

Principles of use of antibacterial agents

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Proper selection of an antibacterial agent is based on a number of factors, including the identity of the pathogen, the site of infection, the pharmacokinetics (PK) and pharmacodynamics (PD) of the agent, potential toxicity to the patient, possible drug interactions, cost, and convenience of administration. The initial choice of an antimicrobial agent may be modified during the course of treatment as the patient's clinical status evolves (eg, response to therapy, function of major organ systems, and so forth) and as more information about the nature of the infection comes to light. For example, when a patient presents severely ill, with signs and symptoms suggesting overwhelming bacterial infection, one must choose antimicrobial agents empirically. In such emergent circumstances, an initial regimen is selected based on the best information about the nature of the infection that can be gleaned from the available history, physical examination, and preliminary laboratory studies. Possible pathogens are identified based on these findings, and drugs are targeted against the likely culprits, based on known patterns of antimicrobial activity. Estimates of antimicrobial susceptibility of likely pathogens must take into account various factors that might predict resistance, such as the setting in which the infection was acquired (community, hospital, or nursing home); the previous use of antibiotics in the patient; and the potential of likely pathogens to produce extended-spectrum β -lactamases in the presence of β -lactam antibiotics.

Principles of PK and PD must also be considered in designing empiric regimens and in modifying those regimens in accordance with changes in the clinical condition of the patient. Patients who are severely ill almost always are treated with intravenous agents to bypass potentially slow and erratic oral absorption so that therapeutic levels are reached as soon as possible. Loading doses often are given under these circumstances to achieve a steady state more rapidly.

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Combinations of antimicrobial agents may be chosen not only for breadth of spectrum, but for favorable PD effects, such as synergistic killing, in which two agents demonstrate greater than additive activity. Toxicity is important to consider in formulating an empiric regimen. This is especially true in severely ill patients in whom organ function may be tenuous already. Therapy may be modified as the clinical course evolves. When the identity of the etiologic organism has been confirmed by culture, antibacterial therapy can be refined based on precise measures of susceptibility of the strains to antimicrobial agents. Depending on the patient's clinical progress, changes in dosage, route of administration, and even class of agent may be necessary or desirable. In general, an empiric regimen ultimately should be refined to the narrowest antimicrobial spectrum, least toxicity, least invasive route of administration, and lowest cost that is effective.

This article discusses the principles outlined previously, particularly those of PK, toxicity, monitoring, and related reasons for treatment failure, and briefly addresses the topics of susceptibility testing and PD. Susceptibility testing and PD are discussed in detail elsewhere in this issue.

Antimicrobial susceptibility testing

Susceptibility testing is indicated for clinically relevant isolates when antimicrobial susceptibility cannot be predicted with confidence. Broadly speaking, susceptibility testing may be either qualitative as provided by such methods as the Kirby-Bauer technique, or quantitative, as provided by tube dilution methodologies, E-test, and so forth. Quantitative testing of inhibitory and bactericidal activity by serial dilution is considered to be the gold standard, and results are reported as the lowest concentration of the agent, usually in micrograms per milliliter, at which inhibitory (minimal inhibitory concentration [MIC]) or bactericidal (minimal bactericidal concentration [MBC]) activity occurs. A detailed discussion of susceptibility testing can be found elsewhere in this issue.

Pharmacology

Once an antimicrobial agent is selected based on known or suspected pathogens, the goal of therapy is to deliver the drug to the site of infection. Effective treatment of serious infections is believed to depend on concentrations of the anti-infective agent in excess of the MIC of the organisms, at the site of the infection. The optimal dose and route of administration needed to achieve therapeutic concentrations, and appropriate monitoring for efficacy and toxicity, depend in large measure on the study of PK (ie, the absorption, distribution, and elimination of drugs). Related observations include the fact that with some agents, such as aminoglycosides and fluoroquinolones, antibiotic concentrations that are many multiples of the MIC for

the pathogen are more effective than concentrations that exceed the MIC by smaller proportions [1]. With other agents, such as β -lactams, higher multiples of the MIC make no difference, but maintenance of steady levels just higher than the MIC results in the greatest efficacy [1]. Such differences in activity and efficacy with regard to factors of time and concentration are discussed briefly next and in more detail elsewhere in this issue.

