

Antimicrobials and Resistance

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Abstract

Although infection prevention traditionally has approached the problem of resistance primarily from the aspect of preventing transmission from an infected patient to a noninfected patient, more needs to be done to improve how antimicrobials are commonly used. Antimicrobial use is the main selective pressure responsible for the increasing resistance seen in hospitals. Patients come to possess a resistant pathogen either by transmitting bacteria that already have the resistance gene in place or by having their bacteria acquire a gene that codes for resistance. The former is more common because it merely requires a handshake while the latter takes days to weeks to develop. To have an impact on antimicrobial use so as to reduce resistance, infection preventionists (IPs) need a working knowledge of available antimicrobials, principles for their appropriate use, the mechanisms by which these drugs inhibit microbial growth, and the mechanisms by which microorganisms develop resistance. In addition, IPs need to understand promising new strategies to improve antimicrobial use and how members of the infection prevention community can become more involved.

Key Concepts

- Although infection prevention traditionally has approached the problem of resistance primarily from the aspect of preventing transmission, more needs to be done to control how antimicrobials are commonly used.
- Antimicrobial stewardship is the best investment for preventing the proliferation of multidrug-resistant pathogens and the adverse events associated with the drugs used to treat such pathogens.

- An antibiogram is a useful tool for IPs to determine the status of strategies in place to reduce multidrug-resistant pathogens.
- A multidisciplinary approach involving IPs; the departments of infectious diseases, microbiology, and pharmacy; and others is necessary to confront antimicrobial resistance issues in healthcare settings.

Background

Epidemiological forces responsible for clinically important types of resistance include (1) the selective pressure produced by antimicrobial use and (2) the transmission of resistance between microbes and between or among their human and animal hosts. Although most resistance can be traced to the human behaviors that lie behind these forces, the development and spread of resistance also are greatly affected by certain microbial characteristics, such as the ease by which an organism can develop or acquire resistance traits. Infection prevention, by its very nature, traditionally has been concerned with preventing the transmission of resistant organisms between human hosts in the healthcare setting. This chapter discusses available human antimicrobial agents, how they are used, antimicrobial resistance, and the management of antimicrobial use as a means to control resistance.

This chapter reviews all major antimicrobial categories, with special mention of agents that have been released since the last edition of this book. Characteristics and indications for use, particularly for drugs commonly used among inpatients; the determination and interpretation of antimicrobial susceptibility test results; and various factors influencing successful antimicrobial therapy are reviewed. The chapter also reviews microbial mechanisms responsible for antimicrobial resistance and methods to monitor and improve antimicrobial use.

Basic Principles

CHARACTERISTICS OF ANTIMICROBIAL AGENTS

Definition

An antimicrobial is a substance that inhibits or kills microbes (viruses, bacteria, fungi, parasites), whereas an antibiotic is a type of antimicrobial that is synthesized by a living microorganism, usually a fungus. Many newly marketed agents are chemically modified from products synthesized by a microorganism.

Administration

Most antimicrobials are administered by intravenous (IV) or oral routes. Less common routes of administration include intramuscular, rectal, topical, intrathecal, intraventricular, inhalation, intraperitoneal, surgically implanted antimicrobial devices (e.g., orthopedic hardware, beads, or an absorbable antibacterial envelope), and antimicrobial-coated devices (e.g., endotracheal tubes or urinary catheters).

Mechanisms of Action

All antimicrobials are bactericidal/fungicidal or bacteriostatic/fungistatic based on the amount of pathogens they kill in an inoculum. We think of “-cidal” agents as killing and “-static” agents as arresting growth, but a more accurate understanding is that cidal agents kill >99.9%, while static agents only kill 90–99%¹

. Whether a drug exerts “cidal” versus “static” activity can depend on the concentration to which an organism is exposed, but for most drugs the safely achieved concentrations in the human body are limited

to a narrow enough range that this distinction is determined more by the underlying mechanism by which the drug inhibits microbial growth.

There are several mechanisms by which antimicrobials act on microorganisms (Table 26-1). All β -lactam drugs (e.g., penicillins, cephalosporins, monobactams, and carbapenems); glycopeptides (e.g., vancomycin); and the echinocandins (e.g., micafungin) inhibit cell wall synthesis. Cell membrane inhibitors include daptomycin, colistimethate, and the imidazole antifungal agents, such as fluconazole, which inhibits an enzyme responsible for a crucial component of the cell membrane. Aminoglycosides (e.g., gentamicin and tobramycin), macrolides (e.g., azithromycin), tetracyclines, and the oxazolidinones (e.g., linezolid) all inhibit protein synthesis in the bacterial ribosome. Another mechanism inhibits the production of metabolites essential for cell function (e.g., trimethoprim/sulfamethoxazole and ethambutol). Finally, several drugs including the fluoroquinolones (e.g., ciprofloxacin, levofloxacin, and moxifloxacin), the antifungal flucytosine, and many of the antivirals (e.g., acyclovir) inhibit nucleic acid synthesis.

Table 26-1 Major Cellular Sites of Action by Antimicrobial Classes

Site of Mechanism of Action	Antimicrobial
Cell wall	β -lactam (penicillin) Vancomycin Echinocandin
Cell membrane	Cyclic lipopeptide (daptomycin) Triazole (fluconazole)
Ribosome	Macrolide Aminoglycoside Linezolid Tetracycline
Nucleic acid synthesis	Fluoroquinolones Antiviral (acyclovir) 5-Flucytosine
Metabolic pathway	Trimethoprim-sulfamethoxazole Ethambutol

Pharmacodynamic Factors

The effectiveness of antimicrobials can be optimized by understanding what effect varying the concentration of a drug over time in relation to the minimal inhibitory concentration (MIC) has on eliminating infection from the human body.² The MIC is the lowest concentration of drug that still can inhibit microbial growth. The logical assumption would be that for all drugs you would want to keep the concentration of the drug in the blood above the MIC at all times.

In order to explain why this is not the case for every antimicrobial, the concept of half-life should be understood. Half-life is a term used to quantify how long the body takes to metabolize half of a drug, an antimicrobial in this case. Drugs such as aminoglycosides and fluoroquinolones are said to manifest *concentration-dependent activity*. In the case of these drugs, achieving a higher concentration in the blood over a short time is thought to be more effective at eliminating infection than maintaining a lower concentration over a longer period (Figure 26-1). One characteristic of these drugs is that they usually have a prolonged post antibiotic effect; that is, they continue to suppress microbial growth long after drug concentration has declined. The goal with these drugs is to maximize serum or tissue drug concentrations, which often allows for once-daily dosing.

In contrast, the activity of the β -lactams depends on maintaining drug concentrations in the body above the MIC. Drugs that have such *time-dependent activity* are best dosed with lower doses at an increased frequency over time (Figure 26-2). This understanding has led to drugs such as the natural penicillins and vancomycin being increasingly dosed as a continuous infusion, rather than less frequent dosing, in the management of serious infection. Notice that in Figure 26-1 there is a longer period of time between the end of the half-life and the next dose of the concentration-dependent drug compared to the time-dependent drug in Figure 26-2. Also notice that the concentration curve in Figure 26-1 goes below that MIC level while it stays above that level in Figure 26-2.

