

# Pharmacodynamics of antimicrobial drugs

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Pharmacodynamics relates the fluctuating drug concentrations in blood and at the site of infection after a dose of an antimicrobial drug is given (ie, pharmacokinetics) to the time course of the antimicrobial effects at the site of the infection, and to toxic effects. Only the antimicrobial effects are discussed in this article. Knowledge of the antimicrobial pharmacodynamic characteristics of a drug (inhibition of growth, rate and extent of bactericidal action, and postantibiotic effect [PAE]) provides a more rational basis for determination of optimal dosing regimens in terms of the dose and the dosing interval. This article reviews concepts of antimicrobial pharmacodynamics, the effect of pharmacodynamics on the emergence of resistant bacterial subpopulations, and the development pharmacodynamic breakpoints for use in the design of trials of these drugs and in treatment of infected patients.

## **Antimicrobial activity of drugs**

### *Minimal inhibitory concentration and the minimal bactericidal concentration*

Despite acknowledged exceptions with certain drug–bacteria combinations, antibacterial drugs are usually divided into two groups: those that are primarily bacteriostatic (ie, inhibit growth of the organism) and those that are primarily bactericidal (ie, kill the organism). Bacteriostatic drugs require the aid of host defenses to clear tissues of the infecting microorganism; if host defenses are systemically inadequate (eg, agranulocytosis) or host defenses are impaired locally at the site of infection (eg, the cardiac vegetation in left-sided endocarditis and cerebrospinal fluid in meningitis), the residual pathogen resumes growth after stopping the bacteriostatic drug and the

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infection relapses. Bacterial infection in these circumstances requires use of bactericidal drugs. Bacteriostatic drugs are sufficient for most other infections.

Antimicrobial activity of drugs is usually assessed by determination of the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC) of the drug *in vitro* after overnight aerobic incubation in a protein-free liquid medium at pH 7.2. These *in vitro* conditions are likely very different from those expected at the site of infection, where the milieu is frequently acidic and anaerobic, and tissue protein may bind a variable amount of the drug. The MIC and MBC, which are determined at a fixed point in time after exposure to drug concentrations that remain constant throughout an overnight incubation period, do not provide information on the time course of the antimicrobial effect of fluctuating levels that are present in a patient treated with the drug. In addition, the MIC and MBC are measured against a standard bacterial inoculum (about  $10^5$  colony-forming units [CFU] per milliliter) that does not necessarily correspond to bacterial densities at site of infection ( $10^{8-10}$  CFU per gram of tissue or pus). The *in vitro* inoculum is also in the exponential phase of growth, unlike most organisms in an established infection, which are nongrowing.

The MIC is defined as the minimal concentration of antibiotic that prevents the clear suspension of  $10^5$  CFU/mL from becoming turbid after overnight incubation; turbidity usually connotes at least a 10-fold increase in bacterial density. Because clear bacterial suspensions may have bacterial densities of less than  $10^5$  CFU/mL, the MIC determined by the broth dilution may actually be bactericidal to some extent.

If the minimal concentration of the antibiotic that prevented turbidity actually has lowered the bacterial density from  $10^5$  to at least  $10^2$  CFU/mL (ie, a 99.9% [ $3-\log_{10}$ ] reduction in bacterial inoculum), the MIC that prevented turbidity is also the MBC. For bactericidal drugs, the MBC is usually the same as and generally not more than fourfold higher than the MIC. In contrast, the MBC of bacteriostatic drugs are many-fold higher than their MIC. Bacteriostatic drugs include the macrolides, clindamycin, tetracyclines, sulfonamides, linezolid, and chloramphenicol. Bactericidal drugs include the  $\beta$ -lactams, vancomycin, aminoglycosides, fluoroquinolones, daptomycin, and metronidazole.

Time-kill studies, which are used to determine the rate of bactericidal activity, involves sampling the bacterial suspension of  $10^5$  CFU/mL in broth at various time intervals (eg, at 2, 4, 6, and 24 hours of incubation) after addition to a particular concentration of the antibiotic. This method is also used to assess the interaction of two antimicrobial drugs for synergy or antagonism.

