encodes an efflux pump targeting only the macrolides. By comparison, erm enzymes methylate the 23S ribosomal RNA component of the 50S bacterial ribosomal subunit, which causes decreased binding of macrolides, lincomamides (clindamycin), and streptogramin B antibiotics (designated the MLSβ phenotype). In staphylococci, inducible clindamycin resistance is also due to the MLSβ phenotype, but its efflux pump is encoded by the msrA gene.

The MLS resistance phenotype can be either induced or constitutively expressed. Inducible clindamycin resistance cannot be detected by routine MIC or disk testing of clindamycin. Therefore, the 14-
and 15-member macrolides, which are better inducers of clindamycin resistance than is clindamycin itself, must be used for induction of clindamycin in the clinical laboratory. Testing of streptococci and staphylococci for inducible clindamycin resistance is important because clindamycin is frequently used to treat staphylococcal, group B streptococcal, and group A streptococcal infections. In addition, resistance to clindamycin is increasing in prevalence, with a recent estimate of 12.8% inducible clindamycin resistance among S. aureus in the United States. Both inducible and constitutive clindamycin resistance has likewise become increasingly common among β-hemolytic streptococci, with less resistance reported for group A streptococcal than for group B streptococcal infections.

The CLSI has recommended 2 different methods for detection of inducible clindamycin resistance in staphylococci and β-hemolytic streptococci. One method is the disk approximation test, also known as the D-zone test. With this approach, separate erythromycin and clindamycin disks are placed specific distances apart on an agar plate, depending on whether staphylococci or streptococci are being tested. If there is flattening of the zone of inhibition between the 2 disks and the zone resembles the letter “D,” the test result is interpreted as positive for induction of clindamycin resistance. The second method suggested by the CLSI is the use of a single-well microdilution test containing both erythromycin and clindamycin. Whenever inducible MLSB resistance is detected, clindamycin treatment should be avoided, if possible. However, the CLSI states in their guidelines that clindamycin resistance may still be clinically effective in some patients, despite a positive induction test result.

Automated methods for identification of inducible clindamycin resistance have also recently been introduced. Molecular assays using primers for various erm genes have been used in various research settings for the purpose of following resistance trends or validating BMD assays. However, PCR assays for inducible clindamycin resistance are not currently considered the standard of care in the clinical microbiology laboratory.

Constitutive or inducible resistance to clindamycin may also be seen in S. pneumoniae due to expression of a ribosomal methylase encoded by the ermB gene. The methylase alters the binding site on the ribosomes for the macrolides and clindamycin, similar to that seen for β-hemolytic streptococci and staphylococci. Clindamycin is recommended as a second- or third-line antibiotic choice for pediatric patients receiving long-term antibiotic therapy for some conditions, such as pneumococcal osteomyelitis and/or joint infections. Because pneumococci are capable of expressing inducible clindamycin resistance, some authors suggest that isolates of S. pneumoniae be tested for erm-mediated resistance in certain clinical situations involving pediatric patients. Jorgensen et al recently assessed performance of the CLSI-suggested disk and BMD methods for detection of inducible clindamycin resistance in pneumococci.

**DETECTION OF EXTENDED-SPECTRUM β-LACTAMASE PRODUCTION AMONG ENTEROBACTERIACEAE**

Members of Enterobacteriaceae (and other organisms, including P. aeruginosa) can produce β-lactamases, referred to as extended-spectrum β-lactamases (ESBLs), capable of hydrolyzing penicillins, the monobactam aztreonam, and cephalosporins (including expanded-spectrum cephalosporins, such as cefotaxime, ceftriaxone, cefizoxime, and cefazidime). The CLSI guidelines specify screening criteria and confirmatory testing approaches for detection of ESBL production by Escherichia coli, K. pneumoniae, and Proteus mirabilis. For organisms such as Enterobacter spp and Serratia spp, which produce AmpC-type enzymes, ESBL screening should not be performed because false-negative results can occur. These screening and confirmatory tests were necessary because standard disk diffusion and MIC tests did not uniformly identify isolates producing ESBLs. Because ESBLs are usually inhibited by clavulanic acid, the CLSI made use of this property in developing the tests recommended to clinical laboratories for their detection and recommending that isolates producing ESBLs be reported as resistant to all penicillins, cephalosporins, and aztreonam. On establishment of new, lower interpretive criteria for many of these compounds, largely based on pharmacokinetic and pharmacodynamic principles and limited clinical data, the CLSI revised their recommendations for reporting. When the new breakpoints are adopted by clinical laboratories, the CLSI recommends that results for specific cephalosporins and aztreonam be reported and interpreted as they are tested and that the ESBL screening and confirmatory tests need only be performed for epidemiological and infection control purposes. By comparison, although the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for the cephalosporins are similar to those now recommended by the CLSI, EUCAST recommends that laboratories continue to screen and confirm ESBL production due to the limited supporting clinical data and that cephalosporin reports be changed from susceptible to intermediate or intermediate to resistant if an isolate tests positive for ESBL production.
DETECTION OF CARBAPENEMASE ACTIVITY AMONG ENTEROBACTERIACEAE

Carbapenemases, enzymes that hydrolyze carbapenem class antibiotics (ertapenem, imipenem, meropenem, and doripenem), usually hydrolyze all other currently available β-lactams, with the exception of aztreonam for some metallo-β-lactamases. The genome encoding for the production of these enzymes may be located on plasmids (eg, K pneumoniae carbapenemases), a feature that makes them of particular concern from an infection control perspective. There are 3 classes of carbapenemases: serine class A (including KPC, SME, IMI, GES, and NMC), class B enzymes known as the metallo-β-lactamases (such as VIM, IMP, and NDM), and the class D OXA enzymes. Carbapenemases have been identified in a wide range of gram-negative genera. The KPC enzyme, the most frequently identified class A carbapenemase in the United States, is most often found in the Enterobacteriaceae but has also been detected in P aeruginosa. Metallo-β-lactamases are most frequently seen in Acinetobacter spp and P aeruginosa, but recently NDM has become widespread in some regions of the world among species of Enterobacteriaceae, particularly K pneumoniae. OXA carbapenemases are most frequently found in Acinetobacter spp but have also been reported among isolates of Enterobacteriaceae.