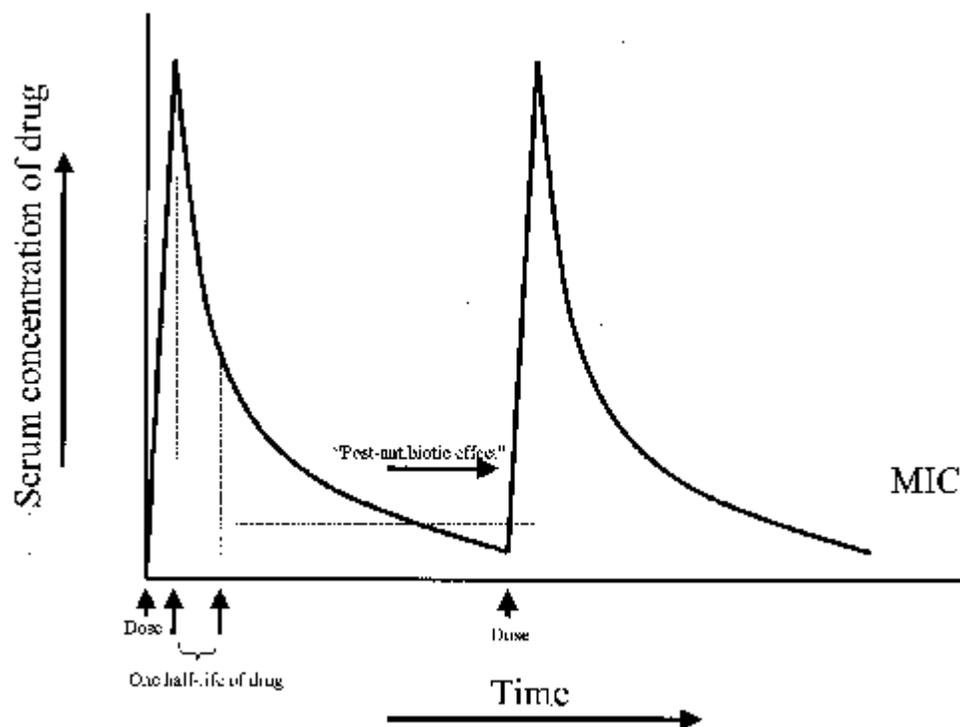


Figure 26-1.

Optimal dosing of antimicrobial drugs possessing concentration-dependent killing action.

[View Image](#)



Figure 26-2.

Optimal dosing of antimicrobial drugs possessing time-dependent killing action.

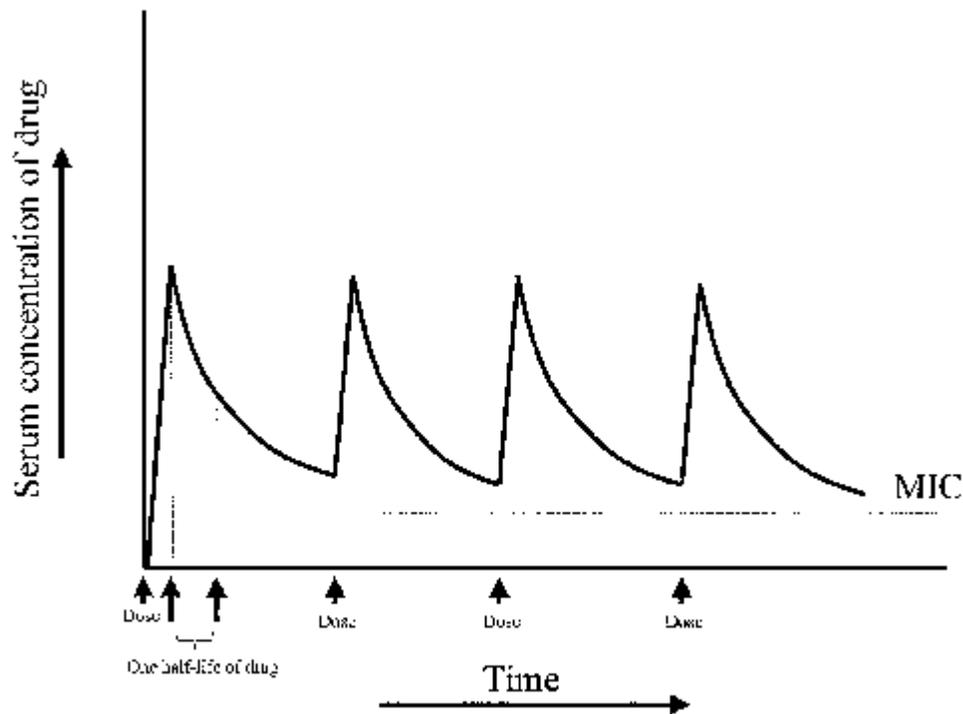
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Side Effects

Two major types of side effects are allergic and gastrointestinal reactions. Allergic reactions, including those manifested by rash, fever, and rare anaphylaxis, are undesirable effects that may occur with

virtually any antimicrobial. Common gastrointestinal disturbances include nausea and vomiting and, because virtually all antimicrobials inhibit microbial growth in the large intestine, diarrhea. Most antibiotic-associated diarrhea is benign and resolves with cessation of the drug, but suppression of the anaerobic bacteria of the colon predisposes to infection with *Clostridium difficile*. Other forms of superinfection resulting from the suppression of normal microbial flora include vaginal candidiasis and oral thrush. Other types of toxicities and their most common manifestations include hepatotoxicity, manifested as elevation of liver enzymes (which is often asymptomatic); myelosuppression, manifested as leukopenia or thrombocytopenia; renal toxicity, manifested as progressive decline in renal function or electrolyte abnormalities; auditory toxicity, manifested as high-frequency hearing loss; vestibular toxicity, manifested as dizziness or vertigo; and central nervous system toxicity, manifested as change in mental status or



seizure. Because they often go unrecognized, drug–drug interactions may be particularly prone to cause serious toxicity.

Classification and Review of Commonly Used Drugs

The major classification of antimicrobials is based on the broad category of microorganisms against which the drugs possess activity; these include antibacterials (Table 26-2), antivirals (Table 26-3), antifungals (Table 26-4),

and antiparasitics.

ANTIBACTERIALS

Penicillins

The first major antibacterials of the antibiotic era were the natural penicillins, which came into widespread use in the 1940s. All penicillins contain a β -lactam ring, which comprises the core structure of not only the natural and semisynthetic penicillins, but also all cephalosporins, monobactams, and carbapenems. All β -lactam drugs possess bactericidal activity by inhibiting cell wall synthesis. The original penicillin, penicillin G, is a natural product synthesized by the mold *Penicillium*, which possesses important activity against spirochetes (such as that which causes syphilis). Natural penicillins also have activity against enterococci, most streptococcal species, and anaerobic bacteria found in the human mouth. Natural penicillin remains the drug of choice for the treatment of group A streptococcal pharyngitis and other infections caused by this pathogen, despite more than 70 years of use.

As a result of penicillin G's lack of activity against Gram-negative bacteria, the aminopenicillins, including ampicillin and amoxicillin, were developed. These drugs possess activity against Gram-negative organisms such as *Escherichia coli* and *Haemophilus influenzae*, while retaining all of the Gram-positive and anaerobic activity of the natural penicillins. In response to the rapid spread of penicillin-resistant staphylococci throughout the United States in the 1950s, penicillinase-resistant penicillins were developed. The first of these, methicillin, was released in 1962 and now has been replaced by nafcillin and oxacillin (IV) and dicloxacillin (oral). To combat the rising incidence of *Pseudomonas* infections in the late 1960s and 1970s, penicillins with antipseudomonal activity were developed, including piperacillin. Then, β -lactamase inhibitors were added to existing penicillins to inhibit bacterial enzymes from lysing the β -lactam chemical ring structure and to broaden the activity of the base penicillin for three groups of pathogens: anaerobic bacteria, methicillin-susceptible but penicillin-resistant *Staphylococcus aureus* (MSSA), and Gram-negative bacteria. Currently used β -lactam/ β -lactamase inhibitor combinations include amoxicillin/clavulanate, ampicillin/sulbactam, and piperacillin/tazobactam.

