Chapter 5: Antimicrobial Therapy

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The selection and management of antimicrobial therapy has become increasingly complex over the past decade. In response to the emergence of new microorganisms and novel mechanisms of microbial resistance, many antibiotics have been developed for general use (Finland, 1979). There are dozes of antimicrobial agents that are effective against a broad spectrum of bacterial, fungal, parasitic, rickettsial, and viral pathogens. Continued education is therefore necessary for proper antibiotic use. One study showed that 28% of therapeutic courses and 64% of prophylactic courses of in-hospital antibiotic use were inappropriate (Jogerst and Dippe, 1981). These figures probably would be higher regarding inappropriate office-based antibiotic use if strict criteria were applied.

Several factors should be considered when making decisions concerning antimicrobial therapy. By considering these factors, the otolaryngologist - head and neck surgeon can develop a rational approach to antibiotic use.

Clinical Setting

The initial selection of antibiotics depends on the clinical situation. For potentially life-threatening bacterial infections, there is an initial period of 1 to 2 days during which limited microbiologic data are available. During this period, broad-spectrum antibiotic coverage should be instituted. However, after microbiologic data are available, definitive narrow-spectrum therapy should be directed against the isolated organism. Obtaining appropriate material for culture may not be possible or may not be clinically indicated in many patients. In selected patients with specific diseases (eg, otitis media, acute maxillary sinusitis), selection of antibiotic therapy is based on research trials outlining the spectrum of microbial pathogens. In all settings, the physician should be alert to changes in patient status that indicate a need for changes in therapy.

Certain sites of infection are difficult to treat with antibiotics. The impermeability of the blood-brain barrier to many antibiotics is the best example of the importance of determining the site of infection. Recognizing that patients have abscesses and infected foreign bodies is also important because antimicrobial therapy alone will not be effective in these cases.

Several patient factors should be considered in the selection of antimicrobial therapy. A history of allergy or prior reaction to a similar antibiotic should be sought before administering any antimicrobial agent. The patient's age may be an important factor. Renal function declines with age, and certain toxic reactions to antibiotics are age related (eg, isoniazid-related hepatitis in patients over the age of 35, increased risk of aminoglycoside nephrotoxicity in elderly adults, "gray baby syndrome" secondary to chloramphenicol in neonates). Genetic factors, such as glucose-6-phosphate deficiency, may predispose some patients to severe side effects from certain antibiotics, and patients with underlying multisystem disease (eg, diabetes mellitus) may also be at more risk for adverse effects. Virtually all antibiotics cross the placenta, and only a few are considered relatively safe in pregnancy. The pregnant patient should be identified before antibiotics are prescribed. Many

abnormalities exist in host defense mechanisms that may make an individual susceptible to infections. Neutropenia, immunoglobulin or complement deficiency, alteration in mucosal and epithelial barriers, inadequate vascular supply, or foreign bodies may cause an individual to be an immunocompromised host. Type, dosage, and duration of antibiotic therapy may be affected by these host factors. Many authors advocate the use of "-cidal" antibiotics in an immunosuppressed host and would also consider the use of synergistic therapy (Hermans, 1977; Kalstersky and Zinner, 1982).

Pharmacology

Key features concerning the clinical pharmacology of antimicrobial agents include method of absorption and excretion, dosage, body fluid levels with various routes of administration, drug half-life, penetration into and stability in body fluids, and method of metabolic degradation (Kunin, 1981). For patients with severe infections or immunocompromised individuals, antimicrobial agents should be given parenterally. Higher blood levels are obtained with parenteral administration of antibiotics with some exceptions - doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole, and ciprofloxacin - for which oral and parenteral routes achieve the same blood levels. Foods, especially antacids, impair absorption from the intestinal tract for all antibiotics administered by mouth.

Antibiotic excretion usually occurs in the kidney or liver. For most antibacterial agents, renal clearance is the most important factor in determining blood levels (Bennett et al, 1980). Antibiotics that are secreted by the renal tubules (eg, penicillins) have a shorter serum half-life than antibiotics without considerable tubular secretion (eg, aminoglycosides). Protein binding also has an important effect on serum half-life. Higher protein binding is associated with a longer half-life. However, protein-bound antibiotics have little or no antimicrobial activity, and in general, antibiotics with relatively low protein binding are favored. Having a working knowledge of the mechanism of excretion of antibiotics is extremely important to predict dosage adjustments that would be necessary for patients in renal or hepatic failure. In addition, knowledge of the excretion method is useful for predicting the toxicity of an antimicrobial agent (Appel and Neu, 1977).

The best guide for the dosage and route of antibiotic therapy is the tissue concentration of the drug. However, because information on tissue concentrations is not readily available, most dosing recommendations are based on providing a blood level exceeding the minimum inhibitory concentration (MIC) by twofold to eightfold. Antimicrobial agents that have a wide margin between therapeutic and toxic levels, such as penicillin, cephalosporins, and erythromycin, may be given to an adult in a standard dose independent of the patient's weight. However, for agents with a narrow margin between therapeutic and toxic levels, such as the aminoglycosides, dosage should be calculated based on the patient's weight. All antibiotics should be given to children based on body weight.

The penetration of antibiotics into body fluids and their stability in various fluids are important considerations. Some antimicrobial agents, such as tetracycline and methenamine, are more active at an acid pH, which may be found in the urine or in an abscess cavity. Other antibiotics, such as erythromycin, aminoglycosides, and clindamycin, are more active at an alkaline pH. In general, antimicrobial therapy alone will not be effective for treating large abscesses or for treating infection in areas of tissue necrosis.

The appropriate duration of antimicrobial treatment is usually based on clinical experience. For many infections the optimal duration of therapy has not been well defined. In general, therapy should be continued for at least 2 to 3 days after all symptoms and signs of the infection have subsided. However, numerous exceptions to this general rule exist, such as with patients who develop drug fevers or have continued fevers from other medical problems (eg, collagen vascular diseases) and patients who have continuing laboratory abnormalities (eg, persistent radiographic abnormalities of the chest following bacterial pneumonia). The physician should follow published guidelines for duration of therapy but remain flexible with respect to the clinical status of the individual patient.