In 2009 the CLSI Subcommittee on Antimicrobial Susceptibility Testing (SAST) recommended the modified Hodge test for the detection of carbapenemase activity in Enterobacteriaceae. Advantages of this assay include its ease of performance, the ability to test several isolates on a single plate, and the detection of different classes of carbapenemases with one test. The primary disadvantages are subjectivity in reading the results, its inability to differentiate the various carbapenemases (potentially useful from an epidemiological perspective), and the false-positive results that can occur with some organisms producing AmpC or ESBL enzymes.

The modified Hodge test was originally recommended for the detection of carbapenemases in bacteria for which carbapenem MICs were elevated but still fell within the susceptible range. When isolates tested positive, the SAST recommended that they be designated carbapenemase-producing strains in the patient report with a warning indicating that the therapeutic outcomes of patients infected with such organisms and treated with the relevant carbapenem were unknown, particularly when alternative dosing regimens were used (eg, continuous or prolonged infusion). In 2010, though, the SAST lowered the carbapenem breakpoints to capture most carbapenemase-producing strains, which would now test either as resistant or intermediate to these compounds. Implementation of the revised breakpoints eliminates the need for laboratories to routinely perform the modified Hodge test, although such testing may in some cases still be of value from an epidemiological or infection control perspective.

A number of phenotypic tests allow detection and differentiation of class A (eg, inhibition by boronic acid) and class C (eg, inhibition by chelating agents such as ethylenediaminetetraacetic acid) carbapenemases, but these tests fail to detect class D (OXA) and are primarily used for strain characterization rather than for clinical purposes.

DETECTION OF PLASMID-MEDIATED AMPC-TYPE β-LACTAMASES

Chromosomally mediated, inducible, AmpC-type β-lactamases are produced by several gram-negative species. Often referred to as the ASPACE or ASPICE organisms, these include, but are not restricted to, Aeromonas spp, Serratia spp, P aeruginosa, Acinetobacter spp indole-positive Proteae (Providencia spp, Morganella morgani, and Proteus vulgaris), Citrobacter spp, and Enterobacter spp. Resistant to the currently available β-lactamase inhibitors, such as tazobactam, sulbactam, and clavulanic acid, these enzymes result in resistance to a wide range of β-lactam antibiotics. The combination of a porin deletion with an AmpC-type enzyme can result in resistance to carbapenems. The genome encoding AmpC-type β-lactamases may also be harbored on transmissible plasmids and has been reported among a number of species that do not naturally produce inducible chromosomally mediated AmpC-type enzymes, including K pneumoniae, E coli, P mirabilis, and Salmonella spp. Similar to the plasmids carrying the genes encoding ESBLs, those with AmpC-type genes often harbor resistance determinants for multiple classes of drugs.

Because detection of plasmid-mediated AmpC-producing pathogens may have epidemiological and infection control importance, several assays have been developed in an attempt to accurately detect this resistance type. None, however, has been sufficiently standardized or tested against an adequate number of organisms producing plasmid-mediated AmpC-type enzymes to be considered superior in performance to the other assays.

TESTING TO DETECT BACTERICIDAL ACTIVITY

The AST methods used in the clinical microbiology laboratory typically assess only the inhibitory activities of antimicrobial agents. This is generally sufficient for patient management for most bacterial infections encountered by clinicians. In some, albeit rare, situations it may also be of value to determine
the bactericidal activity of an antibiotic against a specific patient bacterial pathogen. Serious infections in which a bactericidal effect is generally considered necessary for optimal treatment include bacteremia in neutropenic patients, patients with chronic osteomyelitis, and patients with bacterial endocarditis.\textsuperscript{95-97}

**Minimum Bactericidal Concentration Testing**

After determination of MICs in a broth system under standard conditions, measured aliquots of growth media may be subcultured quantitatively to solid media to assess bactericidal activity. To calculate the extent of killing at each antibiotic concentration, plates are incubated under appropriate conditions, colony counts are performed, and results are compared to that of the growth control tube or well. The accepted definition of the minimum bactericidal concentration (MBC) is the lowest concentration of antibiotic at which a 99.9% (3 log) or greater reduction in growth compared with the initial inoculum is observed.\textsuperscript{99} As with the MIC, the antibiotic MBC is reported in micrograms per milliliter or in some regions of the world in milligrams per liter. Determination of the MBC allows one to detect potential tolerance by the patient’s specific isolate to an antibiotic usually considered bactericidal, a phenomenon reportedly leading to clinical failure among some patients.\textsuperscript{99-101} Tolerance occurs when the antibiotic MIC for an organism is low (within the susceptible range) but the MBC is elevated, frequently at a concentration beyond that generally considered clinically achievable from a pharmacokinetic perspective. Tolerance is specifically defined as an MBC 32-fold or more higher than the MIC for the antibiotic under consideration.\textsuperscript{99,100} Failure to demonstrate at least a 3-log\textsubscript{10} decrease in colony-forming units per milliliter in the time-kill assay is also considered to represent tolerance.\textsuperscript{99}

**Time-Kill Kinetic Assays**

Time-kill assays allow one to assess the rate of bactericidal activity at varying antibiotic concentrations over time. Although these assays are time-consuming and laborious to perform because they require subculture of media at specific times during a 24-hour period, results of combinations of antimicrobial agents can also be assessed. In 1999, standard methods for performance of the assay were published by the CLSI (previously the National Committee for Clinical Laboratory Standards).\textsuperscript{99} Results of time-kill assays are typically presented graphically, plotting colony counts for each antimicrobial agent and concentration tested at each time point at which subcultures were performed (usually at 0, 4, 8, 12, and 24 hours). As with the MBC, bactericidal activity is defined as a 99.9% or greater killing at a specified time. When antibiotics are tested in combination using the time-kill approach, synergy is typically defined as a 2-log decrease or more in the number of colony-forming units achieved with the combination of antibiotics when compared with that achieved by the most active agent tested alone.

**TESTS FOR ASSESSMENT OF INTERACTIONS AMONG ANTIMICROBIAL AGENTS**

The value of in vitro testing to assess antibiotic interactions (ie, synergy testing) remains highly controversial. With a few bacterial species and antibiotic combinations, synergistic bactericidal activity is actually predictable and need not be routinely determined (eg, ampicillin, penicillin, or a glycopeptide plus gentamicin or streptomycin against susceptible strains of enterococci). When synergy testing is performed, the results should be interpreted with caution because they do not take into account drug interactions from a pharmacokinetic or a patient safety (adverse effect) perspective.