Table 26-2 Classification of Antivirals and Representative Drugs

Class	Subclass	Representative Drug(s)
Drugs for Herpesviridae	For herpes simplex	Acyclovir
	For cytomegalovirus	Ganciclovir
Drugs for influenza	For influenza A and B	Oseltamivir and zanamivir
Miscellaneous	For respiratory syncytial virus	Ribavirin
Antiretrovirals (drugs for HIV)	Nucleoside reverse transcriptase inhibitors	Emtricitabine
	Nonnucleoside reverse transcriptase inhibitors	Efavirenz
	Protease inhibitor	Atazanavir
	Fusion inhibitor	Enfuvirtide
	Entry inhibitor	Maraviroc
	Integrase inhibitor	Raltegravir

Table 26-3 Classification of Antifungals and Representative Drugs

Class	Subclass	Representative Drug(s)
Polyenes	Nonlipid formulation	Amphotericin B
	Lipid formulations	Amphotec, Abelcet, and Ambisome
Azoles	Triazole	Fluconazole and voriconazole
Other	Echinocandin	Caspofungin
	Nucleoside analogue	Flucytosine

Cephalosporins

Several generations of cephalosporins are available. The first-generation cephalosporins include cefazolin and cephalexin with activity primarily against Gram-positive bacteria, most *E. coli*, a significant amount of *Klebsiella pneumoniae* at most institutions, and most strains of *Proteus mirabilis*. Second-generation drugs include cephalosporins with enhanced activity against *H. influenzae* (e.g., cefotaxime, cefuroxime) and cephalosporins with enhanced anti-anaerobic activity (e.g., cefoxitin). Both categories of second-generation cephalosporins possess increased activity against enteric Gram-negative bacilli and *Neisseria* spp.

Third-generation cephalosporins (e.g., cefotaxime and ceftriaxone) have enhanced activity against Gram-negative bacilli. They achieve high blood concentrations and penetrate into relatively sequestered body sites, such as the central nervous system. Third-generation cephalosporins are important in the treatment of community-acquired meningitis. However, penicillin and cephalosporin resistance among *Streptococcus pneumoniae* is increasing and may limit the usefulness of these drugs as empiric therapy. Cefditoren is an oral agent with increased potency against *S. pneumoniae*, including strains that have only intermediate susceptibility to penicillin. Cefdinir has the benefits of being once daily, having an oral suspension and a similar spectrum of activity compared to other agents in the same class. Although the antipseudomonal third-generation drug ceftazidime is important in the treatment of nosocomial meningitis due to Gram-negative bacilli, its use alone is discouraged because of its association with extended-spectrum β -

lactamases.³ Now it is available combined with the β -lactamase inhibitor avibactam. Another new and similar drug is ceftolozane/tazobactam. Both cover multidrug-resistant Gram-negative bacteria including *Pseudomonas aeruginosa* and those that express extended-spectrum β -lactamases (ESBLs), but not metallo- β -lactamases (e.g., New Delhi type). In addition, ceftazidime/avibactam also covers carbapenem-resistant Enterobacteriaceae that produce carbapenemases, such as *Klebsiella pneumoniae*.⁴

Cefepime, a fourth-generation cephalosporin, has broad-spectrum activity against Gram-negative bacteria, including *Pseudomonas* spp., and Gram-positive bacteria. It is recommended by the Infectious Diseases Society of America for use in patients with neutropenia. However, cefepime covers neither methicillin-resistant *Staphylococcus aureus* (MRSA) nor the anaerobic bacteria responsible for many lung, abdominal, and soft tissue infections. Ceftaroline, the fifth-generation cephalosporin, has activity against MRSA and penicillin-resistant *S. pneumoniae*, *P. aeruginosa*, and enterococci. It is intended for use in community-acquired pneumonia and skin and soft tissue infections. Both cefepime and ceftaroline are IV antimicrobials.

Miscellaneous β -Lactams

There are two additional classes of β -lactam drugs: monobactams and carbapenems. Aztreonam is the only available monobactam and is unique among the β -lactam drugs in possessing a spectrum of antimicrobial activity limited only to aerobic, Gram-negative bacilli, including *P. aeruginosa*. It also is unique in that there is no allergic cross-reactivity between it and other β -lactam drugs, meaning that patients with a history of even serious reactions to penicillins or cephalosporins may be given aztreonam safely. The carbapenems imipenem, meropenem, and doripenem are broad-spectrum agents with significant activity against a wide range of Gram-negative bacilli, including *Pseudomonas*, and are potent drugs in the treatment of serious infections involving anaerobic bacteria (e.g., intra-abdominal infections with sepsis). They possess activity against streptococci and staphylococci except for MRSA. Ertapenem has a spectrum of activity similar to that of other carbapenems except that it does not cover resistant Gram-negative bacilli, such as *P. aeruginosa* or *Acinetobacter* spp.

Fluoroquinolones

Ciprofloxacin was the first highly potent fluoroquinolone; it still is used widely for the treatment of infections caused primarily by Gram-negative bacilli, including *P. aeruginosa*. Fluoroquinolones possess bactericidal activity by inhibiting the bacteria's DNA gyrase enzyme responsible for unwinding the chromosome during replication and cell division. Most of the available fluoroquinolones are limited in their activity against staphylococci and anaerobes, and ciprofloxacin has limited activity against streptococci. Levofloxacin and moxifloxacin were developed primarily for increased activity against *S. pneumoniae* for their use in the treatment of community-acquired pneumonia. They also have important coverage against atypical pathogens such as legionella, a pathogen that may be acquired from a water source in or out of a hospital. In addition, levofloxacin covers *P. aeruginosa* (although resistance is increasing), whereas moxifloxacin covers anaerobic bacteria.

Macrolides, Lincosamides, and Streptogramins

Azithromycin and clarithromycin have activity against Gram-positive bacteria and the atypical bacteria that cause pneumonia, such as *Legionella*, *Mycoplasma*, and *Chlamydia* spp. The macrolides and the closely related lincosamides and streptogramins (dalfopristin/quinupristin) inhibit 50S protein synthesis in the bacteria's ribosome. Because they are bacteriostatic and possess a limited spectrum of activity, macrolides are used most commonly to treat less serious community-acquired infections. In addition to the treatment of upper and lower respiratory tract infections, macrolides (excluding erythromycin) have unique indications

for the treatment of *Helicobacter pylori*-induced gastric and duodenal ulcers and infections due to nontuberculous mycobacteria.

Clindamycin is the principal lincosamide currently in use in the United States. Because clindamycin possesses activity against aerobic Gram-positive bacteria and anaerobic Gram-positive and Gram-negative bacteria, it historically has been used in the treatment of aspiration pneumonia and intra-abdominal infections. Its use has increased since the epidemic of community-associated MRSA strains, which commonly cause skin and soft tissue infections. Due to the possibility of treatment failures related to clindamycin-inducible resistance in some staphylococcal strains, a D-test should be performed on staphylococcal isolates to ensure that the drug will be effective.

Aminoglycosides

Aminoglycosides, such as gentamicin, tobramycin, and amikacin, have long been used in combination with other drugs against difficult-to-treat, Gram-positive, and Gram-negative infections. Although they act at the site of the bacterial ribosome, aminoglycosides are bactericidal against most aerobic Gram-negative bacteria. Because of the risk of serious renal toxicity and ototoxicity associated with their use and the fact that they do not have good levels of activity at some sites of infection, use of aminoglycosides now is limited at many centers to only serious or multidrug-resistant, Gram-negative infections. In addition, either gentamicin or another aminoglycoside, streptomycin, used in conjunction with penicillins or vancomycin is needed to achieve cure in the treatment of endocarditis due to susceptible *Enterococcus* spp.

Miscellaneous Agents

Vancomycin is a glycopeptide that inhibits cell wall and cell membrane synthesis and is bactericidal against *Streptococcus*, *Enterococcus*, and *Staphylococcus* spp. It has been a commonly used antimicrobial in U.S. hospitals for MRSA infections for decades but is being used less as newer drugs for enterococci and *S. aureus* are available. Resistance emerged in the late 1980s among enterococci and in the late 1990s among *S. aureus*. The new MICs for vancomycin against *S. aureus* are sensitive ≤ 2 , glycopeptide-intermediate *S. aureus* (GISA) 4 to 8, and vancomycin-resistant *S. aureus* (VRSA) ≥ 16 .