Adverse Effects

Antimicrobial agents cause many adverse reactions, which may be divided into minor and major side effects. Minor side effects include nausea and vomiting with oral antibiotics, phlebitis associated with intravenous drugs, and pain on intramuscular use. Antimicrobial agents potentially have major adverse effects on all organ systems. The physician should be aware of the side effects of antibiotics on major organ systems as listed in Table 5-1. In addition, expense should be considered when choosing an antimicrobial agent because the annual cost of antibiotic use in this country has risen dramatically in the past decade.

Spectrum of Activity

Selection of antimicrobial agents ideally should be based on in vitro susceptibility tests of the isolated pathogen. During the first 24 to 48 hours of infection, while awaiting culture, a Gram-stained smear of infected material can provide preliminary information to direct antibiotic therapy. However, when no material is available the physician must select an antibiotic based on the pathogens that are likely to be causing the infection. For example, the organisms most likely to cause acute maxillary sinusitis in a patient are pneumococcus, *Haemophilus influenzae,* or *Moraxella catarrhalis*. In such a patient, amoxicillin-clavulanate or trimethoprim-sulfamethoxazole would cover the spectrum of likely organisms.

Several methods are available for testing microbial susceptibility in vitro, including the disk diffusion method, broth dilution, and agar dilution. In general, an organism is considered susceptible if the antibiotic concentration needed to inhibit growth is lower than the typical blood level. Many factors affect antibiotic susceptibility test results including inoculum size, incubation conditions, growth medium, and the preparation of antibiotics. It is especially important to realize that preliminary sensitivity studies may be affected by inoculum and differ significantly from final studies.

The disk diffusion method is the most commonly used method of susceptibility testing and has been standardized among different laboratories. Organisms are rated as *susceptible, intermediate,* or *resistant* based on the size of the zone of inhibition around each antibiotic disk. The reference zone sites have been developed using large numbers of control microorganisms. The agar or broth dilution techniques provide a more quantitative assessment of antimicrobial susceptibility, but variation with these methods will be observed among different laboratories. In general, the lowest concentration of antibiotic preventing visible growth after overnight incubation is called the *minimum inhibitory concentration* (MIC). Tubes that show inhibition may be subcultured to new growth media to determine the

minimum bactericidal concentration (MBC). Antimicrobial agents with low MBCs (bactericidal agents) are preferred for the treatment of selected severe infections (eg, bacterial endocarditis, meningitis) and for patients who are immunocompromised.

Susceptibility testing can be performed for selected combinations of antibiotics, and synergy studies may be performed using broth or agar dilution methods (eg, penicillin plus gentamicin activity against enterococci). Susceptibility testing for anaerobic bacteria has not been studied as extensively as testing for aerobes has been. For the majority of anaerobic bacteria, antibiotic susceptibility is predictable. An important exception is *Bacteroides fragilis,* which may be resistant to many antimicrobial agents.

Although most microorganisms should be treated with a single antibiotic, several organisms respond best to combinations of antimicrobial agents. Invasive *Pseudomonas aeruginosa* infections and enterococcal bacteremia are examples of infections for which synergistic antibiotic therapy would be recommended.

A basic principle of antimicrobial therapy is to choose a drug directed against a specific organism, that is, one having the narrowest spectrum. In many situations, however, broad-spectrum therapy may be indicated. Table 5-2 presents an outline of the categories of commonly used antimicrobial agents including a general description of the spectrum of action and examples of appropriate clinical situations.

Reasons for Apparent Failure of Antimicrobial Therapy

If a patient has persistent or recurrent fever during "appropriate" antimicrobial therapy, several possible explanations should be considered for this apparent antibiotic failure. These include (1) presence of an abscess requiring drainage; (2) drug fever (see Lipsky and Hirschmann, 1981); (3) superinfection with a new pathogen; (4) microbial resistance; (5) poor compliance (with patients on oral antibiotics); (6) poor antibiotic penetration for the site of infection; (7) decreased absorption or increased excretion of the antimicrobial agents; (8) impairment of host defense; and (9) presence of another infection (viral or parasitic) or a noninfectious process that may mimic an infection.

Prophylactic Antibiotics

Although there have been many trials of antimicrobial prophylaxis, only a few circumstances meet stringent criteria for prophylactic antibiotic use (Hirschmann and Inui, 1980). These situations include, among others, vaginal and abdominal hysterectomies, high-risk cesarean sections, elective colorectal surgery, vascular grafts of the abdominal aorta, total hip replacement, and head and neck cancer surgery. For most patients, the prophylactic antibiotic can be an inexpensive agent given for a brief period of time. Excessive duration of drug administration increases the expense and risk of side effects. For surgical prophylaxis, the presence of adequate tissue levels of an appropriate agent during the operation appears to be the important factor determining the effectiveness of the regimen. A single preoperative dose usually achieves adequate tissue levels. Antibiotics are not, however, a substitute for excellent surgical technique, and some surgeons can achieve low infection rates without antibiotic prophylaxis in situations in which others have found prophylaxis to be necessary.

Antimicrobial Agents Used by Otolaryngology - Head and Neck Surgeons

Penicillins

The several distinct categories of penicillins include (1) natural penicillins (penicillin G, procaine penicillin, benzathine penicillin, phenoxymethyl penicillin); (2) penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin, dicloxacillin)); (3) amino penicillins (ampicillin, amoxicillin, bacampicillin); (4) antipseudomonal penicillins (carbenicillin, ticarcillin, piperacillin, mezlocillin); and (5) combinations of amino penicillins and beta-lactamase inhibitors (ampicillin-sulbactam and amoxicillin-clavulanate).

