General Principles of Antimicrobial Therapy

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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 injudiciously, 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.

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AST = antimicrobial susceptibility testing; CSF = cerebrospinal fluid; ESBL = extended-spectrum β-lactamase; G6PD = glucose-6-phosphate dehydrogenase; HIV = human immunodeficiency virus; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; OPAT = outpatient parenteral antimicrobial therapy; UTI = urinary tract infection

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[1] 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.

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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, 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-

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ing.[2] 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 microbiological 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.[3,4] 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 (ceftriaxone) plus vancomycin would be recommended as empiric therapy.[5] 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.[6]

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,[7] 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 cephalosporins. In clinical practice, susceptibility to cephamycins (cefoxitin, cefotetan) but resistance to a third-generation cephalosporin (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 cephalosporin 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 sulfonamides, 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.[8] For example, the combination of certain β-lactams and aminoglycosides exhibits synergistic activity against a variety of gram-positive and gram-negative bacteria[9] 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).[10,11]

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.[8] 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.[15] 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.[10]

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.[11] 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.[16] 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.[17] 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.[18] 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.[8] 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.[19] 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.[6] 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 *S 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,[20] 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)[21] or therapeutic failure at low drug levels (eg, vancomycin)[22,23] but is usually a combination of both (eg, voriconazole).[24] 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).[24]

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,[25] community-acquired pneumonia to 5 days,[26] and ventilator-associated pneumonia to 8 days.[27] However, when administering abbreviated treatment courses, it is important for clinicians to ensure that their patients fit

TABLE. **Classification of the Adverse Effects of Antimicrobial Drugs**

Direct		
Allergy		
Toxicity		
Drug-drug interaction		
Therapeutic failure		
Indirect		
Effects on commensal flora		
Human	*Clostridium difficile* infection	
Animal	Increased chance of infection with drug-resistant pathogens	
Effects on environmental flora		

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 (best described for penicillin) can reliably exclude the possibility of developing an IgE-mediated reaction (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,[19] 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; creatine 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."[35] 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, rifampin[38] and fluoroquinolones[39]) have better activity against staphylococci in biofilms and are recommended in the management of infections of prosthetic valves[10] and joints[40] 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.[6] 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 immunosuppressive 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[42]).

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 bites[44] and after penetrating brain injury[45]). 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.[50] 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.[54] 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*.[55] This is not surprising because acute upper respiratory illnesses account for the highest proportion of ambulatory antibiotic prescriptions,[56] with most being dispensed in situations in which antibiotics were not even indicated.[57] Clearly, the emergence of antimicrobial resistance can be prevented or delayed through judicious prescribing, which can be characterized as follows: avoidance of antibiotic treatment for community-acquired, mostly viral, upper respiratory tract infections; use of narrow-spectrum antibiotics when possible; and use of antibiotics for the shortest duration that is effective for the treatment of a particular clinical syndrome. In the past few years, interest has been increasing in the development of rapid and accurate diagnostic tests for detection of viral respiratory pathogens with the ability to distinguish between viral and bacterial infections, such as measurement of procalcitonin levels and nucleic acid tests. Although not yet widely available in clinical practice, these tests have the potential to curtail the use of antibacterial agents for clinical syndromes that are clearly caused by viruses.

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.[6]

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*,[58] 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.[59] 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.

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