Daptomycin, a lipopeptide, disrupts the cell membrane and has activity against Gram-positive cocci similar to vancomycin. It has favorable activity in the treatment of skin and soft tissue infections and right-sided endocarditis. However, daptomycin is not reliable for the treatment of primary pneumonia. Studies are in progress for high-dose use.

There are three new lipoglycopeptides: telavancin, dalbavancin, and oritavancin. They are essentially vancomycin with a hydrophobic side chain. They inhibit cell wall synthesis as well as cell membrane function. They have a limited number of drug interactions, but telavancin has a propensity to prolong the QTc interval. They are all indicated for skin and soft tissue infections, whereas telavancin is also indicated for hospital-acquired pneumonia due to MSSA, MRSA, and GISA.

A new class of compounds, the oxazolidinones, was developed mainly to address the growing concern over emerging vancomycin resistance. Linezolid and tedizolid inhibit protein synthesis and are considered bacteriostatic against Gram-positive organisms. They are indicated principally in the treatment of infections caused by vancomycin-resistant enterococci and MRSA. They have nearly 100% bioavailability; therefore they may be given orally. Monitoring for thrombocytopenia should occur with long treatment durations (>2 weeks), and caution should be advised if a patient is taking a monoamine oxidase inhibitor or selective serotonin reuptake inhibitor to avoid precipitating the serotonin syndrome.

Polymyxin is a class of antibiotic that was used in the 1960s and 1970s for Gram-negative infections, especially pneumonia, but was abandoned because of its association with renal toxicity. The two forms

available are colistin sulfate and colistimethate sodium. Physicians are using polymyxin again because of the emergence of multidrug-resistant Gram-negative infections, such as *P. aeruginosa* and *A. baumannii*, which are resistant to all other available agents, including carbapenems and aminoglycosides.

Trimethoprim/sulfamethoxazole is a synergistic combination of drugs that together exhibit a bactericidal effect by inhibiting bacterial folate synthesis, an important metabolic pathway. Current clinical use includes the treatment of *Pneumocystis jirovecii* pneumonia (PCP), infections due to *Nocardia* spp., and infections involving *Stenotrophomonas maltophilia*, a multidrug-resistant, Gram-negative nosocomial pathogen. In addition, this drug may be used in its oral form to treat the epidemic of unique strains of MRSA that cause community-acquired skin and soft tissue infections, but caution should be used because the drug has been associated with acute kidney disease.⁵

Rifampin, a rifampicin, is likely familiar to the IP because it is used as prophylaxis in significant exposures to patients with meningitis due to *Neisseria meningitidis*. Rifampin also has activity against most MRSA. However, when used alone, resistance often develops quickly due to point mutations in the gene encoding the bacterial RNA polymerase, where rifampicins exert their effect on bacterial growth and survival. Rifampin typically is used as adjunctive therapy for MRSA infection in a patient with an infected prosthetic device or mechanical valve. Rifampin and rifabutin are used in combination with other agents in the treatment of latent or active disease due to *M. tuberculosis*. Rifaximin is used in the treatment of *C. difficile* colitis.

Metronidazole is the only nitroimidazole currently in use in the United States. It is virtually unsurpassed for its activity in treating anaerobic infection. Because the active drug precursor requires conversion into its active form by an enzyme found only in anaerobic bacteria, metronidazole has no activity against aerobic bacteria. It usually is used as part of combination therapy to treat bacterial infection. Exceptions include the treatment of colitis due to *C. difficile*. Additional, unique indications for metronidazole include parasitic infections, such as vaginitis caused by *Trichomonas vaginalis* or intestinal infections due to *Entamoeba histolytica* or *Giardia lamblia*.

No discussion of antibacterials would be complete without mention of topical and orally nonabsorbable antimicrobials used for treating superficial infections as prophylaxis against infection under certain circumstances, and for eradicating colonization. A wide variety of drugs have been used for this purpose, including bacitracin, neomycin, polymyxin B, mupirocin, and fusidic acid. Among these agents, mupirocin is of special interest to IPs. This agent, when applied topically to the anterior nares, is part of a regimen for decolonization with MRSA. That process is described in **93. Staphylococci**.

ANTIVIRALS

Antivirals are available for many common and life-threatening viruses. Acyclovir was the first widely used antiviral drug, owing to its infrequent toxicity and activity against a common family of human viruses, the *Herpesviridae*. Although acyclovir is available in an oral form, it is poorly absorbed; the derivatives of acyclovir, valaciclovir and famciclovir, overcome this problem and for most indications are the preferred oral agents. All of these agents are active against herpes simplex viruses (type I and II). Most patients infected with herpesviruses are managed as outpatients; however, severe infections in immunocompromised patients and encephalitis require inpatient treatment with IV acyclovir therapy.

Although acyclovir and related agents are less active against varicella-zoster virus, they retain meaningful activity against this virus, which is responsible for chickenpox as a manifestation of primary infection and shingles, or herpes zoster, as a manifestation of secondary or recurrent infection. Most cases of chickenpox in immunocompetent individuals do not require inpatient therapy; however, treatment of

patients with herpes zoster using acyclovir or one of its derivatives may reduce the commonly seen complication of postherpetic neuralgia.

Acyclovir and related drugs possess some activity against the cause of infectious mononucleosis, Epstein-Barr virus, but this infection does not routinely require antiviral therapy in immunocompetent patients. In contrast, cytomegalovirus (CMV) commonly infects immunocompromised patients, but acyclovir and its derivatives have little or no activity against it because it relies on a viral-produced enzyme, thymidine kinase, which CMV does not have. Ganciclovir and valganciclovir are the first-line drugs used to treat most CMV infections. IV ganciclovir is the drug of choice for serious life-threatening pneumonitis in solid organ and bone marrow transplants. Ganciclovir and valganciclovir are associated with significant bone marrow toxicity. In patients who cannot tolerate or fail to have a response to ganciclovir, foscarnet may be used as second-line therapy to treat serious CMV infections.

Other antivirals include cidofovir with activity against herpesviruses 6 and 8, Epstein-Barr virus, and a variety of other DNA viruses, including papillomavirus, polyomavirus, poxvirus, and adenovirus. Anti-influenza drugs include amantadine and rimantadine (tricyclic amines) for influenza A and zanamivir (inhaled), oseltamivir (oral), and peramivir (IV) (neuraminidase inhibitors) for influenza A and B. Ribavirin covers a wide range of RNA and DNA viruses and is used in transplant patients with severe respiratory syncytial virus. Interferons stimulate the patient's own immune system to control and in some cases clear hepatitis B, hepatitis C, herpesvirus, and papillomavirus. The major categories of antivirals for hepatitis C include replication protein inhibitors, RNA polymerase inhibitors, protease inhibitors, and interferons.

Antiretrovirals revolutionized the care of patients infected with HIV with the advent of antiretroviral therapy (ART). ART consists of combinations of various drugs that act in combination to suppress viral replication effectively; the therapy has improved survival markedly. Although the focus of ART is long-term therapy among outpatients, these drugs are now commonly used for postexposure prophylaxis of healthcare workers exposed to HIV, and outpatients with high-risk behavior for acquiring HIV. The major categories of antiretrovirals include the entry inhibitor, the fusion inhibitor, nucleoside or nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors. Treatment requires specific combinations of these drugs.

ANTIFUNGALS

The availability of highly active imidazoles, such as fluconazole and itraconazole, has had a major impact on the treatment of some human fungal infections, such as candidemia. Fungal sensitivities are now available to ensure treatment is appropriate and to alert the IP when a resistant strain is increasing in the hospital. Attention should be given when instructing patients to take imidazoles because absorption is better during certain times. The newer triazoles, voriconazole and posaconazole, are used for invasive aspergillosis and disseminated candidiasis, and voriconazole has a unique indication for serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium*. The newest triazole, isavuconazole, is indicated for invasive aspergillosis and also invasive mucormycosis. The echinocandins are a class of compounds that inhibit the synthesis of glucan, an essential component of the fungal cell wall. Among the echinocandins, micafungin and caspofungin are indicated for refractory aspergillosis, candidiasis, and some invasive candidal infections.