Pharmacokinetics

Absorption

Absorption of drugs given by the intravenous route is rapid and complete as soon as the infusion is finished. Peak serum levels of the antibiotic are achieved almost immediately. For this reason, the intravenous route is most often chosen when antimicrobial therapy is administered to a patient with a severe infection. Other routes, such as intramuscular and oral, are less rapid and less certain, because they are more likely to be affected by physiologic alterations. Peak serum levels are delayed and usually are not as high as those achieved by intravenous infusion. A few antibacterial agents, however, have excellent bioavailability; they are very well absorbed by the gastrointestinal tract, possibly by virtue of facilitated diffusion or active transport across gastrointestinal epithelium, so that a high percentage of active drug reaches the bloodstream [2]. The fluoroquinolones, metronidazole, doxycycline, and trimethoprim-sulfamethoxazole are examples of very well absorbed drugs.

Intramuscular and oral absorption (of even highly bioavailable agents) may be impaired by poor circulation associated with hypotension. Gastrointestinal absorption also may be altered by ileus, colitis, bowel ischemia, and changes in gastric pH. Many of these conditions may be present in sepsis. Oral absorption may also be affected by food; some agents, such as erythromycin, are absorbed more slowly or less completely in the presence of food and some, such as cefditoren, are better absorbed in the presence of fatty food. Drug interactions can also alter absorption by the oral route. For example, fluoroquinolones and tetracyclines may be chelated by concurrently administered antacids and may be more poorly absorbed.

Distribution

As the drug is absorbed, it is distributed to various body compartments. An important determinant of drug concentration is the volume through which it is distributed, or in simple terms, the extent to which it is diluted by body fluids (intravascular, interstitial, and intracellular). The volume of distribution is defined mathematically as $VD = A/C_p$, where VD is the volume of distribution, A is the total amount of drug present, and C_p is plasma concentration. Some drugs are avidly sequestered in certain tissues

(eg, nafcillin in the liver), or are highly fat soluble and penetrate body compartments not accessible to drugs that are only water soluble. In such cases, the volume of distribution, calculated for practical purposes based on measured serum levels, is very high, often exceeding total body volume. In those cases, the volume of distribution becomes a mathematical construct rather than a true measurable volume. Similarly, in patients who are very obese or who have a high fluid volume (cirrhosis, congestive heart failure, pregnancy), the volume of distribution for a given drug may be larger than expected, and the serum level correspondingly low [3]. Sepsis and fever alone may increase the volume of distribution [4,5].

It should be noted that this process is a dynamic one, and that as soon as drug absorption is underway, distribution, metabolism, and elimination begin, albeit often at different rates. All of these factors affect antibiotic concentrations in serum, and subsequently in tissue, at the site of infection. For example, even when a drug is infused intravenously, the concentration in serum can be influenced by the rate of infusion. Although the processes of distribution and elimination begin almost immediately, a rapid infusion can overwhelm the rates of distribution or elimination, and result in a higher peak serum level than a slower infusion.

Delivery of drug to the site of infection depends initially on the circulation. Once in the bloodstream, whether by intravenous injection or absorption from other sites, the agent can, theoretically at least, reach all sites through which blood circulates. Poor vascularity, either by the nature of the infection (eg, an abscess, which is not penetrated by blood vessels), the site of the infection (eg, the eye and the prostate, which are supplied by nonfenestrated capillaries), or disease (eg, large or small vessel peripheral vascular disease), results in impaired drug delivery and difficulty in achieving effective concentrations in the infected tissue.

Most sites of infection are extravascular, and treatment of infections in these sites depends on movement of the antimicrobial agent out of the bloodstream and into interstitial and sometimes intracellular fluid. The ability of a drug to do so depends on a number of factors. The first of those is the permeability of the capillary membrane. Capillaries in most parts of the body are fenestrated, and the walls of these vessels are easily permeated by most antibiotics. Furthermore, vascular permeability may be increased either locally or systemically by the cytokine-mediated inflammatory response induced by infection, especially when the infection is acute. In some areas, however, capillaries are nonfenestrated, relatively impermeable to most agents, and less affected by chemical mediators of inflammation. The eye, the prostate, and the central nervous system are all supplied by nonfenestrated capillaries. In these areas, ability of the antimicrobial agent to move out of the vascular space into the extravascular space depends on its lipid solubility (ie, its ability to move through, not between, endothelial cells). Lipid-soluble drugs, such as chloramphenicol, metronidazole, and rifampin, penetrate these areas better than agents that are more water

soluble, such as β -lactams, aminoglycosides, and glycopeptides. In some circumstances (eg, in the use of β -lactams to treat bacterial meningitis) this disadvantage can be overcome by increasing the dosage of the drug, provided there is a favorable therapeutic index. In other situations, such as the treatment of intraocular infections, topical or direct instillation is necessary to convey the drug to the site of infection [6,7]. Penetration of the antimicrobial agent into the eye and the central nervous system is further complicated by the presence of efflux pumps that actively transport some drugs, notably β -lactams and quinolones out of cerebrospinal fluid and β -lactams out of vitreous humor [8,9].