The checkerboard BMD test, wherein 2 antimicrobial agents are serially diluted in a 2-dimensional fashion to include all combinations during a specified clinically relevant range, is a somewhat less labor-intensive approach to assessing antibiotic interactions in vitro than the time-kill assay. This same approach to drug interaction testing can be taken using an agar dilution approach, although the method is even more laborious. Using these methods, one is able to recognize synergistic, additive, indifferent, or antagonistic interactions occurring with the agents being tested. By this method, a fractional inhibitory concentration (FIC) is calculated by comparing the MIC of each drug alone to the MIC of that drug in combination with the second agent. Synergy is usually defined as a 4-fold decrease in the MIC of the agents in combination when compared with the antibiotics tested alone.\textsuperscript{102} The FIC is calculated and interpreted as follows:

\[ \Sigma \text{FIC} = \text{FIC of agent A} + \text{FIC of agent B} \]

\[ \text{MIC of agent A in combination} \]
\[ \text{MIC of agent A alone} \]

\[ \text{FIC of agent A} = \frac{\text{MIC of agent A in combination}}{\text{MIC of agent A alone}} \]

\[ \text{MIC of agent B in combination} \]
\[ \text{MIC of agent B alone} \]

\[ \text{FIC of agent B} = \frac{\text{MIC of agent B in combination}}{\text{MIC of agent B alone}} \]

Synergy is defined as \( \Sigma \text{FIC} \leq 0.5 \)

Indifference is defined as \( 0.5 < \Sigma \text{FIC} \leq 4 \)

Antagonism is defined as \( \Sigma \text{FIC} > 4 \)

Some investigators consider compounds additive when \( >0.5 \Sigma \text{FIC} \leq 1 \).
The time-kill approach appears to correlate more closely with in vivo studies of combined antibiotic effects than does the checkerboard method.\textsuperscript{103,104} A simpler approach, albeit less standardized, is the use of Etest strips. Using this method, synergy is again defined by the FIC as described earlier.\textsuperscript{105}

## Serum Bactericidal Testing (Schlichter Assays)

Another approach to assessing bactericidal activity and determining the effects of antibiotic combinations is serum bactericidal testing. Determinations of serum inhibitory titers and serum bactericidal titers (SBTs) are performed in a manner analogous to that for MIC and MBC testing, except that the patient’s serum, rather than serially diluted concentrations of antibiotic, is used. A guideline outlining the specifics for performance of SBT testing has been published by the CLSI.\textsuperscript{106} To perform the testing, 1 or more blood samples are collected from the patient (usually attempting to draw the specimens when antibiotic peak and trough levels are achieved). Serial 2-fold dilutions of the patient serum in pooled, pretested human serum are then prepared in tubes or wells of microtiter plates. Each tube or well is then inoculated with a standardized suspension of the patient’s infecting pathogen in an applicable growth medium. The serum inhibitory titer is defined as the highest dilution of the patient’s serum preventing visible growth after an appropriate incubation period. Similar to MBC testing, quantitative subcultures are then performed from each dilution of the patient’s serum that prevented visible growth. The SBT is defined as that dilution resulting in a 99.9% or greater decrease in the original inoculum based on standardized rejection value tables. Results are then reported as titers (dilutions) of the patient’s serum. The purpose of this assay is to determine whether the dosage regimen chosen for treatment of the infection results in sufficient bactericidal activity in the patient’s blood.\textsuperscript{96,107} Higher serum titers suggest that adequate patient dosing has been achieved, unexpected antibiotic elimination has not occurred, and the bacterial pathogen is not tolerant. A peak SBT of 1:64 or higher and a trough SBT of 1:32 or higher have been shown to correlate with rapid bacterial eradication from the blood and optimal time to cardiac vegetation sterilization in cases of endocarditis.\textsuperscript{96,108} Lower bactericidal titers, however, do not necessarily predict a poor clinical response. Limited data have indicated that in cases of acute and chronic osteomyelitis a peak SBT of 1:16 or higher and a trough SBT of 1:4 or higher are predictive of therapeutic efficacy.\textsuperscript{96,109}

Major disadvantages of this assay include its labor-intensive nature and the requirement to obtain, pre-pare, and pretest pooled human serum for use in the procedure.

## Antifungal Susceptibility Testing

There have been major advances in the standardization and clinical interpretation of antifungal susceptibility testing in recent years. The number of antifungal agents is increasing as the incidence of systemic and other infections due to \textit{Candida} spp, \textit{Aspergillus} spp, \textit{Zygomycetes}, and other filamentous fungi is increasing.\textsuperscript{110} Susceptibility testing of clinically significant isolates, especially those from usually sterile sites, is important both epidemiologically and clinically for guiding treatment. Antifungal susceptibility testing standards for yeasts and molds have been developed by both the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for a variety of antifungal agents.\textsuperscript{111-115}

The standard antifungal reference testing method against which many other susceptibility testing methods are measured is the BMD method.\textsuperscript{112} The BMD methods proposed by different organizations vary by the media used, supplements and inoculum added, incubation conditions, and end point interpretations. The CLSI provides MIC breakpoint and interpretive data for \textit{Candida} spp for several antifungal agents, including fluconazole, itraconazole, voriconazole, anidulafungin, caspofungin, micafungin, and fluconazole.\textsuperscript{111} The CLSI breakpoints for fluconazole, voriconazole, and the echinocandins have recently been revised for \textit{Candida} species.\textsuperscript{116-118} The susceptible dose-dependent category for the azoles infers that susceptibility to these antifungals by \textit{Candida} spp is dependent on achieving the maximal possible blood level. In addition, the fluconazole data for the CLSI breakpoints were gathered from studies involving patients with oropharyngeal candidiasis and invasive candidial infections in non-neutropenic patients. Therefore, the clinical relevance of fluconazole breakpoints in clinical situations other than those mentioned has not been established. Interpretive data for the echinocandin class of drugs are based primarily on experience with nonneutropenic patients with candidemia, and clinical relevance of these data in other patient populations is uncertain. Finally, itraconazole data are based on experience with mucosal infections only, and data supporting the CLSI breakpoints for invasive infections are not available. Although there are no CLSI breakpoints currently approved for amphotericin B when testing \textit{Candida} spp, isolates for which the MICs are greater than 1.0 \(\mu\text{g/mL}\) are generally considered resistant.\textsuperscript{111} Although the CLSI documents only provide guidelines for Candida spp, some investigators have applied the CLSI breakpoints to \textit{Cryptococcus} spp, and correlations have
been demonstrated between higher MICs and treatment failures.\textsuperscript{110} Because the BMD testing method is difficult to perform in daily practice in clinical microbiology laboratories, other testing approaches have been investigated. Disk diffusion antifungal susceptibility testing is a simple and cost-effective method for both yeasts and molds. Fluconazole disk diffusion testing of \textit{Candida} spp has been available for several years. The CLSI has also established guidelines for disk diffusion testing of filamentous fungi, which is a relatively simple, rapid, and cost-effective alternative to BMD testing.\textsuperscript{115} Etest results are likewise less labor intensive than BMD and are relatively simple and reproducible for the testing of antifungal agents, especially against molds.\textsuperscript{120} Sensititre YeastOne (Trek Diagnostic Systems) is a colorimetric antifungal susceptibility testing MIC plate that exhibits high agreement with the CLSI BMD method.\textsuperscript{121} A new disk agar diffusion method, the Neo-Sensitabs tablet diffusion assay (Rosco, Taastrup, Denmark) has also been developed and tested for antifungal testing of molds and yeasts.\textsuperscript{122} Finally, commercial automated systems for MIC determination of yeasts are simple alternative methods and are comparable to other established antifungal susceptibility testing methods.\textsuperscript{123}