The MIC is a measure of the potency of an antimicrobial drug. Isolates of a particular species have varying MICs; sensitive strains have relatively low MICs and resistant strains have relatively high MICs. The breakpoint MIC (ie, the MIC that separates sensitive and resistant strains) was traditionally

selected on its ability to select two disparate populations, one population with MICs below the breakpoint (ie, susceptible) and one with MICs above the breakpoint (ie, resistant). Another attribute of the breakpoint MIC was correspondence to achievable serum drug levels with standard dosing. Concentrations may be much higher than serum levels for drugs that concentrate at intracellular sites or at excretory sites, such as urine or bile, however, or may be considerably lower than serum at secluded foci, such as the cerebrospinal fluid, the eye, the prostate, or centers of abscesses. For example, the breakpoint concentration for susceptibility to azithromycin, 2  $\mu\text{g/mL}$ , is significantly higher than the usual peak serum level of 0.4  $\mu\text{g/mL}$ , which may be fine for predicting effectiveness against intracellular pathogens, such as legionella, mycoplasma, or chlamydia, but may be problematic for extracellular pathogens, such as *Streptococcus pneumoniae*. In addition, drugs that are highly bound to serum protein may have reduced antibacterial activity in serum and not penetrate tissues as well as drugs that are less protein bound. In these cases, the results of in vitro testing may not predict the in vivo effect.

### Pharmacodynamics

After a dose of a bactericidal drug, the bacterial count may decline in the early portion of the dosing interval when levels of the portion of the drug not bound to protein exceed the MBC as a result of both the drug's effects and host defenses (Fig. 1). When unbound drug levels fall below the MBC,

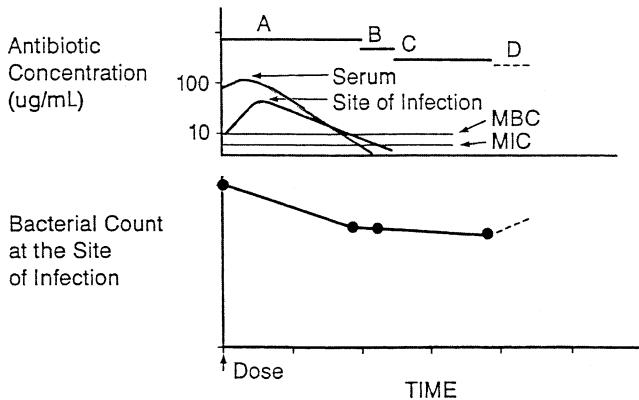


Fig. 1. Antibiotic pharmacodynamics. A, Time during which free drug levels at the site of infection exceed the MBC; B, time during which free drug levels at the site of infection are less than the MBC, but exceed the MIC; C, persistent antimicrobial effects (PAE, MAC, and PALE) when free drug levels at the site of infection are less than the MIC; D, regrowth of residual bacteria. MAC, minimal antibacterial concentration; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; PAE, postantibiotic effect; PALE, postantibiotic leukocyte enhancement. (From Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic affects. *Infect Dis Clin N Am* 1995;9:483–95.)

but still exceed MIC, the bacterial count may remain stable or continue to decline as a result of host defenses [1]. With a bacteriostatic drug, when drug levels are in excess of the MIC, the bacterial count declines as a result of host defenses alone. Eventually unbound drug levels fall below the MIC, at which point any persistent antibacterial effect can be the result of several causes: (1) a persistent suppression of bacterial growth after a brief exposure of bacteria to an antibacterial agent may occur even in the absence of host defenses and has been called the PAE; (2) after antibiotic exposure, organisms may be more susceptible than untreated bacteria to the antibacterial activity of phagocytes, the so-called “post-antibiotic leukocyte enhancement”; and (3) drug concentrations below the MIC have been shown to alter bacterial morphology, slow the rate of bacterial growth, and prolong the PAE. The minimal drug concentration that alters bacterial cell morphology has been termed the “minimal antibacterial concentration.”

Eventually, residual drug effects wane and the remaining bacteria begin to resume growth [1]. The extent of regrowth before the next dose is given depends in part on the inherent doubling time of the organism, on available nutrients being present in the infected tissues, and the adequacy of host defenses. For example, in the absence of host defenses, such as occurs in left-sided cardiac vegetations and cerebrospinal fluid in early meningitis, microorganisms can double every 20 minutes, similar to the doubling time during logarithmic phase of growth under optimal *in vitro* conditions (Fig. 2). In contrast, the tubercle bacillus and *Treponema pallidum* double every 36 hours. Some regrowth may, in fact, restore susceptibility to  $\beta$ -lactam antibiotics [2].