Protein binding is another major determinant in the delivery of a drug to an extravascular site and in the antibacterial activity of the agent. Most drugs bind to serum proteins to a greater or lesser extent. Bound drug becomes part of a large molecular complex that does not diffuse easily out of capillaries. Although protein binding occurs as a dynamic equilibrium, the greater affinity a drug has for plasma proteins, the less likely it is to diffuse out of the vascular space [10,11]. This has been shown by blister and skin window studies, in which substantially lower concentrations are measured in blister fluid than in serum when protein binding is high [12,13]. Furthermore, only unbound drug is believed to be active against organisms. The concentration of free (active) drug at the site of infection may actually fall below the MIC of the pathogen, despite apparently adequate (total) serum levels. The clinical significance of this phenomenon was shown by the failure of cefonicid, an agent that is highly active against *Staphylococcus aureus* in vitro but that is highly protein bound in vivo, to cure endocarditis caused by *S aureus* [14].

When the drug ultimately reaches the site of infection, local factors may play a role in the effectiveness of its antibacterial activity. For example, aminoglycosides and erythromycin have decreased activity in an acid pH, such as occurs in an abscess. Aminoglycosides are also less active against facultative organisms in an anaerobic environment because their penetration into cells depends on an oxygen-dependent reaction [15]. Substances that inactivate or lessen the antibacterial activity of antimicrobial agents may be present at the site, such as β -lactamases and other deactivating enzymes [16]. Aminoglycosides become less active as the concentration of calcium ions increases. Additionally, dense populations of organisms, such as occur in an abscess, tend to be slow growing, and antibiotics that are active against dividing cells, such as β -lactams, may be less effective in that setting [17]. Bacterial meningitis is another infection in which bacterial growth rates tend to be slow, decreasing the effectiveness of β -lactams [18]. The presence of a foreign body may also adversely influence the effectiveness of an antimicrobial agent. The foreign body acts as a nidus around and within which organisms may grow with relative protection from host defenses, which may not penetrate these areas well. Bacteria on infected intravascular devices and possibly other foreign bodies may be coated by a layer of

“slime,” a substance produced by organisms that acts as a shield against host defenses and that decreases penetration of many antimicrobial agents [19,20].

Although many infections occur in the interstitial fluid, some (eg, those caused by *Salmonella*, *Listeria*, *Chlamydia*, *Mycobacteria*, *Mycoplasma*) occur within cells, and antimicrobial agents effective against these pathogens must reach the intracellular space [21]. Most antimicrobial agents simply diffuse into cells, but some agents, such as clindamycin, the macrolides, and linezolid, may be actively transported into cells [9,21,22]. Most drugs are also actively transported out of cells, however, so the intracellular concentration reflects a balance between ingoing and outgoing processes [23,24]. Finally, just as in interstitial fluid, local factors within the cell may affect the activity of a drug within the cell (eg, pH, enzymatic activity, and so forth).

Elimination

Metabolism and elimination begin as soon as a drug is administered, and a balance between absorption and these processes ensues. The rate of elimination is expressed in terms of the half-life of the drug in serum. More than 90% of a single dose is eliminated by four half-lives. When agents are administered intermittently, the dosing interval is usually calculated as three to four times the half-life of the drug. As redosing, elimination, and accumulation of residual drug continue, an equilibrium, or steady state, is reached after four to five dosing intervals. A higher initial dose, or loading dose, accelerates this process.

Most antimicrobial agents, including most β -lactams, aminoglycosides, tetracyclines, vancomycin, and sulfonamides, are excreted by the kidneys, either by glomerular filtration, tubular secretion, or both. Aminoglycosides, fluoroquinolones, most tetracyclines, and vancomycin are excreted primarily by glomerular filtration. Only that fraction of antibiotic not bound to serum protein is excreted by this process, however, so a high degree of protein binding can prolong the half-life in serum. Tubular secretion, or active transport into the urine, contributes to the elimination of many β -lactam antibiotics. Probenecid, which blocks active transport, may prolong the half-life of these agents. Erythromycin, clindamycin, rifampin, nafcillin, and cefoperazone are excreted mainly by the liver, and doxycycline in the stool.