Antifungal susceptibility testing of \textit{Candida albicans} and other \textit{Candida} spp is fairly simple to perform, with determination of fluconazole susceptibility as the most important first step. If the \textit{C albicans} isolate is fluconazole resistant or if the isolate is non–\textit{C albicans}, further susceptibility testing will often be required. In contrast, antifungal susceptibility testing of molds is not currently as useful clinically because of both the long turnaround time of such testing and the difficulties in developing accurate breakpoints for molds.\textsuperscript{124}

\section*{CONCLUSION}
The goal of this article was to provide a review of current concepts in laboratory methods and approaches that serve to assist clinicians in making optimal antibiotic decisions for treatment of infections in this era of ever-evolving antimicrobial resistance. By its nature, the review could not be all-inclusive. For example, a standard has been developed for the susceptibility testing of \textit{Mycoplasma} spp and \textit{Ureaplasma urealyticum}.\textsuperscript{125} Until recently, \textit{M pneumoniae}, an important cause of community-acquired pneumonia, was thought to be universally susceptible to the macrolide class of antibiotics. Not only has macrolide resistance now been reported, but it is in fact widespread in some countries, including China and Israel, rendering availability of standardized methods for testing, heretofore of limited value but now of clinical importance.\textsuperscript{126,127} A topic that warrants consideration is the influence and effect of standards-setting organizations (eg, CLSI, EUCAST, and FDA) on AST and reporting. This is, however, beyond the scope of this article but has been addressed in another recent publication.\textsuperscript{128} Many of the testing approaches reviewed in these discussions have been used, essentially unchanged, for decades. As molecular techniques increasingly become a part of the daily routine in clinical laboratories, the day may come when such highly sensitive and specific methods replace many of the assays currently being used to predict antimicrobial susceptibility and resistance. As bacterial pathogens continue to exhibit increasing antibiotic resistance and appropriate empirical antibiotic decisions become more and more difficult, AST will take on an even more important role in managing patient infections.

\textbf{Correspondence:} Address to Stephen G. Jenkins, PhD, Department of Pathology, Weill Cornell Medical College, East 68th Street, Starr 737A, New York, NY 10065 (stj2005@med.cornell.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.org.

\textbf{The Symposium on Antimicrobial Therapy will continue in an upcoming issue.}

\section*{REFERENCES}
LABORATORY TESTING TO GUIDE ANTIMICROBIAL THERAPY


LABORATORY TESTING TO GUIDE ANTIMICROBIAL THERAPY

104. Cappelletty DM, Rybak MJ. Comparison of methodologies for synergism testing of drug combinations against resistant


HIV Screening in the Health Care Setting: Status, Barriers, and Potential Solutions

Stacey A. Rizza, MD; Robin J. MacGowan, MPH; David W. Purcell, JD, PhD; Bernard M. Branson, MD; and Zelalem Temesgen, MD

Abstract

Thirty years into the human immunodeficiency virus (HIV) epidemic in the United States, an estimated 50,000 persons become infected each year: highest rates are in black and Hispanic populations and in men who have sex with men. Testing for HIV has become more widespread over time, with the highest rates of HIV testing in populations most affected by HIV. However, approximately 95% of adults in the United States have never received an HIV test. Because of the individual and community benefits of treatment for HIV, in 2006 the Centers for Disease Control and Prevention recommended routine screening for HIV infection in clinical settings. The adoption of this recommendation has been gradual owing to a variety of issues: lack of awareness and misconceptions related to HIV screening by physicians and patients, barriers at the facility and legislative levels, costs associated with testing, and conflicting recommendations.

The Centers for Disease Control and Prevention (CDC) recently estimated that each year approximately 50,000 Americans are infected with human immunodeficiency virus (HIV) and that 18,000 people with AIDS die. 1 The number of people living with HIV in the United States is estimated to be almost 1.2 million, and it continues to grow annually, thereby providing more opportunities for transmission. 2 From 2007 through 2010, the number of diagnoses of HIV infection in adults and adolescents remained stable in the 46 states and 5 US-dependent areas with long-term confidential name-based HIV infection reporting. 3 In 2010 specifically, an estimated 48,079 adults and
adolescents were diagnosed as having HIV infection; of these, 79% of diagnoses were in males and 21% were in females, a ratio that was stable from 2007 through 2010.\textsuperscript{3}

Some populations are particularly burdened by HIV and account for a disproportionate number of cases owing to social, economic, and demographic factors, such as stigma, discrimination, income, education, and geographic region.\textsuperscript{4} The percentage of HIV infection diagnoses in adults and adolescents exposed through male-to-male sexual contact increased from 55% in 2007 to 61% in 2010, and this was the only group to experience an increase during those years. The percentages of diagnosed HIV infections attributed to injection drug use (IDU) (8%), male-to-male sexual contact and IDU (3%), and heterosexual contact (28%) remained relatively stable from 2007 through 2010. Gay and bisexual men and other men who have sex with men (MSM) are the most severely and disproportionately affected by HIV. Although composing only an estimated 4% of men,\textsuperscript{5} MSM accounted for 77% of new HIV diagnoses in men in 2010.\textsuperscript{3}