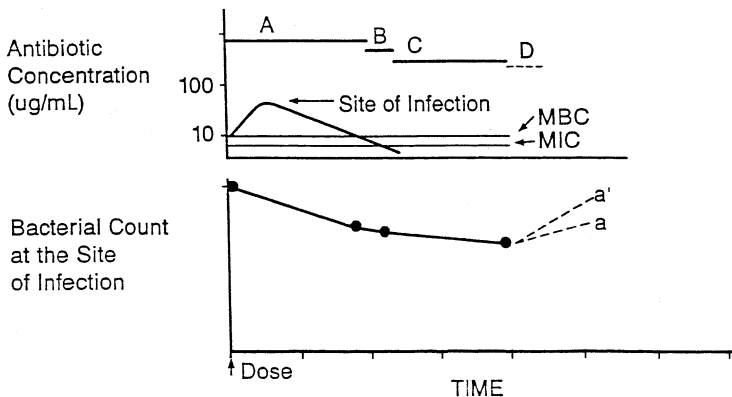


Fig. 2. A, Time during which free drug levels at the site of infection exceed the MBC; B, time during which free drug levels at the site of infection are less than the MBC, but exceed the MIC; C, persistent antimicrobial effects (PAE, MAC, and PALE) when free drug levels at the site of infection are less than the MIC; D, regrowth of residual bacteria, with (a) and without (a') adequate host defenses. MAC, minimal antibacterial concentration; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; PAE, postantibiotic effect; PALE, postantibiotic leukocyte enhancement. (From Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic affects. *Infect Dis Clin N Am* 1995;9:483–95.)

The next dose ideally is given before clinically significant regrowth has occurred (Fig. 3), so that after multiple doses the tissues are cleared of the pathogen. If the doses are spaced too far apart, however, as a result of resumption of residual bacterial growth in the later portion of each dosing interval, the bacterial count may become equal to, or perhaps exceed, the bacterial count at the beginning of the dosing interval and compromise drug efficacy (Fig. 4) [1]. The size of the residual bacterial population at the end of each dosing interval, and ultimately the efficacy of the antimicrobial regimen, depends on the interplay of a variety of bacterial, drug, and host factors that include (1) the size of the initial bacterial population, (2) the potency (MIC and MBC) and pharmacokinetic characteristics of the antimicrobial agent, (3) the rate and extent of any bactericidal effect, (4) the presence of a PAE, (5) the rate of regrowth of persistent organisms, and (6) the presence of host defenses.

Antimicrobial drugs can be divided into three main groups based on pharmacodynamic characteristics that effect bacterial clearance [3]. The first group is drugs that exhibit time-dependent bactericidal action that has little relation to drug concentrations above the MIC ( $\beta$ -lactam antibiotics and vancomycin). These drugs have relatively slow bactericidal action and no or short PAEs; the duration of time that drug levels exceed the MIC relative to the dosing interval and consequently the frequency of drug administration are important determinants of outcome for these drugs. The second group includes drugs that exhibit concentration-dependent bactericidal action and prolonged PAEs (the aminoglycosides, fluoroquinolones, daptomycin,