Amphotericin B deoxycholate, a suspension of a polyene compound that weakens the fungal cell membrane through interaction with ergosterol, has been replaced by the antifungals already discussed because they are efficacious without the renal and hepatic side effects. The decrease in side effects is significant, even in comparison with the lipid formulations of amphotericin B (Amphotec, Abelcet, and AmBisome). Should they need to be used, they are still effective against cryptococcosis, histoplasmosis,

invasive aspergillosis, and other serious infections caused by yeasts or molds, with the exception of *S. apiospermum*. Of note, *C. lusitaniae* has intrinsic resistance to amphotericin B. Flucytosine (5-FC) is a nucleoside analogue that is additive with amphotericin in the treatment of infections due to *Candida* spp. and *Cryptococcus neoformans*.

ANTIPARASITICS

Although parasitic infections constitute many of the most common infections in the world, they occur relatively infrequently in the United States. Drugs such as chloroquine, primaquine, quinine, mefloquine, and doxycycline are used for the treatment or prophylaxis of malaria, a protozoan infection associated with significant morbidity and mortality in endemic regions. Schistosomiasis, caused by a platyhelminth, is treated with praziquantel. The treatment of nematodes (roundworms) includes ivermectin and albendazole. Some antiparasitics are only available in the U.S. from the CDC.

Indications for Antimicrobial Use

PROPHYLAXIS

Appropriate reasons for antimicrobial use are categorized as pathogen directed, empirical, or prophylactic. Antimicrobial use that is designed to prevent infection rather than treat known or suspected infection is deemed prophylactic. Surgical antimicrobial prophylaxis is the most common type of prophylaxis and it is indicated for surgical procedures in which the risk of wound infection is high enough to show significant benefit of prophylaxis.⁶ This is exemplified best in operations involving placement of a prosthetic device, in which an infection would be a major cause of morbidity or mortality (e.g., prosthetic heart valve placement), and operations in patients with severe immunosuppression.

Basic principles of antimicrobial prophylaxis in surgery should be recognized. The antimicrobial spectrum of the drug chosen should be appropriate for the organisms most likely to cause infection. These are most commonly *Staphylococcus* spp. or *Streptococcus* spp., even in abdominal surgeries, in which other organisms predominate in the bowel flora. Adequate tissue levels of the antimicrobial, usually a first-generation cephalosporin, should be present throughout the operative procedure from the time of first incision onward. The duration of prophylactic antimicrobial use should be as short as necessary to minimize the emergence of resistant organisms, reduce the incidence of side effects, and reduce cost; this translates in most cases to a single preoperative dose and occasionally an additional dose or two if surgery duration is prolonged. In general, any time the skin or mucosa is incised, prophylaxis should be considered, whether the wound is clean, clean-contaminated, contaminated, or dirty. Surgical prophylaxis is given to patients who meet certain criteria established by relevant association (the American Association of Anesthesiologists, the American Heart Association). Other unique medical conditions requiring antimicrobial prophylaxis include the prevention of endocarditis in patients with high-risk valvular lesions, spontaneous bacterial peritonitis in patients with ascites, and malaria in patients traveling to endemic areas. Certain types of prophylaxis are given immediately after exposure to a high-risk pathogen that causes disease, such as meningococcal meningitis or HIV.

EMPIRICAL THERAPY

When no definitive information about a causative pathogen is available (although Gram stain can be highly suggestive), therapy is said to be empirical. Typically, hospitalized patients are sufficiently ill to warrant treatment before culture and sensitivity results are available, and therapy while the results of cultures are pending may represent most empirical therapy. Especially in hospitalized patients, appropriate cultures,

usually including more than one blood culture, should be collected before the initiation of therapy. The site of infection determined clinically (e.g., lung, urinary tract) and host factors (e.g., HIV, organ transplant patient) give an indication of likely pathogens and should shape the decision regarding empirical therapy. Empirical therapy, compared with pathogen-directed therapy, is broader in spectrum due to uncertainty about the causative agent.

PATHOGEN-DIRECTED THERAPY

Pathogen-directed therapy describes antimicrobial use when the microbial pathogen has been determined based on the results of traditional culture, serology, or other methods, such as polymerase chain reactions (PCR), to detect distinct nucleic acids of the microbial pathogen.⁷ If a culture has been used to recover the offending microbe and that microbe is a bacterium or yeast, antimicrobial susceptibility results may be made available. In pathogen-directed therapy, the use of the narrowest spectrum antimicrobial is believed to reduce the emergence of antimicrobial resistance and superinfection. Minimizing the cost of therapy also is important whenever equivalent alternatives are available.

Although therapy based on a positive nucleic acid amplification (e.g., PCR) test or other nonculture diagnostic test is considered pathogen directed, susceptibility results are not available to tailor therapy. To overcome this problem, a culture sometimes is performed in tandem to confirm the nonculture diagnostic test result and provide an organism for future susceptibility testing. Whenever a nucleic acid amplification test is performed on a sputum sample for tuberculosis, a smear and culture also should be performed for confirmation and susceptibility testing. However, the nucleic acid amplification test result may be able to provide a much more rapid answer as to whether the patient likely has tuberculosis, rather than waiting the full four to six weeks for *Mycobacterium tuberculosis* culture results.

In other instances, the nonculture result directs therapy against a pathogen with a predictable susceptibility pattern. A nucleic acid amplification test result that is positive in the case of a sexually transmitted disease caused by gonorrhea or *Chlamydia* routinely triggers therapy that has been recommended by consensus public health guidelines, but these sexually transmitted diseases, as well as *C. difficile* colitis, PCP, and other infections, are treated immediately on the basis of a consistent clinical picture.

Figure 26-3.

ICU PATIENTS

Includes isolates obtained from: LDR, 3S, 5E, 5S, 6S, 7E, 7S, 8E, 9E, and 9S patients

	Total # Isolates	Ampicillin	Ampicillin/Subactam	Amoxicillin/Clavulanate	Nafcillin	Penicillin	Piperacillin/Tazo	Cefazolin	Ceftiozone	Cefepime	Meropenem	Aztreonam	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Clindamycin	Nitrofurantoin	Tetracycline	Trimeth/Sulfa	Vancomycin	Daptomycin	Linezolid	Azithromycin	Erythromycin
Gram Negative	<i>E. coli</i>	88	47	50			93	79	92	96	100	91	91	93	100	72	73			75	73					
	<i>E. coli (urine only)</i>	69		74															99							
	<i>Klebsiella pneumoniae</i>	30		70			93	93	100	97	100	100	100	100	100	97	100			55	80	97				
	<i>Pseudomonas aeruginosa (2013-14)</i>	48					79			77	83	45	79	92	94	69	67		0							
Gram Positive	<i>Enterococcus faecalis</i>	53	100										76 ¹									98	100	98		
	<i>Staphylococcus aureus</i>																									
	Methicillin Sensitive (MSSA)	37			100		100											70 ²		100	100	100	97	100		
	Methicillin Resistant (MRSA)	36			0		0											64 ²		89	97	100	100	100		

1. High level Gentamicin testing. Susceptibility indicates synergy with an active cell wall agent.
 2. Clindamycin susceptibility indicates confirmatory D-test results

Sample of an antibiogram for patients from ICU locations within the University of Louisville

Strategies to Predict and Improve Patient Outcome

[View Image](#)

FACTORS THAT AFFECT OUTCOME

Five major factors contribute to successful antimicrobial therapy: (1) prompt institution of an appropriate antimicrobial; (2) the “bug” factor, related to the virulence and susceptibility of the infecting organism; (3) the “drug” factor, related to the activity of the antimicrobial at a particular site of infection; (4) the “host” factor, related to the underlying condition and immunocompetence of the patient; and (5) the “site” factor, related to the fact that infections at certain body sites (e.g., meninges, heart valves) are inherently more difficult to treat for a variety of reasons.⁸ Although one usually can have an impact only on the first factor, an awareness of each of the remaining four is essential for choosing the most appropriate antimicrobial. Selection of an antimicrobial agent that is highly active according to in vitro susceptibility test results is crucial; however, under some circumstances, this intervention alone is of limited value. In the management of infected prosthetic material, the removal of the prosthesis rather than the result of in vitro susceptibility testing would be most predictive of patient outcome. Likewise, the outcome of a patient with an abscess or intra-abdominal infection in most cases is affected much more by surgery or percutaneous drainage than by antimicrobial therapy.