Black individuals are the most affected racial/ethnic group, comprising 14% of the population and 44% of estimated reported cases in 2010 in the 46 states and 5 US-dependent areas with long-term confidential name-based HIV infection reporting.\textsuperscript{3} Hispanic adults and adolescents are also disproportionately affected by HIV. Hispanics/Latinos represent approximately 16% of the population but accounted for 22% of new HIV diagnoses in 2010.\textsuperscript{3} In 2010, the estimated rate (per 100,000 population) of HIV infection diagnosis for black males (116.0) was more than 7.5 times higher than the rate for white males (15.3) and more than 2.5 times higher than the rate for Hispanic/Latino males (44.7). For female adults and adolescents, the estimated rate of HIV infection diagnosis for blacks (41.7) was approximately 20 times higher than the rate for white females (2.1) and approximately 4.5 times higher than the rate for Hispanic/Latino females (9.2).\textsuperscript{3}

HIV TESTING IN THE UNITED STATES

In 1985, when the US Food and Drug Administration approved the first tests for the detection of antibodies to HIV, the primary purpose was to screen blood donations to prevent HIV transmission from blood transfusion.\textsuperscript{6} To dissuade persons from using blood donation centers to obtain an HIV test, HIV counseling and testing programs based at “alternative testing sites” were established to provide these services. During the past 25 years, HIV testing has become more widely available and acceptable.

Since 1987, numerous national surveys have been conducted to estimate the proportion of US adults who have ever received an HIV test. Although the sample populations and methods have varied, the results for various periods have been consistent across surveys. By the late 1980s, 1 in 6 adults in the United States had been tested for HIV.\textsuperscript{7,8} As access to HIV testing services increased, by the mid-1990s estimates of the percentage of adults in the United States who had been tested for HIV, excluding via blood donations, ranged from 31% to 40%.\textsuperscript{9} Between 2000 and 2006, the percentage of adults who had been tested for HIV remained at approximately 40%, and since then, there has been a gradual increase to approximately 45%, leaving 55% of adults in the United States who have never been tested for HIV (with considerable variation by demographic groups).\textsuperscript{10}

Although most HIV/AIDS cases in the United States continue to be in males, a higher percentage of women report HIV testing. In 1985, 92% of AIDS cases were in men,\textsuperscript{11} and HIV/AIDS was viewed as a disease affecting primarily MSM and IDUs; by 1988, HIV testing was higher in men than in women.\textsuperscript{8} As HIV infection became more prevalent in the heterosexual population, HIV testing significantly increased in women. A variety of factors may have contributed to this increase, including women accessing medical services more frequently than men, clinicians being more comfortable offering an HIV test to women, and the CDC recommending HIV screening for all pregnant women in 1995.\textsuperscript{12,13} In the 2002 National Survey of Family Growth, a higher percentage of females (57%) reported HIV testing than males (47%).\textsuperscript{7} and in the 2008 National Health Interview Survey (NHIS), 48% of women and 41% of men reported ever being tested for HIV.\textsuperscript{10}

Testing for HIV also has differed significantly by race and ethnicity during the epidemic. In 1988, a greater proportion of white adults (17%) reported having been tested for HIV compared with black (14%) and Hispanic (14%) adults.\textsuperscript{6} By 1999, percentages of HIV testing were higher in black (46%) and Hispanic (33%) individuals than in white individuals (29%), and these patterns have persisted.\textsuperscript{14} In 2008, 62% of black individuals, 48% of Hispanic individuals, and 41% of white individuals reported ever being tested for HIV,\textsuperscript{10} with comparable percentages reported in other surveys.\textsuperscript{15,16}

A key driver of testing during the past 25 years has been recommendation by the CDC regarding who should be tested for HIV. Early in the epidemic, HIV testing in the United States was predominantly recommended for persons considered at risk for HIV infection, and HIV testing programs primarily targeted persons who regarded themselves to be at risk. In 1988, 1 in 3 adults who acknowledged at least one risk behavior (from a list of behaviors) for HIV testing in the United States was predominantly recommended by the CDC regarding who should be tested for HIV. Early in the epidemic, HIV testing in the United States was predominantly recommended for persons considered at risk for HIV infection, and HIV testing programs primarily targeted persons who regarded themselves to be at risk. In 1988, 1 in 3 adults who acknowledged at least one risk behavior (from a list of behaviors) for
HIV infection had received an HIV test,8 a percentage twice that in adults overall. In the 1995 NHIS and the 1996 National Household Survey on Drug Abuse, 70% of adults at increased risk (eg, those who have sex with an at-risk partner, IDUs, and MSM) reported that they had ever been tested for HIV.9 In 1995, 48% of females aged 15 to 44 years at increased risk for infection reported being tested for HIV, and by 2002, this percentage had increased to 68%.7 The NHISs conducted in 1999 and 2008 showed little change in the percentage of persons aged 18 to 64 years who reported an HIV risk factor and had been tested for HIV, approximately 72% in both surveys.10,14 A high percentage of the populations at greatest risk for HIV infection, MSM and IDUs, report that they have been tested for HIV. Recent data from the CDC’s National HIV Behavioral Surveillance surveys indicate that 90% of each of these populations report ever being tested for HIV.17,18 Given the continued transmission of HIV in these populations, particularly MSM, testing more frequently than once a year may be needed to identify undiagnosed cases earlier in the course of infection and to link infected persons to treatment services.10 Rates of HIV testing are higher in regions where disproportionately affected populations are greatest. Data from the Behavioral Risk Factor Surveillance System in 2001 and 2008 have documented that the percentages ever tested and recently tested (within the past 12 months) were typically higher in states with high AIDS case rates.10,20

THE CRITICAL ROLE OF HIV TESTING IN CURBING THE HIV EPIDEMIC

Testing for HIV plays a prominent role in the National HIV/AIDS Strategy released by the White House in July 2010.21 As shown in the Figure, of the estimated 1.2 million persons living with HIV in the United States, 80% are aware of their infection, 62% have been linked to HIV care, 41% stay in HIV care, 36% are receiving antiretroviral therapy, and only 28% have a suppressed viral load.19 Transmission rate modeling estimates that the 20% of persons living with HIV who are unaware of their infection account for 49% of HIV transmissions.22

To prevent further HIV transmission, improve the quality of life of persons with HIV, and reduce disparities associated with HIV infection, intensified effort is needed to increase the percentage of persons at each stage of this continuum of care. Increasing HIV diagnoses is the first step in this critical process.