Penicillin G (benzyl penicillin), the most commonly used natural penicillin, provides excellent antimicrobial activity against most gram-positive cocci except penicillinase-producing *Staphylococcal aureus.* It is also effective against a few gram-negative organisms (eg, *Neisseria gonorrhoeae, N. meningitidis, Pasteurella multocida*), gram-positive bacteria (eg, *Listeria monocytogenes, Erysipelothrix rhusopathiae, Corynebacterium diphtheriae*), most anaerobic bacteria except *Bacteroides fragilis,* and spirochetes. Penicillin G is usually administered intravenously at 4-hour intervals for severe infections. Procaine penicillin G has been developed for intramuscular use and achieves therapeutic levels for up to 12 hours after injection. Benzathine penicillin G provides low serum levels for as long as 30 days after intramuscular injection. Because penicillin G is not stable at acid pH in the stomach, phenoxymethyl penicillin (penicillin V), which is more acid stable, is preferred for oral therapy. Penicillin V has a spectrum of activity similar to that of penicillin G except for poor activity against *Neisseria* species.

The penicillinase-resistant penicillins are used primarily for documented *S. aureus* infections. For organisms sensitive to penicillin G, the penicillinase-resistant antibiotics generally provide less activity. These antibiotics should not be used for *Neisseria* species, *L. monocytogenes,* enterococci, or anaerobic bacteria.

Amino penicillins are derived from penicillin G by minor modification of the side chain. Ampicillin, the prototype amino penicillin, is effective against a larger number of gram-negative organisms than is penicillin G. Low concentrations of ampicillin provide activity against *E. coli, Proteus mirabilis, Shigella, Salmonella,* and *H. influenzae.* However, each *H. influenzae* isolate must be tested for beta-lactamase production, which inactivates ampicillin. All organisms susceptible to penicillin G should also be susceptible to ampicillin, and no major differences exist between the spectrums of activity of ampicillin and amoxicillin. Combinations of amino penicillins and beta-lactamase inhibitors were developed to expand the activity of ampicillin and amoxicillin. Currently, both intravenous ampicillin-sulbactam and oral amoxicillin-clavulanate are available in the USA. These preparations increase the spectrum of activity of both ampicillin and amoxicillin to include beta-lactamase-producing *S. aureus, H. influenzae, Moraxella catarrhalis, B. fragilis,* and aerobic enteric organisms.

The antipseudomonal penicillins are less active than ampicillin on a weight basis but are effective against the same organisms. In addition, because gram-negative beta-lactamases do not inactivate these antibiotics, they are effective against many strains of *Proteus, Enterobacter,* and *Pseudomonas aeruginosa.* It is important to remember, however, that MICs

for *P. aeruginosa* are high (50-100 microg/mL). Serum levels above this range can be achieved with parenteral administration but not with the oral form of carbenicillin against *P. aeruginosa* and may be used at a lower dose. The new agents, piperacillin and mezlocillin, are more active against Enterobacteriaceae than are carbenicillin or ticarcillin. In addition, piperacillin may provide more activity against *P. aeruginosa.* The antipseudomonal penicillins should not be used alone for the treatment of gram-negative bacillary infections except when the infection is limited to the urinary tract. An increase in bacterial resistance may be seen in patients with gram-negative infections treated with carbenicillin alone. Simultaneous treatment with an aminoglycoside or a cephalosporin may delay the development of resistance to the antipseudomonal penicillins.

Cephalosporins

Over the past 20 years a large number of cephalosporins have been developed and released for clinical use. These antibiotics have gained wide acceptance because of their minimal side effects and their broad spectrum of activity. However, the newer cephalosporins are expensive, and the indications should be considered carefully before one of these antibiotics is prescribed. For cases in which the bacterial pathogen has been isolated, choosing a more narrow-spectrum and inexpensive antibiotic may be possible.

The proliferation of cephalosporins in the past 15 years has led to a classification system based on "generation". The first-generation cephalosporins include several preparations designed for intravenous use (cephalothin, cefazolin, cephapirin) and for oral use (cephalexin, cephadroxil). These agents have a virtually identical spectrum of activity, providing coverage against most gram-positive cocci, including penicillin-resistant *Staphylococcus aureus,* and against most strains of *E. coli, Proteus mirabilis,* and some *Klebsiella pneumoniae.* Most anaerobic bacteria with the exception of *Bacteroides fragilis* are susceptible to first-generation cephalosporins. However, many important pathogens are resistant to these agents. Among the gram-positive organisms, methicillin-resistant staphylococci, enterococci, and *Listeria monocytogenes* are resistant. *H. influenzae* has variable susceptibility to the first-generation cephalosporins, and in general, these agents should not be used for documented severe *H. influenza* infections.

Second-generation cephalosporins were developed to expand the spectrum of activity of cephalothin and cefazolin. Cefuroxime, which is available in both oral and parenteral preparations, is more active than cephalothin against several gram-negative bacteria. It is effective against many *Proteus* and *Klebsiella* species and provides consistent activity against *H. influenzae* and *Moraxella catarrhalis.* Cefuroxime is resistant to the beta-lactamase enzyme produced by *H. influenzae* and *M. catarrhalis.* Although cefuroxime penetrates well into the cerebrospinal fluid, documented failures of cefuroxime in the treatment of *H. influenzae* meningitis have been reported. Certain third-generation cephalosporins are now preferred for the treatment of meningitis. Cefoxitin and cefotetan, both designed for intravenous use, also provide coverage against most *Proteus* species and, in addition, are effective against some strains of *Bacteroides fragilis* and *Serratia marescens.* Both drugs are somewhat less effective than cephalothin against common gram-positive cocci. In general, penicillins or first-generation cephalosporins are preferred over second-generation agents for documented infections with gram-positive cocci. Cefaclor is an oral second-generation cephalosporin with a spectrum of activity similar to that of cefuroxime.