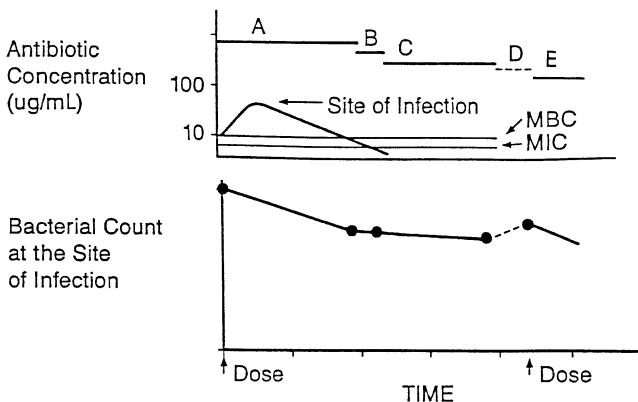


Fig. 3. A, Time during which free drug levels at the site of infection exceed the MBC; B, time during which free drug levels at the site of infection are less than the MBC, but exceed the MIC; C, persistent antimicrobial effects (PAE, MAC, and PALE) when free drug levels at the site of infection are less than the MIC; D, regrowth of residual bacteria; E, bactericidal effect following the next dose. MAC, minimal antibacterial concentration; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; PAE, postantibiotic effect; PALE, postantibiotic leukocyte enhancement. (From Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic effects. *Infect Dis Clin N Am* 1995;9:483–95.)

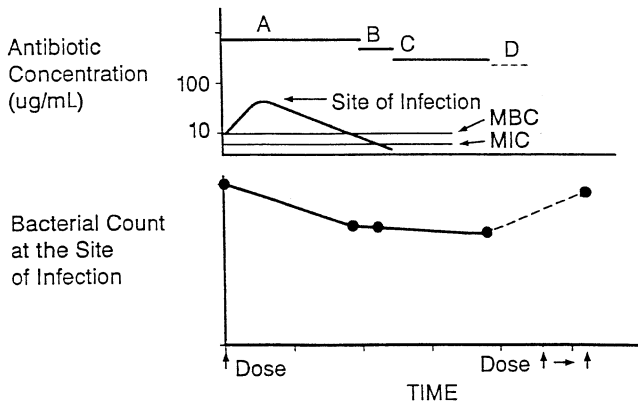


Fig. 4. Regrowth as a result of a longer dosing interval, which compromises drug efficacy. MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration. (From Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic effects. *Infect Dis Clin N Am* 1995;9:483–95.)

metronidazole, possibly the azalide, azithromycin, and the ketolides). Both the rate of cidal action and duration of PAE for these drugs are concentration-dependent. Consequently, the amount of drug (eg, peak concentration [C<sub>max</sub>]) and area under the concentration curve (AUC) relative to the MIC, rather than the dosing frequency, determines efficacy for these drugs. The third group includes drugs that are predominantly bacteriostatic and produce moderate to prolonged PAEs (macrolides, clindamycin, streptogramins, tetracyclines, and linezolid). Because of their prolonged PAE, their efficacy is determined less by time and more by AUC once concentrations exceed the MIC.

Usually drug concentrations in blood are used to determine pharmacodynamic parameters, such as percent of time drug levels exceed the MIC, and peak drug AUC/MIC level, because of the relative accessibility of this body fluid and the correlation of pharmacodynamic parameters, based on serum levels to antimicrobial effects. Use of serum levels, however, to determine pharmacodynamic parameters may not always be appropriate [3]. Because infection usually occurs at extravascular sites, the use of drug concentrations in blood is only satisfactory if the blood levels are a satisfactory surrogate for levels at the site of infection. Theoretically at equilibrium, free drug levels in plasma and extracellular tissue fluid should be equal [4]. Depending on the ratio of surface area of the capillary bed to volume of the tissue compartment, the physicochemical characteristics of the drug, and special anatomic barriers (eg, in the brain, eye, and prostate), however, drug levels at the site of certain infections can be much lower than free drug levels in plasma. For meningitis, cerebrospinal fluid levels are appropriate for determination of pharmacodynamic parameters [5]. Recent studies also suggest that epithelial lining fluid concentrations are important

determinants of efficacy of treatment of bacterial pneumonia, such that epithelial lining fluid concentrations better predict outcome for certain antibiotics (eg, vancomycin) than serum concentrations [6]. Serum drug levels are also poor predictors of intracellular concentrations, which is of major importance for intracellular pathogens.  $\beta$ -Lactams and vancomycin penetrate cells poorly, whereas other drugs, such as azithromycin, achieve intracellular concentrations many-fold higher than serum levels.

In vitro and animal model studies have documented that the magnitude of the pharmacodynamic parameter required to achieve a specific target (eg, bacteriostasis, or various degrees of cidal action) is similar for different drugs within the same class [3]. For those drugs that are highly protein-bound, efficacy is predicted by the percentage of time that serum concentrations of drug not bound to protein exceed the MIC or the Cmax or AUC for concentrations of drug not bound to serum protein relative to the MIC, rather than the total drug levels [3]. Pharmacodynamics derived from in vitro and animal data are concordant with those derived from human data. Consequently, pharmacodynamics can predict efficacy in patients and are useful for establishing optimal dosing regimens [7].