After testing, it is important to immediately link newly identified HIV-positive persons to care so that their disease status and need for treatment can be evaluated. Between 2005 and 2007, 41.4% of persons with a new HIV diagnosis from the 37 states with name-based reporting systems had no CD4 cell count reported within 12 months, indicating that they were likely not receiving care for their HIV infection.23 In addition, 33.8% of those with a new diagnosis had a CD4 cell count of less than 200/μL, which since 1993 has indicated an immunologic diagnosis of AIDS.24 Such a low CD4 cell count at the time of HIV diagnosis indicates that HIV was first identified late in the course of infection.23

Despite the increase in HIV testing during the first 30 years of the epidemic in the United States, an estimated 236,000 persons with HIV are unaware of their infection.2,25 The CDC has continued to promote HIV testing in the US populations and specifically in persons disproportionately affected by HIV. In 2003, the CDC launched an initiative to increase access to early diagnosis and to services for persons with HIV.26 In 2006, the CDC revised the recommendations for HIV testing for adults, adolescents, and pregnant women in health care settings to reduce barriers to providing HIV testing. The major modifications included the following recommendations: (1) opt-out testing should be provided unless...
the patient declined, (2) persons at high risk for HIV infection should be screened at least annually, (3) informed consent for medical care should cover HIV testing on the same basis as other diagnostic or screening tests, (4) prevention counseling should not be required in conjunction with HIV testing for diagnostic or screening purposes, and (5) HIV screening should be a routine component of prenatal screening. These guidelines encourage physicians to incorporate HIV screening into clinical practice for all adults, regardless of risk, when the prevalence of undiagnosed HIV infection is 0.1% or greater and to offer HIV screening to high-risk persons more frequently. The recommendations also seek to reduce barriers associated with determining risk status and the requirement for prevention counseling to the extent that this was a barrier to testing. In 2007, the CDC funded the Expanded HIV Testing Initiative, under which 25 health departments were funded to facilitate HIV testing and increase diagnosis of infection in disproportionately affected populations, especially non-Hispanic black individuals.

The increase since 2006 in the percentage of adults tested has coincided with CDC efforts to promote HIV screening and earlier diagnosis of infection. The use of point-of-care rapid HIV tests and reduced barriers to HIV testing have enhanced the ability of providers to conduct testing in settings in which time can be a limiting factor, such as jails and clinical and acute care settings. Through the Expanded HIV Testing Initiative, nearly 2.8 million tests were performed, many of them in clinical settings, and more than 18,000 people were newly diagnosed as having HIV infection.

**BARRIERS TO ROUTINE HIV TESTING IN THE HEALTH CARE SETTING AND POTENTIAL SOLUTIONS**

Health care professionals in the United States have been slow to implement the 2006 CDC recommendations for HIV screening of individuals aged 13 to 64 years. For example, only 33% of community health care personnel from Massachusetts incorporated HIV screening into their practices. In another study, only one-quarter of eligible patients in an emergency department were offered HIV screening, and less than 5% of adults seen in an emergency or urgent care setting were tested for HIV. These studies demonstrate that significant barriers to implementation of universal HIV testing in health care settings in the United States still exist. These barriers are multifactorial and complex and require a multipronged approach and strategy to overcome.

**Physician Awareness and Perception**

Inconsistent levels of awareness of the 2006 CDC recommendations for universal HIV screening among health care professionals in the United States have created perceived barriers to implementing the recommendations. Among medical directors and administrators from non-Ryan White–supported community health centers in Massachusetts, only 27% were aware of the CDC recommendations compared with 60% in Ryan White–supported centers. Most health care professionals surveyed also believed that they needed to obtain written consent and provide counseling before obtaining an HIV test. Physicians also expressed concerns that patients would not have time to reflect on the significance of an HIV test and make an informed decision about whether to accept the testing.

Health care professionals also report feeling insecure about broaching the topic of HIV testing with their patients, particularly those from low-risk backgrounds, citing that discussing HIV testing would be uncomfortable for the patient and might damage the patient-physician bond. Physicians were also concerned that they would not receive support from the administration at their health care facility to initiate HIV screening, believing that it would be regarded as more of a burden than a help. Moreover, many physicians did not feel equipped to answer all the patient’s questions regarding HIV testing and did not feel that they were capable of convincing the patient that the test should be performed.

The primary solution to overcome this particular barrier to HIV testing is education. Physicians should be familiar with the CDC’s revised recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings and the rationale behind them. Providers should understand that despite the availability of effective treatment, HIV infection remains a leading cause of death and illness in the United States and that substantial numbers of previously unrecognized infections are diagnosed each year. Also, people who are aware of their infection can not only receive treatment that is effective for improving their health and reducing transmission but also adopt behaviors to avoid transmitting their infection to others. Physicians should be informed that the processes and procedures that have previously impeded HIV testing, such as pretest and posttest counseling and separate written consent, are no longer required and that the currently recommended screening for HIV uses an opt-out strategy. This information should be accompanied by an explanation of what an opt-out strategy is together with simulation of how to use it for HIV screening in various clinical settings. The CDC has developed free materials for physicians on these topics.
An important component of physician education is correcting misperceptions regarding HIV screening in the clinical setting. Physicians may believe that their patients are at low risk for HIV based on patients’ own lack of reported risky behavior but not uncommonly also because of inherent biases related to race, ethnicity, age, sex, and socioeconomic status and their associations with risk of HIV. Physicians may not realize that some patients may simply choose not to disclose high-risk behaviors and that as many as 10% to 25% of people testing positive for HIV had reported no high-risk behaviors before their diagnosis.

Public Awareness and Perception
The HIV epidemic is now more than 30 years old. Although perceptions regarding HIV have improved during the past 3 decades, HIV still carries a stigma that concerns many patients. In a poll conducted by the Kaiser Family Foundation in 2003, more than one-third of people stated that they feared people would think less of them if they were infected with HIV. They expressed additional worry that they would be discriminated against or be seen as morally inferior if others knew they were HIV positive. In a more recent study, patients presenting to an emergency department without a life-threatening illness or psychiatric diagnosis cited fear and denial as the most significant barrier to HIV screening. However, this was reported in less than 5% of those surveyed, with participants expressing overwhelming (>85%) support for the CDC recommendations to perform HIV screening.