Third-generation cephalosporins were developed to increase the spectrum of activity of cephalosporins against gram-negative bacteria. Cefotaxime, the first of the third-generation agents to be released in this country, provides a very broad spectrum of activity against many gram-negative organisms, including *E. coli, Klebsiella, Enterobacter, Citrobacter,* and *Serratia* species. In addition, cefotaxime provides activity against most anaerobic bacteria, including some strains of *Bacteroides fragilis.*

Ceftriaxone, which can be administered at 12- to 24-hour dosing intervals, has a spectrum of activity similar to that of cefotaxime. Both ceftriaxone and cefotaxime penetrate well into body fluids, including the cerebrospinal fluid. This is a distinct advantage over the first- and second-generation cephalosporins (except cefuroxime), which do not penetrate adequately into the cerebrospinal fluid. Therapy with either cefotaxime or ceftriaxone has been successful in treating patients with meningitis caused by pneumococcus, susceptible gram-negative bacteria, and *H. influenzae* (including beta-lactamase-producing strains).

Cefoperazone is another third-generation agent with a broadly extended spectrum of action. In addition, cefoperazone may provide increased coverage against *Pseudomonas aeruginosa.* However, ceftazidime has the greatest activity against *Pseudomonas aeruginosa* of the third-generation cephalosporins.

Ceftizoxime is the desacetoxymethyl derivative of cefotaxime and provides slightly more activity against *Klebsiella, Serratia,* and *Enterobacter* species.

Cefixime is a new oral third-generation cephalosporin. Its role in clinical therapy has yet to be established.

All of the third-generation cephalosporins are ineffective against enterococci and *L. monocytogenes.* In addition, these agents may be less effective than first-generation cephalosporins against some gram-positive cocci. Alternative antibiotics, such as penicillins or first-generation cephalosporins, are preferred for most well-documented infections with gram-positive cocci.

Trimethoprim-sulfamethoxazole and sulfonamides

The sulfonamides were used clinically before penicillin was available and provide a broad spectrum of activity against many gram-positive cocci except enterococcus, and many gram-negative bacilli. The penicillins and cephalosporins have replaced the sulfonamides in many clinical settings. Uncomplicated urinary tract infection is the main indication for single sulfonamide therapy.

Trimethoprim has a spectrum of activity similar to that of sulfonamides, and the combination of trimethoprim and sulfamethoxazole acts synergistically to inhibit the growth of susceptible bacteria at two separate steps in folic acid synthesis. This combination agent eliminates one of the major problems with single sulfonamide therapy, the emergence of bacterial resistance. The combination drug is available in both oral and intravenous preparations and is effective against a variety of organisms, including pneumococci, *H. influenzae, E. coli, Klebsiella,* and *Shigella* species, and other gram-negative organisms. It has been used commonly for the treatment of acute otitis media in children and for treating

patients with acute exacerbations of chronic bronchitis. In addition, it has gained wide acceptance as a prophylactic agent against acute and chronic urinary tract infections. Trimethoprim-sulfamethoxazole also provides effective coverage against some more exotic pathogens, including *Nocardia* and *Pneumocystis carinii* species.

Trimethoprim alone is available for the treatment of uncomplicated urinary tract infections. Patients who are allergic to sulfa drugs may be able to tolerate trimethoprim.

Erythromycin

Erythromycin is primarily a narrow-spectrum antibiotic active against most gram-positive bacteria. In addition, *Mycoplasma pneumoniae, Legionella pneumophila, C. diphtheriae, Listeria monocytogenes, Bacillus anthracis,* and *Campylobacter fetus* are susceptible. The major clinical use of erythromycin is for respiratory tract infections. Erythromycin is available for both parenteral and oral use; most patients are treated by oral administration. Intravenous therapy has been reserved primarily for patients who are severely infected with *Legionella* species.

Aminoglycosides

Currently six aminoglycosides are available for systemic use in the USA, and one additional preparation is available for topical and oral administration for bowel sterilization. An additional antibiotic, spectinomycin, is an aminocyclitol but does not contain an amino sugar component.

Streptomycin was one of the first antibiotics available for use in the USA. Many patients received streptomycin in the 1940s and 1950s, but recently its use has been limited. Currently streptomycin may be used (1) with penicillin to treat patients with *Streptococcus viridans* endocarditis; (2) as part of a triple drug regimen in patients with tuberculosis; and (3) for patients with brucellosis, tularemia, or bubonic plague. Vestibular nerve toxicity may be more prominent with streptomycin than with some of the other aminoglycosides.

Among the newer aminoglycosides, gentamicin and amikacin have similar structure and common pharmacokinetic characteristics. Amikacin is a semisynthetic derivative of kanamycin and provides greatly improved coverage for *Pseudomonas aeruginosa.* Kanamycin and tobramycin are similar aminoglycosides except that tobramycin is more active by weight against most strains of *P. aeruginosa.* Also, tobramycin may be less nephrotoxic than gentamicin.

Most aminoglycosides are effective against the Enterobacteriaceae. The aminoglycosides require oxygen-dependent active uptake by the bacterial cell. Anaerobes and facultative organisms grown under anaerobic conditions are resistant to these agents. Streptococci and *Listeria monocytogenes* are also resistant, but aminoglycosides will act synergistically with penicillin against these organisms. *P. aeruginosa* is almost always resistant to kanamycin. Tobramycin and gentamicin are similar in efficacy except that *P. aeruginosa* may be more sensitive to tobramycin, and *Serratia* species may be more sensitive to gentamicin. Netilimicin is similar in activity and toxicity to gentamycin.

Neomycin cannot be used as a systemic antibiotic because of its severe nephrotoxicity and neurotoxicity. However, it provides a broad spectrum of activity and may be used topically for cutaneous infections or orally to eradicate bowel flora in several clinical situations, such as preoperative bowel management and hepatic encephalopathy.