In addition to choosing the most appropriate antimicrobial, the most appropriate dose and route of administration must be selected to improve outcome. The dose must be high enough to be therapeutic (i.e., sufficient to inhibit or kill the organism at the site of infection) but low enough to minimize toxicity. In certain circumstances, host factors require modification of the dose. The presence of renal failure requires a dose reduction of antimicrobials excreted primarily by the kidney (e.g., aminoglycosides, fluoroquinolones, trimethoprim, tetracycline, vancomycin, and all β -lactams except nafcillin and ceftriaxone). Likewise, hepatic insufficiency requires a dose reduction of antimicrobials excreted primarily by the liver (e.g., chloramphenicol, clindamycin, doxycycline, macrolides, metronidazole, rifampin, sulfamethoxazole, ceftriaxone, nafcillin). The site of infection also may influence administration of the antibiotic. In central nervous system infections, the antimicrobial dose frequently needs to be increased for a successful outcome, whereas in urinary tract infections, lower antimicrobial doses are appropriate.

The initial administration of antimicrobials to hospitalized patients is usually via the IV route so that therapeutic levels can be achieved quickly and reliably. IV administration in most cases also results in higher blood levels than can be achieved via the oral route. The exception is for drugs that are exceptionally well absorbed by the gastrointestinal tract, such as fluconazole, the fluoroquinolones, linezolid, and metronidazole. However, even in the case of drugs that are not as well absorbed, sufficient levels usually can be achieved via oral administration so that infected hospitalized patients can be switched rapidly from IV to oral antimicrobials after an initial response to therapy. This is termed *switch therapy* and has been studied most widely as a means to reduce length of hospitalization and overall healthcare costs for patients with community-acquired pneumonia.⁹

Antimicrobials interact in a variety of ways when coadministered. Some antimicrobials directly inactivate others; for example, piperacillin/tazobactam and aminoglycosides inactivate each other when added to the same IV bottle. Antagonism, which is distinct from inactivation, describes the condition of two coadministered antimicrobials that become less effective than either one administered alone. Tetracycline, a bacteriostatic drug, may interfere with the action of penicillin, a bactericidal and cell wall synthesis inhibitor, by preventing cell growth and division. *Synergy* describes the condition when two coadministered antimicrobials are more effective than what the simple addition of the two agents would predict. In the treatment of endocarditis due to *Enterococcus* spp., in which bactericidal activity is necessary to achieve

cure, this can be provided by the synergistic combination of a protein inhibitory agent, such as an aminoglycoside, with a cell wall active agent, such as penicillin or vancomycin.

DESCRIPTION OF ANTIBIOGRAM

Although the responsibility of publishing an antibiogram traditionally has been assumed by the clinical laboratory, periodic preparation and dissemination of institutional resistance patterns provide infection prevention personnel insights into what antimicrobial classes are most used and potentially misused. IPs should be involved in the preparation of the antibiogram and aware that there are guidelines regarding this issue available from the Clinical and Laboratory Standards Institute (CLSI).¹⁰

An antibiogram simplifies multiple patients' antimicrobial sensitivity information at an institution into a single number for pathogens of interest in an effort to monitor trends emerging in drug resistance. Antibiograms help answer questions in two main areas: clinical care (What antimicrobial would be best to use in this hospital for this pathogen?), and infection prevention strategies (Has the resistance of this pathogen to this antimicrobial changed in this hospital to warrant augmenting or diminishing our infection prevention interventions?). With resistance increasing, limited resources, and clinical questions pending, antibiograms are a useful tool in medicine.

The technical details of generating an antibiogram are contained in the CLSI document M39-A4, whereas the following is a brief, pertinent summary for the IP.^{10,11} An antibiogram report should be presented at least annually. Some hospitals will have the technology to generate antibiograms as frequently as they want. Data should be analyzed when at least 30 isolates are tested for a given pathogen, and only the first isolate should be included from patients with multiple positive cultures, regardless of the body fluid tested or the antimicrobial susceptibility pattern. Incidentally, because an antibiogram considers only the first isolate, from a patient who may have had several positive cultures, IPs should know that the microbiology laboratory is the place to inquire about the number of any multidrug-resistant isolates of interest. At least 30 diagnostic, not surveillance, isolates of a species should be included in an analysis to provide a meaningful number, and only then for drugs that are routinely tested. Antibiograms should report the proportion of susceptible isolates, not isolates with intermediate susceptibility. However, penicillin-intermediate susceptibility is of interest for *S. pneumoniae*. For *S. pneumoniae*, the proportion susceptible to cefotaxime or ceftriaxone using both the meningitis and nonmeningitis breakpoints should also be included. When calculating the proportion of susceptibility for *S. aureus*, include the subset for MRSA.

An antibiogram should include a table with pathogens with the total number of isolates listed against antimicrobials (Figure 26-3). The figure reveals, for example, that there were 48 isolates of *S. pneumoniae* with 81% sensitive to tetracycline. The value for penicillin and *S. pneumoniae* has two values, one each for the meningitis and nonmeningitis breakpoints. The 2009 CLSI document M39-A3 emphasizes that an antibiogram may be generated for specific units in an institution; note that Figure 26-3 is only for patients outside of the intensive care unit (ICU). It also highlights that antibiograms could underestimate the activities of drugs for multidrug-resistant strains in specific units. For example, if *Klebsiella* strains are analyzed together, the activities of drugs against non-*Klebsiella pneumoniae* carbapenemase producers will be underestimated.

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Antimicrobial Resistance

Antimicrobial resistance is an important global public health problem that is particularly acute among hospitalized patients._The detrimental impact of antimicrobial resistance on the treatment outcome of healthcare-associated infections (HAIs) has been increasingly documented, not only in terms of increased morbidity, but also as a contribution to increased mortality. In addition, resistance contributes significantly to increased healthcare costs. The excess U.S. healthcare costs attributed to just six common forms of resistance in nosocomial pathogens has been estimated to exceed \$13.3 million.¹²

Antimicrobial Susceptibility Testing

In vitro (laboratory) susceptibility testing provides important predictive information of whether an infection is likely to respond to a particular antimicrobial in vivo (patient). The most commonly used test method includes the microtiter broth dilution systems using trays of small-volume wells consisting of various

concentrations of antibiotic read via an automated, commercial instrument.¹³ Other test methods include agar disk diffusion (Kirby-Bauer) and the antimicrobial gradient diffusion method (E-test or D-test) in which a reagent strip consisting of a gradient of antimicrobial is placed on an agar plate to produce a gradient of concentrations in the medium.

Each of the above-mentioned test methods is performed and interpreted using standardized criteria according to published recommendations of the CLSI.¹⁴ Although disk diffusion test results are expressed qualitatively, broth, agar, and E-test results may be expressed quantitatively as an MIC. Although these systems consist of a broth dilution test, manufacturers commonly limit the number of concentrations tested to only breakpoint concentrations that separate susceptibility categories. For example, breakpoint concentrations for ciprofloxacin tested against *E. coli* would be 1 µg/mL (a low concentration of the drug at which there *is inhibition of growth, and thus the E. coli* is considered susceptible); and a breakpoint of 4 µg/mL (a high concentration of the drug at which there is *growth, and thus the E. coli* is considered resistant). If growth is present at 1 µg/mL but inhibited at 4 µg/mL, the ciprofloxacin is considered intermediate.