Another contributing factor for suboptimal HIV testing in the United States is that many individuals feel that they do not require HIV testing because they have no HIV risks. In fact, when HIV-infected patients were asked why they had not been tested earlier for HIV, the most common answer (69%) was that they did not feel that they were at risk for HIV infection. Patients also expressed concerns about the confidentiality, access, and anonymity of HIV testing in a health care setting. Furthermore, a recent survey of patients in a health care setting demonstrated that most were unaware that 20% of people infected with HIV in the United States are unaware of their diagnosis and that the CDC recommends HIV screening without regard to risk, and they assumed that consent for HIV testing would be overwhelming or intimidating.

Education plays a primary role in raising awareness and removing negative perceptions regarding HIV testing among the public. This education can be provided in various forms and at various levels of society. The CDC leads the national effort to promote HIV awareness and prevention in collaboration with other public health organizations and organizations that represent the populations hardest hit by the HIV epidemic. On a regional and local level, community-based agencies, hospitals, clinics, physician groups, and managed care organizations should participate in this national effort and educate their patients and clients about HIV. Schools also have the responsibility of teaching their students about HIV and sexually transmitted infections. Finally, physicians should have the appropriate knowledge and education to be able to discuss behavioral risk factors for HIV and motivate their patients to be tested for HIV.

The public should be made aware of the magnitude of the HIV epidemic in the United States, the persistent substantial numbers of new infections, and the contribution of those who are not aware of their infection to new transmissions. In addition, the public should be made to realize that effective treatment, although not curative, exists for HIV infection and that this treatment is associated with substantial improvement in survival and quality of life. It is now clear that treatment has an additional public health role as it provides protection for sex partners of HIV-infected persons who themselves are not HIV infected. Education should also involve making the public aware of how HIV is diagnosed and reported to state health departments, the confidentiality of testing, and the implications of a positive result on health insurance coverage and employment.

Systemic Barriers
A variety of systemic issues at the facility, state, and national levels have been identified as barriers to universal HIV screening in health care settings.

Systemic Barriers at the Facility Level. The CDC recommendations to perform HIV screening asks most health care providers to change their traditional way of thinking. Conventionally, a patient’s presenting illness has always been the focus of the limited time and resources available. Asking the physician to consider, offer, and order what may be a completely unrelated laboratory test can be seen as intrusive and unwelcome. In fact, physicians cite that lack of time is the leading reason they have been reticent to implement HIV screening in their practices. Health care professionals’ concerns about adequate time relates to obtaining written consent before testing each patient for HIV and time to counsel and discuss the implications of a positive or equivocal HIV test result with their patients. This was a particularly important issue to physicians in emergency departments and urgent care settings, where many physicians averaged 10 minutes per patient visit. Further concerns arose that time and resources would be needed to train staff and develop protocols in each health care setting to initiate HIV testing.
Conventional HIV testing requires a blood test that may take 24 to 48 hours for results to return in clinical settings. Therefore, after an HIV screening test is performed in a health care setting, a patient must return or be called for results of the test. A rapid test might alleviate this barrier; however, especially in high-volume settings, rapid tests can be labor intensive and disrupt patient flow. Even if a rapid HIV test is used, a preliminary positive result requires a confirmatory test, typically Western blot analysis, which takes several days for results to be returned. To overcome these barriers, some high-volume emergency departments have used opt-out screening and conventional (nonrapid) testing technology to screen all patients who have blood collected by batching the blood hourly. 48

Linkage-to-care concerns are enhanced in the scenario in which a patient is diagnosed as having HIV after being screened in a health care setting but does not seek HIV care. 49 In one study, only 48% of patients sought HIV care within 3 months of their HIV diagnosis, with 22% not seeking HIV care at 12 months. 50 Possible reasons an HIV-infected individual would not seek follow-up HIV care are complex and may include lack of health care insurance, mental illness, substance abuse, lack of sophisticated maneuvering through the health care system, and denial of HIV status. 51 This dichotomy between prevention and care remains a significant hurdle for health care workers who do not have the infrastructure needed to follow up on HIV test results and ensure that all HIV-positive patients are referred for HIV care. 47,52

The current CDC recommendation for HIV screening in the health care setting does away with many of the facility- and physician-level systemic barriers, such as the need for counseling and separate written informed consent. However, it does not remove all the barriers, perceived or otherwise, associated with the mechanics of ordering tests, as well as interpreting and reporting test results, or informing patients of their test results. Solutions to overcome these barriers include full integration and incorporation of HIV testing into standards of care and standard clinic operating procedures. All relevant staff in the facility must be engaged and participate in this practice. Clinical informatics solutions have been found to be useful in enabling and accelerating integration of HIV testing into the clinic work flow by identifying eligible patients and prompting clinicians to order the test. These informatics solutions can also be used to facilitate linkage for those found to be HIV infected and increase overall program efficiency. 34

Legislative and Legal Barriers. The legal implications of HIV screening continue to make health care providers anxious. 33,36,52 Although national recommendations influence state law, HIV testing laws remain under state jurisdiction. Given that most health care professionals are not directly involved in providing HIV care, many would not be familiar with state laws pertaining to HIV testing. Physicians have expressed concerns about their legal obligation to document consent for HIV testing, to adequately counsel patients before testing, and to ensure that patients receive the test result and, if positive, are linked to HIV care. There is also a general sense of insecurity regarding partner notification and the physician’s legal roles and obligations. 52

Because HIV screening programs must comply with state laws about HIV testing, physicians should have a clear and easily accessible source of information about state laws relevant to their practice. The Compendium of State HIV Testing Laws from the National HIV/AIDS Clinicians’ Consultation Center provides state profiles of key HIV testing laws and policies and is updated periodically. 53 However, revisions depend on input from individuals or knowledge about newly passed legislation, and, as a result, the information may not always be up-to-date. It would facilitate testing substantially if such information were provided by each individual state department of health with clear and unambiguous language and were posted prominently in all relevant clinical facilities. Note that many states have made changes in their laws to make them compatible with the CDC recommendations, and, at present, HIV testing laws no longer present a barrier to routine screening for HIV in the clinical setting in nearly all states.