Tetracyclines

Tetracyclines are broad-spectrum antibiotics active against many gram-positive and gram-negative organisms. However, *Staphylococcus aureus* and group A streptococci may be resistant. Tetracyclines are effective against *H. influenzae, N. gonorrhoeae,* and *N. meningitidis,* in addition to having activity against many enteric gram-negative bacilli. *Pseudomonas aeruginosa* and *Proteus* species will usually be resistant to these drugs. Tetracyclines may be the drugs of choice for several unusual infections caused by rickettsiae, chlamydiae, mycoplasmata, *Yersinia pestis, Brucella* species, and *Francisella tularensis.*

All tetracyclines are well absorbed when taken orally. Several different preparations are available with different half-lives. Short-acting agents, including tetracycline and oxytetracycline, should be given every 6 hours, whereas intermediate-acting agents (demeclocycline) can be given every 12 hours, and long-acting compounds (minocycline and doxycycline) can be given every 12 to 24 hours. These agents can be given intravenously, but the levels achieved by oral administration will be approximately the same as those achieved by intravenous administration. The tetracyclines are contraindicated in the presence of renal failure.

Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic with a spectrum of activity similar to that of the tetracyclines. This drug is effective against a variety of gram-positive and gram-negative organisms including anaerobic bacteria. In addition, chloramphenicol is active against rickettsiae, chlamydiae, and mycoplasmata. Chloramphenicol penetrates the cerebrospinal fluid very well, and a major use of this drug is for patients with meningitis and brain abscess. *N. meningitidis, Streptococcus pneumoniae* (pneumococcus), and *H. influenzae* (including beta-lactamase-producing strains) are susceptible to this agent.

Like tetracycline, chloramphenicol is well absorbed from the gastrointestinal tract, and blood levels are approximately the same after oral and intravenous administration. Patients treated with chloramphenicol should be monitored for bone marrow suppression. Rarely, chloramphenicol may also cause aplastic anemia by an idiosyncratic, non-dose-related mechanism, particularly when administered orally.

Vancomycin

Most gram-positive cocci are susceptible to vancomycin, a narrow-spectrum antibiotic; these cocci include penicillinase-producing *Staphylococcus aureus,* enterococci, methicillin-resistant *S. epidermidis,* methicillin-resistant *S. aureus,* and even the penicillin-resistant pneumococci. Vancomycin does not provide coverage against gram-negative organisms nor does it provide good coverage against anaerobic organisms.

When first introduced in the 1950s, vancomycin was associated with relatively severe toxicity. However, a purified compound has since been developed, and the only major toxicity at present is ototoxicity. Vancomycin is not absorbed when given by mouth, although it may be useful when given orally for bowel sterilization or in the treatment of pseudomembranous colitis. Intravenous administration is usually given at 12-hour intervals unless renal failure is present. Monitoring of drug levels can prevent ototoxicity and the rare development of nephrotoxicity.

Imipenem

Imipenem is a parenteral carbapenem antibiotic with a remarkably broad spectrum of activity against bacteria, including gram-positive cocci, gram-negative aerobic bacilli, and anaerobes. This drug does not provide coverage against methicillin-resistant *S. aureus* or *S. epidermidis.* When used in the therapy of infections caused by *Pseudomonas aeruginosa,* imipenem should be combined with an aminoglycoside to reduce the risk of resistance developing during treatment.

Imipenem should be reserved for treatment of hospital-acquired infections caused by bacteria that are multiply resistant. It can also be used to treat polymicrobial infections possibly due to *S. aureus,* gram-negative enteric bacilli, and anaerobes. At high doses, imipenem may precipitate seizures in patients with renal failure. In addition, this drug can induce anaphylaxis in patients with a history of anaphylaxis to penicillins or cephalosporins.

Quinolones

The fluoroquinolones represent a unique class of oral antibiotics that exert their antibacterial activity via the inhibition of bacterial topoisomerase II. These drugs have excellent activity against gram-positive cocci and aerobic gram-negative bacilli, including Enterobacteriaceae, *Klebsiella* species, and *Pseudomonas aeruginosa.* The quinolones have no activity against anaerobic bacteria. Three broad-spectrum quinolones are currently available. Ciprofloxacin and ofloxacin achieve greater tissue levels than norfloxacin. These drugs are especially useful in complicated urinary tract infections (including pyelonephritis and bacterial prostatitis), osteomyelitis, bacterial dysentery, and malignant otitis externa. However, clinical failures have been reported when these agents have been used for the treatment of pneumococcal infections. Another recent problem has been the rapid emergence of quinolone resistance by *S. aureus.* An intravenous preparation of ciprofloxacin is now available; its role in patient care has yet to be determined.

Miscellaneous antibacterial agents

Metronidazole and clindamycin provide excellent coverage against most anaerobic bacteria including *Bacteroides fragilis.* Although these antibiotics have a similar spectrum of activity against anaerobic bacteria, the chemical structures, side effects, and pharmacokinetics of these agents are different. Metronidazole is absorbed well from the gastrointestinal tract and penetrates well into most body fluids including cerebrospinal fluid. It provides excellent activity against most gram-positive and gram-negative anaerobic organisms except for anaerobic nonsporulating gram-positive bacilli and microaerophilic streptococci. Metronidazole is not active against most aerobic bacteria, however, and should not be used as a single agent

in patients with mixed anaerobic and aerobic infections. Clindamycin has a spectrum of activity against aerobic gram-positive bacteria that is similar to that of erythromycin. Clindamycin's activity against anaerobic organisms (including *B. fragilis*) is excellent although some strains of clostridia and peptococci may be resistant. Like metronidazole, clindamycin has no activity against aerobic gram-negative bacilli. Clindamycin may be given either intravenously or orally. Patients treated with this agent should be monitored for the well-known complication of pseudomembranous colitis.

Aztreonam is a new monobactam antibiotic with activity against only aerobic gram-negative bacteria. Its use should be restricted to the treatment of gram-negative bacterial infections in patients at high risk for nephrotoxicity from aminoglycosides. Unlike the aminoglycosides, the addition of aztreonam to a penicillin or cephalosporin does not produce synergistic antibiotic activity. Aztreonam can be used safely in patients who are allergic to penicillins.

Several antimicrobial agents have been used exclusively for urinary tract infections. These agents achieve adequate urine levels for effectiveness but are not associated with therapeutic blood levels. Nitrofurantoin has been used to treat acute urinary tract infections and for prophylaxis in patients with recurrent infections. It is active against the Enterobacteriaceae and enterococci but is not effective against *P. aeruginosa.* Nitrofurantoin is associated with several severe but rare side effects. Methenamine is active against most bacteria but only at an acid pH (urine pH less than 5.5). Methenamine has been effective only as a prophylactic agent and has not been used for treating acute infections.