Clinical laboratories typically report results using the recommended qualitative result categories of susceptible, intermediate-susceptible, and resistant based on the breakpoints set by CLSI. *Susceptible* means that the drug is likely to be effective for the treatment of infection using a standard dosage. *Intermediate-susceptible* means that the drug is likely to be effective only at body sites where it is physiologically concentrated (e.g., the urine for most drugs) or at other body sites if higher-than-usual dosing regimens are used. *Resistant* means that the drug is unlikely to be effective for the treatment of infection, unless predictably toxic dosages are used. Laboratories should consider not including MIC or breakpoint concentrations without interpretation provided because they may be misinterpreted.

MECHANISMS

Major mechanisms of antimicrobial resistance include drug inactivation and alteration in target site, decreased permeability or efflux, and bypass of a metabolic pathway (Figure 26-4). Drug inactivation occurs when a bacterium produces an enzyme that can destroy or inactivate the antimicrobial; bacteria may produce β-lactamase enzymes that destroy penicillins and cephalosporins. Alternatively, drug receptor or target sites may undergo alteration, as observed in MRSA when the penicillin-binding protein (PBP) is altered to PBP2a, coded for by the better-known *mecA* gene. Changes in drug permeability or an efflux of drug may be observed, as in the case of *P. aeruginosa* that has developed resistance to the carbapenems. Finally, bacteria may develop alternative metabolic pathways to bypass the pathway that was inhibited by the antimicrobial; resistance to trimethoprim/sulfamethoxazole commonly occurs in this manner.

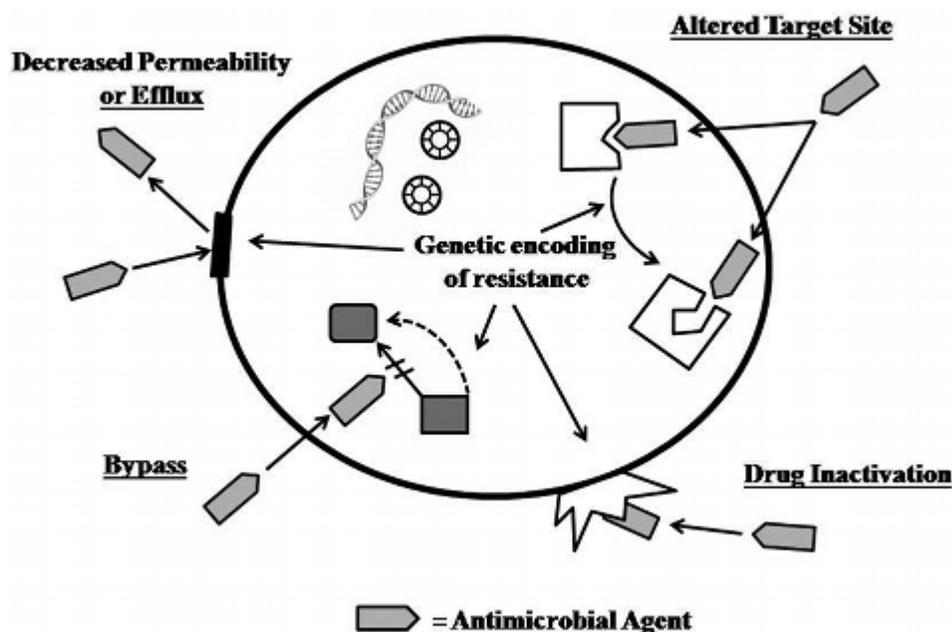
Figure 26-4.

Major cellular mechanisms of antimicrobial resistance.

[View Image](#)



Resistance develops in microorganisms as a result of either point mutations in existing genes or the acquisition of new genes. Point mutations are random errors that occur during DNA replication, resulting in the substitution of one base pair for another, which may result in the substitution of one amino acid for another in a protein structure or enzyme. These mutations occur infrequently at the correct locations of the bacterial genome necessary to cause resistance (10^7 to 10^{12} per generation); when point mutations are responsible for resistance, it usually is because they have a slight structural change in a drug receptor or target site. However, because most forms of antimicrobial resistance require complex structural or enzymatic changes, most forms of resistance result from newly acquired genes.



TRANSMISSION

Point mutations that result in resistance usually occur in the chromosome of the microorganism and are passed on only to daughter cells via cell division; however, mobile genetic elements also exist that can promote the transmission of genes between strains. These include plasmids and transposons; together these mobile genetic elements or “jumping genes” are known as *resistance factors* (R factors). Plasmids consist of a circular segment of extrachromosomal DNA that

can replicate itself. A *transposon* is a segment of DNA that can insert itself in the chromosome and be transmitted between cells via a plasmid or even a virus. Resistance that is carried on R factors is potentially more serious than resistance caused by point mutations in the chromosome because resistance can be spread to different strains or even different species of microorganisms. R factors commonly contain multiple genes conferring resistance to several antimicrobials, whereas point mutations generally confer resistance to only one class of antimicrobial.

Certain resistance genes acquired by a microorganism via an R factor may become stably inserted into its chromosome and, similar to a chromosomal point mutation, be passed on only to daughter cells via cell division. The transmission of such chromosomal resistance may be distinguished epidemiologically from the transmission of R factors in the hospital. Chromosomal resistance is spread among patients as a single strain or clone, and in this sense the resistance is said to be “clonal,” whereas R factor resistance usually involves multiple strains or clones (plural) and is said to be “polyclonal.” Distinguishing a clonal from polyclonal outbreak of resistance in a single species often requires molecular characterization of isolates from several patients. A description of the molecular techniques to perform such characterization in the laboratory is outside the scope of this chapter. See [93. Staphylococci](#).

EXAMPLES

Antimicrobial resistance has been documented in hospitals since the advent of penicillin and the discovery of penicillinase-producing *S. aureus* in the 1940s. MRSA first were detected in the early 1960s, shortly after the introduction of methicillin, and aminoglycoside resistance among Gram-negative bacilli first was noted in the 1970s. During the 1970s and 1980s, MRSA spread widely so that vancomycin had to be used increasingly to treat these infections. This set the stage for the development and spread of vancomycin-resistant enterococci (VRE), first in Europe in the late 1980s and then in the United States by the early 1990s. A large study reported that nearly one in five adults hospitalized with a MRSA infection die.¹⁵

The 1990s saw the spread of fluconazole resistance increased among *Candida* spp. (e.g., *C. krusei*, *C. glabrata*, and occasionally *C. albicans*). During this same time, identification of expanded-spectrum β -lactamases (ESBLs) increased in some hospitals. ESBLs are β -lactamases found in common Gram-negative bacteria, such as *E. coli* and *K. pneumoniae*, which confer resistance to all β -lactam drugs

except the carbapenems. The most recent form of antimicrobial resistance that has caused concern are the β -lactamases associated with carbapenem-resistant Enterobacteriaceae (CRE). The media has publicized CRE as a “superbug.” CRE is the group of Gram-negative pathogens that are resistant to most antimicrobials, including carbapenems that have been useful for multidrug-resistant pathogens until now. The resistant enzyme may be encoded within a bacteria’s own DNA chromosome affecting a whole species, or acquired on a transposon or plasmid affecting a strain of a species. One of the worst outbreaks was with a plasmid mediated *Klebsiella pneumoniae* carbapenemase at the NIH medical facility in Maryland where 11 of 18 patients died. From an infection prevention perspective, patients with ESBL or carbapenemase multidrug-resistant organisms are typically placed in contact isolation.¹⁶

The late 1990s raised concern for vancomycin resistance in MRSA. In 1996, glycopeptide-intermediate *S. aureus* (GISA) first was reported from Japan¹⁷ and then the United States¹⁸ where vancomycin-resistant *S. aureus* (VRSA) was described in 2002.¹⁹ VRSA resulted from the new acquisition of resistance genes from VRE. Unfortunately, resistance has been reported with linezolid and daptomycin use. Antimicrobial stewardship is critical to preventing antimicrobial prescribing habits that provide an environment conducive to such a resistant pathogen.