Cost and Cost-effectiveness of HIV Testing. The cost of HIV testing is another perceived barrier to HIV screening. There is a considerable amount of uncertainty about insurance coverage for HIV screening. Many health care professionals are concerned that HIV testing will not be reimbursed by insurance or that funding is not available to support each patient’s test. 54 In fact, lack of funding or reimbursement for HIV testing was listed as a major reason by community health care professionals for not performing HIV screening on their patients. 33,36,52

There was also a worry that the health care system in the United States would not be able to bear the burden and cost of caring for increased numbers of people being diagnosed as having HIV infection. 55 What these physicians may not fully appreciate is the substantially increased cost of care for patients diagnosed late in the course of their HIV disease and the increased societal costs of additional cases of HIV when people with undiagnosed infection spread HIV to their partners.
Medicaid currently allows coverage for routine HIV screening in the clinical setting as recommended by the CDC. However, it is considered an optional service, and each state chooses whether to cover it in their Medicaid program. The US Department of Health and Human Services accepted the recommendation of a recent Institute of Medicine report that private insurers be required to cover annual HIV counseling and screening for sexually active women at no cost.

Some health insurance plans do not cover routine HIV screening. Instead, these plans cover HIV tests for patients with known or perceived risk factors (eg, MSM and IDUs) and for patients who show symptoms of AIDS. In 2008, California became the first state to mandate that private insurers pay for HIV testing even when it’s not related to a patient’s primary diagnosis during a medical visit. Cost-effective is not the same as inexpensive or cost-saving. Cost-effectiveness analysis attempts to provide information on the relationship between resources expended on 2 or more alternative health interventions and health outcomes resulting from these interventions. This relationship or ratio (the difference in costs over the difference in effectiveness) is commonly expressed as cost per quality-adjusted life-year (QALY) saved. Several studies on the cost-effectiveness of HIV screening have been published. These studies have found that the cost-effectiveness of HIV screening compares favorably with that of other health interventions that are accepted as good uses of resources. Annual mammography screening of all women in the United States aged 40 to 80 years was associated with a cost of $40,000 per additional QALY, whereas the cost-effectiveness of HIV screening was estimated to be $41,736 per QALY.

Furthermore, HIV screening has been demonstrated to be cost-effective across a variety of risk groups and age ranges, whether conventional or rapid testing was used, and in populations with low HIV prevalence.

Part of the solution to overcoming the perception of cost or cost-effectiveness as a barrier to HIV screening is education. In addition to emphasizing the benefit of testing to the individual and the public, physicians, policy makers, and the public should be made aware that screening for HIV has been shown to be cost-effective, even with a prevalence as low as 0.05% to 0.1%. The issue of insurance coverage for HIV testing needs to be addressed at a national level legislatively, through revision of the US Preventive Services Task Force (USPSTF) recommendations, or both.

Conflicting Recommendation From the USPSTF

Although the revised CDC recommendations were endorsed by many professional societies and organizations, such as the American College of Physicians, the American Academy of HIV Medicine, and the HIV Medicine Association, endorsement has not been universal. Critically, the USPSTF reiterated in 2007 its 2005 recommendation on HIV testing declaring that the USPSTF did not find enough evidence to recommend for or against routine HIV screening in the general population (a “C” recommendation). This USPSTF recommendation is important because coverage and reimbursement for preventive services under Medicare, and most private insurance depends on the level of USPSTF endorsement. Currently, an “A-” or “B-” level USPSTF recommendation is required for coverage and reimbursement for preventive services under Medicare. The discrepancy between the CDC and USPSTF recommendations has also confused physicians and the general public. What many do not realize is that both agencies, despite the differing recommendations, actually agree on most issues that pertain to HIV testing; both acknowledge that targeted screening would miss many infected persons and that identification and treatment of asymptomatic HIV infection can result in marked reduction in clinical progression and mortality. The primary difference seems to be differing conclusions about the strength of the data regarding the effect of routine testing on HIV transmission. In recent years, evidence documenting the impact of antiretroviral therapy on reducing HIV transmission, so-called treatment as prevention, has been accumulating. A landmark study, the HIV Prevention Trials Network 052 (HPTN 052) clinical trial, reported that antiretroviral therapy reduced the risk of heterosexual transmission by 96%. However, the results of the HPTN 052 cannot be applied unless HIV-infected individuals are identified and linked to care and treatment. Evidence supporting earlier initiation of antiretroviral therapy has also emerged, leading to updated treatment recommendations from the Department of Health and Human Services and others. This potentially invalidates one assumption in the evidence model used by the USPSTF in 2005 as a basis for their recommendation: antiretroviral treatment would be initiated only at CD4 T-cell counts of less than 200/μL. The USPSTF is currently reconsidering its recommendation on routine HIV screening.

CONCLUSION

The benefits of antiretroviral therapy are undisputed; it substantially reduces illness and death attributed to HIV infection. In addition, the HPTN 052 clinical trial showed that antiretroviral therapy prevents the transmission of HIV to uninfected sexual partners from HIV-infected persons receiving treatment. There is also emerging data supporting that earlier initiation of antiretroviral therapy results in improved outcomes for the individual and commu-
ties. These benefits of antiretroviral therapy are not available for HIV-infected individuals who have not yet been diagnosed as having HIV infection. A fifth of the 1.2 million people estimated to be living with HIV in the United States remain unaware of their infection and contribute disproportionately to the overall transmission of HIV. The CDC's revised recommendations for HIV testing for adults, adolescents, and pregnant women in health care settings are intended to facilitate the reduction of HIV transmission in the United States by removing barriers to providing HIV testing. Although implementation of these revised recommendations has been limited by a variety of real and perceived barriers, these barriers are not insurmountable. With appropriate education of the public and physicians, and with the involvement of all stakeholders at national, regional, state, and community levels, it is hoped that one of the primary goals of the National HIV/AIDS Strategy, reducing the number of people who become infected with HIV, will soon be achieved.

ACKNOWLEDGMENTS
The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

Abbreviations and Acronyms: CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; HPTN 052 = HIV Prevention Trials Network 052; IDU = injection drug use; MSM = men who have sex with men; NHIS = National Health Interview Survey; QALY = quality-adjusted life-year; USPSTF = US Preventive Services Task Force

Affiliations (Continued from the first page of this article.): and Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA (R.J.M., D.W.P., B.M.B.).

Correspondence: Address to Zelalem Temesgen, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (temesgen.zelalem@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our website www.mayoclinicproceedings.org.

The End of the Symposium on Antimicrobial Therapy.

REFERENCES
22. Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. AIDS. 2012;26(7):893-896.


55. Clark HA, Bowles KE, Song B, Heffelfinger JD. Implementation of rapid HIV testing programs in community and outreach