Antifungal agents

Amphotericin B is the most effective agent available for treating invasive fungal infections. It provides predictable antifungal therapy for patients with candidiasis, cryptococcosis, histoplasmosis, coccidioidomycosis, aspergillosis, and mucormycosis. Amphotericin B must be administered intravenously over a period of several hours. Patients with invasive fungal infections usually require long-term therapy (2 to 4 months). Patients with esophageal candidiasis, however, are an exception to this rule. For these patients, a much shorter course of amphotericin therapy (7 to 14 days) may be adequate to eradicate the infection. Patients treated with amphotericin B on a long-term basis will often experience mild impairment of renal function. The renal toxicity is dose related, and permanent renal damage may occur in patients who require long courses of amphotericin.

For some patients with invasive fungal infection, flucytosine is used in combination with amphotericin B as synergistic therapy. Selected patients with either invasive candidiasis or cryptococcal meningitis are examples of situations in which flucytosine may be considered for synergistic therapy. Flucytosine is an oral agent that is cleared by the kidney; the dose needs to be adjusted for patients with renal failure.

Fluconazole, ketoconazole, and miconazole are relatively new antifungal agents of the imidazole class that may be useful in treating invasive fungal infections such as candidiasis, cryptococcosis, and sporotrichosis. Both ketoconazole and fluconazole may be given orally for the treatment of oropharyngeal and esophageal candidiasis. Oral fluconazole is highly effective as maintenance prophylaxis against cryptococcus following primary treatment of

cryptococcal meningitis. Intravenous fluconazole may be used against systemic candidiasis and causes fewer side effects than amphotericin B. However, its clinical efficacy against invasive fungal infections is less predictable than that of amphotericin B.

Nystatin is another antifungal agent effective against *Candida,* although it is used only for superficial infections. It cannot be administered systemically because of severe toxicity. Nystatin is useful for oral, cutaneous, vaginal, and intestinal candidal infections.

Antituberculous agents

Isoniazid, rifampin, and pyrazinamide are the "first-line" drugs used currently for the treatment of tuberculosis. Isoniazid remains the only agent used for patients with purified protein derivative (PPD) conversion and no evidence of active disease. For patients with active pulmonary tuberculosis, three-drug therapy with isoniazid, rifampin, and pyrazinamide is recommended. Ethambutol is added to this regimen for patients with possible isoniazid-resistant organisms or for patients with more widely disseminated disease such as tuberculous meningitis. Streptomycin and p-aminosalicylic acid are usually the next agents considered for use. Other secondary drugs include cycloserine and ethionamide. Several new agents are currently being studied for treating patients with resistant atypical mycobacterial infections. The role of these new agents, such as ansamycin and clofazamine, remains to be defined.

Antiviral agents

In recent years several effective agents have been developed and tested in clinical trials. Amantadine has been shown to be effective in the prevention of respiratory tract infection caused by influenza A virus. Intravenous administration of acyclovir is effective for the treatment of herpes simplex virus encephalitis, especially when therapy is begun before the onset of severe neurologic sequelae. Acyclovir is also effective in the therapy of disseminated herpes zoster infections and active herpes simplex virus infections. Acyclovir may also be used as prophylaxis against recurrent eruptions of herpes simplex.

Topical preparations including idoxuridine, trifluridine, and adenine arabinoside are available for treating herpes simplex virus keratitis.

Antiparasitic agents

A variety of chemotherapeutic agents is available for the treatment of parasitic diseases. Many of these agents have been recently introduced, and some represent the first effective therapy for previously untreatable diseases (such as clonorchiasis and Chagas' disease). Some of these agents provide broad-spectrum antiparasitic therapy. For example, mebendazole is effective against many intestinal parasites and provides useful single-drug therapy for patients with multiple intestinal infections. Although the newer antiparasitic agents have fewer side effects than the older drugs, they do cause significant systemic reactions. A discussion of antiparasitic agents and their reactions is beyond the scope of this chapter.

Immunocompromised Host

Various abnormalities in host defense mechanisms cause an individual to become an immunocompromised host. The implications for antimicrobial therapy depend on the type of host defense abnormality and the specific infections. Because the surgeon is frequently involved in the care of immunocompromised patients, a brief review of the use of antimicrobial agents in these patients will follow.

Specific abnormalities leading to immunocompromised host status include (1) neutrophil defects, including neutropenia and abnormalities of chemotaxis, phagocytosis, and microbicidal function; (2) humoral defects, including antibody and complement deficiency; (3) abnormalities of T- and/r B-cell function; (4) mechanical defects, including ischemia, impaired drainage, damage to the integument, and the presence of foreign bodies; and (5) alteration of the normal surface bacteria caused by antibiotics.

Neutropenia is a frequently encountered abnormality in phagocytic defenses. Absolute neutrophil counts below $500/mm^3$ are associated with a variety of infections, including bacteremia, pneumonia, perirectal abscess, mucocutaneous infections, and central nervous system infections. The spectrum of bacterial pathogens includes gram-negative bacilli such as *P. aeruginosa* and *E. coli,* gram-positive organisms such as *S. aureus* and *S. epidermidis,* and a variety of more unusual pathogens such as *Aspergillus, Candida,* and *Pneumocystis carinii.* In addition, patients who are neutropenic for more than 1 week often develop fever with no obvious source. Appropriate antibiotic coverage of neutropenic patients has been an area of active research interest.