Toxicity

Impairment of renal or hepatic function may result in accumulation of drug if the dosage or the dosing interval is not altered. Toxic side effects may occur as serum and tissue drug concentrations increase. For example, high levels of imipenem, penicillins, or fluoroquinolones may cause seizures; high aminoglycoside levels may cause or exacerbate renal failure; high levels of vancomycin or aminoglycosides, particularly in combination, may cause hearing impairment or vestibular damage.

Reduction in the creatinine clearance to 30% of normal or less results in an exponential increase in the half-life of those drugs that are eliminated by the kidneys. For drugs with a narrow therapeutic index, even lesser reductions in renal function may necessitate changes in the dose or the dosing schedule. Certain antibacterial agents are contraindicated in the presence of renal insufficiency, whereas others require dosage modification as listed in **Box 1**.

The creatinine clearance can serve as a useful indicator of whether the dose should be adjusted, and if so, by how much. A quick estimate of the creatinine clearance can be made using this equation: clearance = $(140 - \text{age}) / \text{measured serum creatinine}$. The initial dose should not be modified, but subsequent doses may be reduced as a percentage based on the estimated creatinine clearance. For example, if the estimated creatinine clearance is 50 mL/min, the calculated maintenance dose with some agents might be reduced by 50%, if given at the usual dosing interval. An alternative measure is to lengthen the dosing interval. Lengthening the dosing interval results in a concentration versus time curve that approximates the situation in normal renal function, which is preferred by some authors. Using a longer dosing interval, however, runs the risk of longer periods during which the serum level has dropped below the MIC of the organism, and for that reason some favor administration of smaller doses given at the regular interval [25,26]. The use of hemodialysis, peritoneal dialysis, and continuous arteriovenous hemofiltration further confound calculations of dose modification. Guidelines for dosage modification in dialysis patients can usually be obtained from the manufacturer's product literature, and are based on the degree to which the drug is removed by dialysis. In general, the various

Box 1. Antibacterial agents contraindicated or requiring dosage modification in patients who have renal insufficiency

Contraindicated

Tetracyclines (except doxycycline)
Long-acting sulfonamides
Nitrofurantoin
Methenamine
Nalidixic acid

Dosage modification required

Aminoglycosides
Vancomycin
Penicillins (except semisynthetic antistaphylococcal penicillins)
Trimethoprim-sulfamethoxazole
Imipenem
Quinolones

methods of dialysis are at least partially effective in clearing β -lactams and aminoglycosides, but have little effect on vancomycin. This topic is discussed elsewhere in this issue.

Unfortunately there is no clinical measure of hepatic dysfunction that is easily adaptable for use in modifying doses of antibiotics that are excreted or metabolized by the liver [27,28]. In patients with severe liver disease, it may be prudent to reduce doses of erythromycin, metronidazole, chloramphenicol, and clindamycin, but there are no specific guidelines for most antimicrobial agents.

Under ideal circumstances, dosing is adjusted most accurately by a combination of calculated estimates followed by periodic monitoring of measured serum concentrations. Changes in the dosage or interval between doses can be made in response to the measured level, and follow-up serum levels can be obtained at the appropriate time (four to five dosing intervals), whereupon new adjustments can be made. This procedure is particularly helpful in patients whose renal (or hepatic) function is fluctuating. Levels of almost any antimicrobial agent can be measured by bioassay, radioimmunoassay, or high-pressure liquid chromatography. For practical purposes, however, such laboratory studies are usually available only for aminoglycosides and vancomycin, at least within a time frame that is clinically useful.

The likelihood of toxicity also may increase with duration of exposure to a potentially toxic drug, regardless of changes in dose or dosing schedule [29,30]. Duration of potentially toxic drugs should be minimized if an equally effective alternative can be used, once a pathogen is identified.