Antimicrobial Stewardship

Strategies other than simply new drug development must be stressed to curb antimicrobial resistance. Healthcare institutions provide care to patients at increased risk of infection who, because they are exposed to antimicrobial selective pressure, are also at risk of colonization or infection by antimicrobial-resistant pathogens. These patients are in close proximity to one another so that resistance is transmitted easily. Just as there has long been understanding of the role of infection prevention in preventing transmission of antimicrobial resistance, there is an increasing awareness of the need to manage antimicrobial use in hospitals more carefully. Antimicrobial stewardship programs are important components of antimicrobial-resistance management in healthcare institutions. The Infectious Diseases Society of America (IDSA) has multiple relevant guidelines for this purpose available at <http://www.idsociety.org>. (See Supplemental Resources, Dellit, Owens, McGowan, et al.) Furthermore, The Joint Commission announced that effective January 1, 2017, a new standard was being set for hospitals and nursing care centers.²⁰

SURVEILLANCE

The surveillance of antimicrobial resistance is an essential first step to identify priority areas for managing antimicrobial use from an infection prevention perspective versus a pharmacy or cost-containment perspective. In addition to tracking the proportion of isolates that are resistant (i.e., antibiogram), IPs should consider tracking the number of patients who are found on routine cultures to be newly colonized or infected with problem areas of resistance, such as MRSA, VRE, or *C. difficile*. While this is being performed, national reporting is requiring specific patient diagnoses to be reported, such as catheter-related bloodstream infections, MRSA bacteremia, and others. The spread of these forms of resistance may be expressed as episodes of newly detected colonization or infection per 100 admissions or 1,000 patient days; this information is crucial for infection prevention efforts aimed at controlling resistance and antimicrobial use quality improvement. Along with these forms of surveillance, vigilance should be maintained by laboratory and infection prevention personnel with regard to the possible emergence of sentinel resistance patterns, such as vancomycin resistance in *S. aureus*.

ANTIMICROBIAL MANAGEMENT TEAM

The Joint Commission document is comprised of eight “elements of performance.” (Table 26-5) Leadership should show their commitment to antimicrobial stewardship with strategies such as budget plans and the practice of collecting data from the electronic health record. Staff, including new employees, and families should be educated regarding antimicrobial stewardship. Informational tools for families are available online from the CDC.²¹ Core members of the antimicrobial stewardship team are outlined. Essential activities of the team are listed including implementing recommended actions for specific antimicrobial uses, monitoring use and resistance patterns, education, and feedback to relevant groups (e.g., doctors and nurses). Certain committees benefit from that information as well, such as the Pharmacy & Therapeutics Committee and the Medical Executive Committee. The antimicrobial stewardship team should also establish protocols for antimicrobial use for specific infections, such as community-acquired pneumonia and skin and soft tissue infections. The team should evaluate its own performance, antimicrobial prescribing habits, and resistance patterns. Finally, the team should seek to improve itself.

Table 26-4 The Joint Commission’s Eight Elements of Performance for an Antimicrobial Management Team

No.	Element of Performance
1	Leaders establish antimicrobial stewardship as a priority
2	Education of staff and independent practitioners in processing/ordering antimicrobials
3	Education of patients and their families
4	Include core group members (ID physician, IP, pharmacist, and practitioner)
5	Include core elements in program: leadership commitment, accountability, drug expertise, action, tracking, reporting, and education
6	Use organization-approved multidisciplinary protocols
7	Collect, analyze and report data on antimicrobial stewardship team
8	Take action on improvement activities in antimicrobial stewardship program

Source: New Antimicrobial Stewardship Standard. Joint Commission Perspectives®. The Joint Commission. 2016;36(7). https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf

The next step in monitoring and improving antimicrobial use involves antimicrobial auditing. This is accomplished best through the formation of a multidisciplinary antimicrobial team.²² The mission of the team usually includes controlling antimicrobial costs and improving patient care and reducing resistance. The infection prevention team member should emphasize the latter goals.

With so many members, it is easier to think of the team as having an administration arm and a clinical arm. The administration arm is responsible for identification of potential problem areas either from resistance patterns or from drug costs and consumption data from the pharmacy. Decisions can be made regarding whether targeted or general audits should be undertaken. In either case, guidelines of acceptable use are needed against which to compare practice; these should be developed at the institutional level based on available national or international consensus guidelines. Consensus guidelines recommending appropriate empirical therapy of common infections now are increasingly accepted as the standard of care. Other general areas where audits can be undertaken include the appropriateness of dosing, whether surgical antimicrobial prophylaxis is used according to the aforementioned described principles, and whether empirical therapy is routinely narrowed to pathogen-directed therapy when culture results become available.

The clinical arm, usually including clinical pharmacist members and infectious diseases physicians, is responsible for performing audits prospectively or retrospectively. Prospective or “real-time” audits offer the advantage of uncovering additional information regarding why antimicrobials are used and, more importantly, the opportunity to intervene by making recommendations of how to improve antimicrobial use. They also collect and enter data into a database to monitor their interventions over time. The clinical arm of the antimicrobial program is critical for a program’s success because it reiterates the policies and antimicrobial guidelines drafted by the administrative arm of the program.

Success of any program depends on improving practice wherever inappropriate antimicrobial use is found. Elements critical for the success of the antimicrobial team will be determined by a local application of the IDSA guidelines, such as having appropriate personnel, dedicated time, appropriate education, and clear goals.²³ Conducting audits is one method, as discussed earlier. Reports should be a part of feedback, and feedback should be given to prescribers as well as people to whom the prescribers are accountable. For example, a report to the chiefs of medicine and surgery could include lists of the most common infections treated, the most common antimicrobials prescribed in the hospital, and an overall summary of internal medicine and surgeons’ compliance, respectively, with the hospital antimicrobial guidelines.²³ The second method is a paternal approach that restricts access to certain drugs, such as exclusion from the formulary, placement on a list of drugs requiring approval before dispensing, and alternating the use of different classes of antimicrobials to prevent the emergence of resistance (i.e., antibiotic cycling). The third method is an academic approach involving didactic instruction and the promulgation of institutional antimicrobial guidelines among prescribers.²⁴ As an alternative to formal didactic instruction, education of prescribers has been done by means of written information and face-to-face interactions (i.e., counter-detailing) carried out by clinical pharmacists, nurse practitioners, or physicians. Use of a combination of strategies to improve antimicrobial use has been shown to be more efficacious than use of a single method.^{25,26} As part of this collaborative approach, some attention should be paid to the influence of the pharmaceutical industry on prescribing. Whatever method is used, as a general rule, interventions to improve antimicrobial use should be implemented in collaboration with the pharmacy and therapeutics, quality improvement committees, and members of the hospital administration.

International Perspective

There are several aspects to understanding antimicrobial use and resistance in an effort to improve antimicrobial use that require modification to apply to settings outside the United States and North America. Drugs other than those described earlier may be used commonly in the international setting. Certain drugs that have been granted FDA approval are not available overseas and vice versa. In addition, drugs may be used outside the healthcare setting (i.e., in the community or in animal food production) differently and in such a manner that they are more likely to affect resistance in hospitals. For example, the use of avoparcin, a glycopeptide related to vancomycin, has long been used in animal food production in Europe and East Asia but not the United States and has been linked to VRE found among hospitalized patients in regions where it is used.²⁷ Likewise, the availability of antimicrobials over-the-counter without a prescription in many developing countries may influence resistance patterns, albeit predominantly in community pathogens.

Another major area to consider is how cultural differences and differences in healthcare financing may influence the effectiveness of measures designed to improve antimicrobial use. In some cultures, the clinical services are hierarchical, and recommendations made by a clinical pharmacist member of the

antimicrobial team are much less likely to be followed. Instead, physician-to-physician interaction or interaction among senior physicians and administrators may be necessary to effect a change in prescribing patterns.

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