Many authors advocate initial empiric antibiotic therapy to protect neutropenic patients from immediate death (Hughes et al, 1990; Pizzo et al, 1984). Therefore, the antibiotic regimen should cover the major pathogens that are likely to cause bacteremia in neutropenic patients. These organisms include *P. aeruginosa, E. coli,* and a variety of other gram-negative bacilli and gram-positive cocci such as *S. aureus* and *S. epidermidis.* Initial empiric antibiotic therapy for the febrile neutropenic patient usually includes two or three antimicrobial agents. A typical two-drug regimen is a combination of an aminoglycoside (gentamicin, tobramycin, amikacin) and either an extended-spectrum penicillin (carbenicillin, ticarcillin, piperacillin) or third-generation cephalosporin (ceftazimide, cefoperazone). If a third drug were to be added to this regimen most physicians would choose vancomycin. The exact choice of the two- or three-drug regimen depends on the prevailing organisms and their sensitivities. For example, some centers have experienced high rates of bacteremia with methicilin-resistant *S. epidermidis* (Wade et al, 1982). At these centers, vancomycin has been added to the empiric regimens.

Ongoing studies have been designed to investigate the roles of third-generation cephalosporins or imipenem for empiric coverage of the febrile neutropenic patient. Some studies are being performed with single-drug therapy, whereas others use combinations of third-generation cephalosporins and antpseudomonal penicillins. Present data suggest no apparent advantage to three- versus two-antibiotic regimens, but single-antibiotic therapy has not been adequately studied to recommend its use (Hughes et al, 1990; Pizzo et al, 1984). The standard of practice at a single institution should always be based on the spectrum of microbial isolates and their antibiotic sensitivities.

After empiric antibiotic therapy has been started in the neutropenic patient, deciding whether to modify the therapy based on culture results is necessary. Some authors recommend narrowing the spectrum of the antimicrobial regimen to cover the specific organisms isolated. Most investigators suggest, however, that the broad-spectrum, two- or three-drug regimen should be continued even when the specific organism isolated could be treated by one antibiotic.

Another frequent question is what to do for persistent fever when the neutropenic patient has been on two- or three-drug therapy for over 5 to 7 days. Several authors suggest that antifungal therapy should be added on an empiric basis at this point in the clinical course of a neutropenic patient. These recommendations are based on limited clinical studies and may be modified after subsequent investigation (Hughes et al, 1990; Pizzo et al, 1984). Further study is needed to determine the antifungal agent to be used and the exact time at which empiric antifungal therapy should be started in patients with persistent fever and granulocytopenia.

For many immunocompromised patients, predicting the common organisms involved is possible. Table 5-3 presents an outline of host factors, usual infectious agents, and appropriate antibiotics for several examples of infections in immunocompromised hosts.

Table 5-1. Major adverse effects of antimicrobial agents

Reactions	Antimicrobial agents
Anaphylaxis	Penicillins, cephalosporins, sulfonamides, imipenem
Serum sickness	Penicillins, cephalosporins, sulfonamides
Drug fever	All antimicrobial agents

Renal

Acute tubular necrosis	Aminoglycosides, quinolones
Interstitial nephritis	Methicillin, other penicillins, cephalosporins, sulfonamides, vancomycin
Glomerulonephritis	Penicillins, sulfonamides
Hypokalemia	Amphotericin B, carbenicillin, ticarcillin
Prerenal azotemia	Tetracyclines

Hematologic

Aplastic anemia	Chloramphenicol, sulfonamides
Immune hemolytic anemia	Penicillins, sulfonamides, isoniazid, rifampin
Hemolysis in patients with G-6-PD deficiency	Chloramphenicol, nitrofurantoin, sulfonamides
Leukopenia	Penicillins, cephalosporins
Bleeding disorders	Moxalactam, cefoperazone, cefotetan

Hepatic

Cytotoxic effects	Isoniazid, oxacillin, nitrofurantoin
Cholestatic effects	Erythromycin, nitrofurantoin
Mixed cytotoxic and cholestatic effects	Rifampin, nitrofurantoin
Chronic hepatitis	Isoniazid, nitrofurantoin

Intestinal

Pseudomembranous colitis	Clindamycin, ampicillin, cephalosporins, and virtually all antibiotics
Diarrhea	Ampicillin, amoxicillin-clavulanate, erythromycin, penicillins, ceftriaxone, and most other antibiotics

Pulmonary

Fibrosis	Nitrofurantoin
Infiltrates and eosinophilia	Penicillins, sulfonamides, nitrofurantoin

Neurologic

Encephalopathy	Penicillin (overdose)
Ototoxicity	Aminoglycosides, vancomycin
Optic neuritis	Ethambutol
Peripheral neuropathy	Isoniazid, metronidazole, nitrofurantoin
Neuromuscular blockade	Aminoglycosides
Seizures	Imipenem, penicillins (high-dose)

Dermatologic

Maculopapular rash	Penicillins, sulfonamides, cephalosporins, aminoglycosides, nitrofurantoin
Erythema multiforme	Penicillins, cephalosporins, sulfonamides
Hypersensitivity angiitis	Sulfonamides, penicillins
Photosensitivity	Tetracyclines, sulfonamides, penicillins

Drug-induced lupus   Isoniazid, penicillins, sulfonamides.

Table 5-2. Common antimicrobial agents

Agents
    Spectrum of activity
        Typical clinical indications
            Dose adjustment

Penicillins

Penicillin G
    Most streptococci, nonpenicillinase-producing staphylococci, *Neisseria* species, anaerobic bacteria except *B. fragilis* and some *B. melaninogenicus*
        Pneumonia, soft tissue infection with mouth flora, pharyngitis, deep neck abscess
            Renal failure

Ampicillin, amoxicillin
    Most streptococci, *Neisseria* species, non-lactamase-producing *H. influenzae,* some *E. coli, Listeria monocytogenes, Proteus mirabilis, Shigella* species
        Acute maxillary sinusitis, otitis media, meningitis caused by a susceptible organism
            Renal failure

Ampicillin-sulbactam, amoxicillin-clavulanate
    As per ampicillin plus penicillinase-producing staphylococci and *H. influenzae,* and most anaerobic bacteria including *B. fragilis*
        Pneumonia, soft tissue infection with mouth flora, deep neck abscesses, sinusitis, otitis media, cellulitis
            Renal failure