Pharmacodynamics

Although PK describes the absorption, distribution, and elimination of drugs by the body, PD, as it applies to antimicrobial agents, describes the interaction of drugs and microbes. When certain PD relationships exist, dosages of antimicrobial agents and dosing intervals can be manipulated in ways not readily apparent from the classic PK principles outlined previously. For example, synergistic activity between two antibiotics can result in bactericidal activity against an organism that cannot be killed by a single agent, or can result in more rapid killing than can be achieved by either agent alone. In the case of enterococci, for example, no single agent is bactericidal, but a combination of penicillin or vancomycin plus an aminoglycoside produces a bactericidal effect at serum aminoglycoside levels that is subtherapeutic in other settings [31]. Another PD property, the postantibiotic effect, or persistent suppression of bacterial growth after drug levels have fallen below the MIC, is at least partly responsible for the clinical success of regimens that use a single large daily dose of aminoglycoside, in contrast to the traditional shorter dosing interval [32].

Concentration-dependent killing is another PD characteristic of aminoglycosides that contributes to the success of these regimens; the higher the level of aminoglycoside above the MIC, the greater the rate of kill [33]. This observation also applies to fluoroquinolones and metronidazole. For most β -lactams, glycopeptides, macrolides, and clindamycin, however, prolonged exposure at concentrations over the MIC is the important variable (time-dependent or concentration-independent killing) [1,34,35]. Improved mortality rates have been observed when serum concentrations exceed the MIC for 40% or more of the dosing interval [36]. Assuming a constant level above the MIC, increasing that level to higher multiples of the MIC does not increase the rate of kill for these drugs. Some studies show the importance of both time-dependent and concentration-dependent effects with the same agent. In contrast to the previously mentioned observation that β -lactams exhibit primarily time-dependent killing, one study in which cefepime was used to treat patients with serious gram-negative bacterial infections seemed to show the importance of both time and concentration, in that time serum levels that exceeded four times the MIC correlated with therapeutic efficacy [37]. Some studies of clarithromycin similarly show the importance of multiple PD parameters, in that time-dependent and concentration-dependent efficacy can be observed [35,38–40]. Some agents display different PD properties with different organisms. For example, a postantibiotic effect can be demonstrated when staphylococci but not when susceptible gram-negative bacilli are exposed to most β -lactams. A detailed discussion of PD can be found elsewhere in this issue.

Predicting efficacy

Using PK and PD principles, efforts have been made to establish models that predict clinical efficacy. These models depend on various concepts and parameters discussed previously, including peak serum concentration, time above the MIC, postantibiotic effect, and the extent to which the peak concentration exceeds the MIC. Other parameters used in these models are variations on the area under the curve, which is the numerical integration of the area defined by the graphic representation of serum concentration versus time over a dosing interval. Area under the inhibitory curve is a term that has been used variously, but has been refined by Schentag et al [41] to mean the area under that part of the curve during which the serum concentration exceeds the MIC. These areas under the curve are divided by the MIC to result in ratios that have been correlated with efficacy of therapy.

The analysis of PK and PD parameters in combination has led to the practice of dual individualization, or PK-PD optimization, to understand and predict better in vivo efficacy [42–51]. Computerized simulation of serum concentration over time curves is generated using different dosage regimens. Efficacy indices (eg, time above MIC, area under the inhibitory

curve, extent that the peak serum concentration exceeds MIC) are estimated for each. As suggested by some of the previously mentioned observations of PD, different efficacy indices have proved more useful than others for various classes of antibiotics. The degree to which the peak serum level exceeds the MIC generally is the best indicator for efficacy of drugs that exhibit concentration-dependent killing, such as aminoglycosides and fluoroquinolones [42,43,52]. The area under the inhibitory curve is also a good predictor of fluoroquinolone efficacy [42,52–55]. Time that the concentration exceeds the MIC is usually the best indicator for β -lactams and other drugs that exhibit time-dependent killing [42]. Better clinical outcomes have been observed when efficacy indicators meet certain thresholds. For fluoroquinolones and aminoglycosides, better cure rates are observed when the peak serum concentration:MIC ratio is greater than or equal to 10, and for some β -lactams, when time above the MIC exceeds 40% of the dosing interval [36,43,44]. Although the process of PK-PD profiling continues to be refined, it has been used successfully in designing regimens using newer cephalosporins and quinolones [44,56,57].

Monitoring therapy

Although application of PK-PD principles can help to predict efficacy, they depend primarily on serum rather than tissue concentrations. Because of that fact and because of numerous causes of variability among individuals, efficacy cannot be predicted with absolute certainty. Clinical improvement is the best and most comprehensive indicator of adequacy of therapy, but it is often difficult to monitor objectively, especially in critically ill patients with multisystem disease. Furthermore, for infections requiring long-term therapy (eg, osteomyelitis and endocarditis) clinical improvement may be very slow, and it is often desirable to have an objective indicator of the adequacy of therapy before investing weeks of therapy in an ineffective regimen. Finally, monitoring of various parameters may reduce the likelihood of drug toxicity or may at least lead to the early detection of adverse reactions.