### **Time course of time-dependent bactericidal action**

Increasing drug concentrations much above the MBC does not enhance bacterial killing by  $\beta$ -lactam antibiotics, and the bactericidal action of these drugs is relatively slow [1,3]. Consequently, there is a relatively large residual population when levels fall below the MBC. After drug levels at the site of infection fall below the MIC, the residual population can resume growth quickly, because there is either no or short PAEs for most  $\beta$ -lactams [1,3].

$\beta$ -Lactams exhibit an inoculum effect; the lower the bacterial density, the lower the concentration of the  $\beta$ -lactam that is required to inhibit growth [8]. The minimum concentration of these drugs that inhibits growth can progressively fall below the standard MIC (determined using an inoculum of  $10^5$  CFU/mL), because the bacterial count progressively falls during the time course of antimicrobial therapy, and the time levels that exceed the MIC may progressively lengthen.

Efficacy for such drugs as the  $\beta$ -lactams can be optimized by dosing strategies that maximize the duration of drug exposure (ie, time-dependent bactericidal activity), such as smaller fractions of the total daily dose given at frequent intervals; larger doses; use of  $\beta$ -lactams with long serum half-lives, such as ceftriaxone with a half-life of 6 to 8 hours; or use of longer intravenous infusions or even continuous intravenous infusion. There have been few trials, however, of continuous versus intermittent infusions [9]. Because approximately five half-lives are required to attain steady state with continuous infusion, a loading dose is required at the initiation of a continuous infusion to attain an immediate therapeutic concentration.

Effective dosing regimens for time-dependent antibiotics have been shown to require that serum drug concentrations exceed the MIC of the causative pathogen for at least 40% to 50% of the dosing interval. For  $\beta$ -lactam drugs that have high serum protein binding (eg, ceftriaxone and ertapenem), when drug concentrations not bound to serum protein are used the percentage of time above the MIC that predicts efficacy is similar for all  $\beta$ -lactams within a class. The percent of time above MIC that correlates with efficacy varies among classes within the  $\beta$ -lactams, being greater for cephalosporins and aztreonam than penicillins, and greater for penicillins than carbapenems, and varies among bacterial species, being less for staphylococci, for which  $\beta$ -lactams have a PAE, than for streptococci and gram-negative bacilli, for which  $\beta$ -lactams do not have a PAE [3]. The percent of time above the MIC can be used to compare the effectiveness of different time-dependent antibiotics within a class and, as a corollary, those drugs having the greater potency (ie, a lower MIC) are anticipated to have higher percentage of time above MIC and greater effectiveness.

For susceptible pathogens with MICs that are close to the breakpoint MIC of 8  $\mu\text{g}/\text{mL}$ , serum levels of cephalosporins are in excess of the MIC for a smaller percentage of the dosing interval than for strains that have lower MICs. For example, patients infected with borderline cephalosporin-sensitive extended-spectrum beta-lactamase (ESBL)-producing strains of gram-negative bacilli with MICs of 4 to 8  $\mu\text{g}/\text{mL}$  did much worse with cephalosporin monotherapy than did patients infected with strains having lower MICs [10]. Similarly, free drug levels of ceftriaxone may not remain above the MICs for more than 50% of the 24-hour dosing interval for strains of *Staphylococcus aureus*, which have MICs close to the breakpoint, especially with a 1-g dose. Extending the dosing interval of cefoperazone, which has relatively high serum protein binding and short half-life (2 hours), from 6 or 8 hours to 12 hours for *Pseudomonas aeruginosa*, which has MICs close to the breakpoint, may be similarly problematic.

Although there are some conflicting pharmacodynamic data concerning whether glycopeptides exhibit mainly time- or concentration-dependent activity, studies that have used an in vivo model of endocarditis [11] and an in vitro model that simulates methicillin-resistant *S aureus* endocarditis [12] have shown that the glycopeptides exhibit time-dependent action.