Nafcillin
    Penicillinase-producing *S. aureus*
        Any invasive *S. aureus* infection
            Hepatic failure, severe renal failure

Carbenicillin, ticarcillin
    Pseudomonas aeruginosa, some streptococci, some Enterobacteriaceae
        Invasive *P. aeruginosa* infection (plus aminoglycoside), such as invasive otitis externa
            Renal failure

Ticarcillin-clavulanate
    As per ticarcillin plus penicillinase-producing staphylococci and most anaerobic bacteria
        As per ticarcillin with additional coverage of possible concomitant infection with *S. aureus*
            Renal failure

Cephalosporins

Cephalothin, cefazolin
> Streptococci except enterococci, penicillinase-producing staphylococci, many *E. coli, Proteus mirabilis,* some *Klebsiella* species, anaerobic bacteria except *B. fragilis*
>> Pneumonia, soft tissue infections with mouth flora
>>> Renal failure

Cefamandole, cefuroxime
> As per cephalothin plus *H. influenzae* and *Moraxella catarrhalis,* increased coverage of Enterobacteriaceae
>> Broader coverage of hospital-acquired infections, coverage for ampicillin-resistant *H. influenzae*
>>> Renal failure

Cefoxitin, cefotetan
> As per cephalothin plus increased *B. fragilis* and Enterobacteriaceae coverage
>> Broader coverage of hospital-acquired infection with improved anaerobic coverage
>>> Renal failure

Third-generation agents
> As per cefamandole *and* cefoxitin plus some *P. aeruginosa* coverage and consistent activity against many Enterobacteriaceae
>> Broader coverage of hospital-acquired infection
>>> ± Renal failure

Erythromycin
> Streptococci, many staphylococci, *Bordetella pertussis, Campylobacter fetus, Legionella* species, mycoplasma, *Corynebacterium diphtheriae*
>> "Atypical" pneumonia, pharyngitis
>>> Hepatic failure

Trimethoprim-sulfamethoxazole
> *H. influenzae,* pneumococcus, *Moraxella catarrhalis, Neisseria* species, many *E. coli* and other Enterobacteriaceae
>> Acute maxillary sinusitis, otitis media
>>> ± Renal failure

Aminoglycosides
> *E. coli, Klebsiella, Enterobacter, Proteus* species, *Pseudomonas aeruginosa,* synergistic activity with penicillin (or ampicilin) versus enterococcus and *Listeria monocytogenes*
>> Invasive gram-negative bacillary infections such as invasive external otitis (plus ticarcillin or ceftazidime)
>>> Renal failure

Tetracycline
  Neisseria gonorrhoeae, anaerobic bacteria except *B. fragilis,* some Enterobacteriaceae
      Soft tissue infection with mouth flora
          Avoid in renal and hepatic failure

Chloramphenicol
  Pneumococcus, *Neisseria meningitidis, H. influenzae,* rickettsia
      Meningitis, epiglottitis, brain abscess
          Hepatic failure

Vancomycin
  All streptococci, all staphylococci including penicillinase-producing and methicillin-resistant strains
      Alternate antibiotic to penicillin for streptococcal infections, useful for coagulase-negative staphylococcal infections and methicillin-resistant staphylococcal infections
          Renal failure

Clindamycin
  Many streptococci (except enterococcus) and some staphylococci, anaerobic bacteria including most *B. fragilis*
      Anaerobic infections with *B. fragilis* such as brain abscess
          Hepatic failure

Metronidazole
  Anaerobic bacteria including *B. fragilis, Giardia lamblia*
      Anaerobic infections such as brain abscess
          Hepatic failure

Quinolones
  E. coli, Klebsiella, Enterobacter, Proteus sp, Pseudomonas aeruginosa, and most aerobic gram-positive cocci; no activity against anaerobic bacteria
      Oral agent for infections caused by *Pseudomonas aeruginosa* and *Enterobacter* species
          Renal failure

Imipenem
  Broad spectrum of activity against most aerobic and anaerobic bacteria except methicillin-resistant *S. aureus*
      Severe, life-threatening hospital-acquired infections involving mixed organisms
          Renal failure.

Table 5-3. Examples of infections in the immunocompromised host
Host factor
      Sites of infection
            Typical infectious agents
                  Appropriate antimicrobial agents

Neutropenia
      Fever (no obvious cause)
            Gram-negative bacilli, gram-positive cocci
                  Antipseudomonal penicillin or third-generation cephalosporin plus aminoglycoside with or without vancomycin
            Fungi
                  Amphotericin B, fluconazole (depending on sensitivity of isolated organisms)
      Pneumonia, perirectal abscess, bacteremia, meningitis, pharyngitis
            Variety of bacterial, viral, parasitic, and fungal pathogens
                  Based on sensitivity of isolated organisms
Antibody deficiency
      Sinusitis, pneumonia
            S. pneumoniae, H. influenzae
                  Ampicillin, ampicillin-sulbactam, cefuroxime, ceftriaxone, trimethoprim-sulfamethoxazole
Complement deficiency
      Otitis, sinusitis, pneumonia
            S. pneumoniae, H. influenzae, Neisseria species, *S. aureus, E. coli*
                  Based on sensitivities of isolated organism
T-cell deficit (eg, Hodgkin's disease)
      Skin
            Candida
                  Amphotericin B, fluconazole
      Pneumonia
             Variety of bacterial and fungal pathogens
                  Based on sensitivities of isolated organism
      Meningitis
            Cryptococcus
                  Amphotericin B
            Listeria monocytogenes
                  Ampicillin (plus gentamicin), trimethoprim-sulfamethoxazole
Diabetes
      Cellulitis, gangrene, osteomyelitis
            S. aureus, E. coli, other gram-negative bacilli
                  Based on sensitivities of isolated organism
      Sinusitis
            Mucor, Aspergillus
                  Amphotericin B
      Invasive external otitis
            Pseudomonas aeruginosa
                  Aminoglycoside plus antipseudomonal penicillin or ceftazidime.