Measurement of levels of antimicrobial agents in serum may be helpful in several respects. It is vitally important to achieve levels greater than the MIC at the site of infections in which host defenses are limited (eg, in valvular vegetations or in immunocompromised patients). Monitoring of time greater than the MIC, or multiple by which serum levels exceed the MIC may prove to be useful in some clinical circumstances. Indeed, even in normal hosts with gram-negative bacillary bacteremia, better outcomes have been shown if peak levels of gentamicin and tobramycin exceed 5 $\mu\text{g/mL}$, and if peak amikacin levels exceed 20 $\mu\text{g/mL}$ [58].

Even when adequacy of serum levels is ensured, such factors as protein binding may interfere with antimicrobial activity. Documentation of

antimicrobial activity in serum is sometimes desirable. Serum bactericidal activity can be measured by the Schlichter test, in which serial dilutions of the patient's serum are incubated with a standard inoculum of the patient's organism. Similar to minimal bactericidal concentration methodology, an aliquot from each tube is cultured quantitatively, and the highest dilution that kills greater than or equal to 99.9% of the organisms is the serum bactericidal titer. Because the methodology is not standardized with respect to timing (peak or trough), diluent (broth or serum), and various other parameters, correlation with clinical efficacy is uncertain. In general, however, peak serum bactericidal titers of greater than or equal to 1:8 are recommended in bacterial endocarditis, and peak titers of greater than or equal to 1:16 for chronic osteomyelitis [31,59,60].

Newer technologies, such as microdialysis, are being explored for the purpose of documenting true tissue concentrations of antibiotics. Such data may prove helpful both in PK-PD modeling and in monitoring therapy [61–63].

Toxicity may be avoided by maintaining levels below an established threshold. For example, serum vancomycin levels should be kept below 40 or 50 $\mu\text{g/mL}$ to avoid ototoxicity [64]. Elevated aminoglycoside trough levels (the serum level measured at the end of a dosing interval) may result in increased ototoxicity or nephrotoxicity [65,66]. Bone marrow suppression may occur in patients whose renal excretion of flucytosine is impaired. Presumably, close monitoring of drug levels and corresponding dose adjustments may prevent or reduce toxicity. Careful dosage adjustment to achieve optimal peak and trough levels has been associated with improved survival in at least one study [67].

Careful monitoring of clinical manifestations of toxicity is also important in cases where severe or permanent impairment may occur or when the therapeutic index is low. For example, some clinicians advocate the use of serial audiometric testing for patients on long-term aminoglycoside or vancomycin therapy [68]. Periodic measurement of creatinine, electrolytes, liver function tests, and complete blood counts is prudent to detect such occasional side effects as hyponatremia, hypokalemia, and bone marrow suppression.

Failure of therapy

Despite careful consideration of the factors discussed previously, failure of therapy may occur (Box 2).

Summary

Treatment of infection involves complex interactions among the infecting organism (susceptibility to the therapeutic agent); host factors (immune

Box 2. Reasons for treatment failure

1. Delay in diagnosis or therapy
2. Wrong or incomplete diagnosis
 - No infection
 - Nonbacterial infection
 - Polymicrobial infection
3. Errors in antimicrobial susceptibility testing
4. Inadequate concentration of antibiotic at the site of infection
 - Improper dose
 - Decreased absorption from food or drug interaction
 - Increased elimination of agent
 - High protein binding
 - Poor delivery (eg, vascular disease)
5. Decreased activity at the site
 - Chemical factors (pH and others)
 - Antibiotic antagonism
6. Other factors at the site of infection
 - Collection requiring drainage
 - Necrotic tissue
 - Foreign body
7. Other host factors
 - Impaired immune defenses
 - Infection in a protected site (ie, requiring bactericidal drug or combination)
8. Development of resistance to antimicrobial agents
9. Superinfection

function, site of infection, renal and hepatic function); characteristics of the antimicrobial agent (water versus lipid solubility, protein binding); PK (absorption, distribution, elimination); PD (postantibiotic effect, concentration dependent versus time-dependent killing); and so forth. Successful therapy requires careful consideration of these factors, and unsuccessful therapy should provoke a careful reanalysis of the same factors.

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