If the rate of cidal action of  $\beta$ -lactams or vancomycin is increased, lower residual bacterial counts occur during the dosing interval when drug levels fall below the MIC; this prolongs intervals before significant regrowth occurs and either allows for more extended dosing intervals or allows for shorter durations of therapy as a consequence of accelerated clearance of bacteria from sites of infection (Fig. 5). Indeed, combinations of these antibiotics with aminoglycosides can enhance the relatively slow rate of bactericidal activity of  $\beta$ -lactams and vancomycin. For example, a bacterial cell wall-active agent, such as penicillin, ampicillin, or vancomycin, alone is at best only slowly bactericidal against enterococci; an aminoglycoside alone

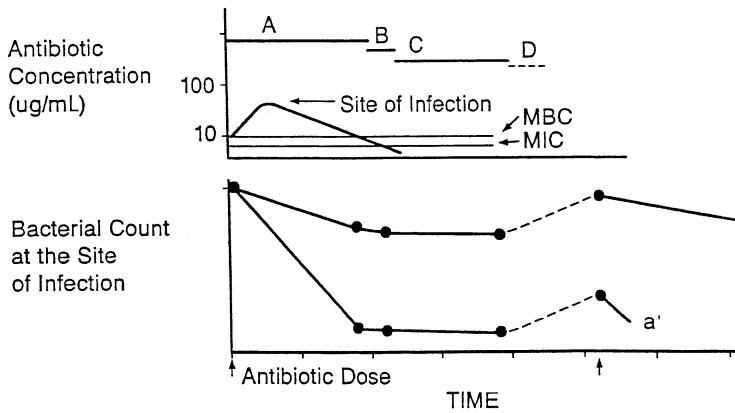


Fig. 5. The effect of more rapid and extensive bactericidal action ( $a'$ ) on the residual bacterial population despite prolongation of the dosing interval. MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration. (Modified from Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic effects. *Infect Dis Clin N Am* 1995;9:483–95.)

at concentrations achieved in serum after standard dosing exhibits at best only inhibitory activity; but the combination of the cell wall–active agent with an aminoglycoside results in rapid bactericidal activity. The synergy achieved by the combination has been shown to be caused by enhanced bacterial penetration of the aminoglycoside in the presence of the cell wall–active agent.

Synergistic bactericidal activity, usually defined as a 2 log<sub>10</sub> or greater or 99% reduction in bacterial count after overnight incubation with the combination in comparison with the most active single drug, has also been shown with cell wall–active agents/aminoglycoside combinations against viridans streptococci, *S aureus*, and many gram-negative bacilli. Synergistic combinations that more rapidly clear the tissues of the infecting microorganism have been used to shorten the course of antimicrobial therapy for viridans streptococcal endocarditis (ie, penicillin or ceftriaxone plus gentamicin for 2 weeks versus penicillin or ceftriaxone alone for 4 weeks) and for uncomplicated methicillin-sensitive *S aureus* right-sided endocarditis (nafcillin plus gentamicin for 2 weeks versus nafcillin alone for 4 weeks).

Some combinations of antimicrobial agents have been found to be antagonistic (eg, penicillin plus a tetracycline). In this case the penicillin's bactericidal effect, which requires the presence of growing organisms, may be converted to a bacteriostatic effect when combined with a tetracycline that prevents microbial growth. This has been the explanation for the findings in the classic paper of Lepper and Dowling [13], in which patients with pneumococcal meningitis treated with penicillin combined with a tetracycline had 2.6-fold greater mortality than those patients treated with penicillin alone.

### Time course of concentration-dependent bactericidal action

For drugs with concentration-dependent bactericidal action, such as aminoglycosides and fluoroquinolones, the rate of bactericidal activity is maximal at the  $C_{max}$  [14–16]. As the drug concentration decreases, the rate of bactericidal activity decreases. Higher doses of the drug not only increase the rate of reduction of bacteria, but also the length of time of drug exposure to bactericidal concentrations. This dependence on both the magnitude and the duration of exposure of bactericidal concentrations implies that concentration-dependent drugs are influenced by both the  $C_{max}$  and AUC, whereas for drugs with time-dependent activity, the extent of bactericidal activity depends solely on the duration of drug exposure.

After drug levels at the site of infection fall below the MIC, there may be persistent suppression of growth because of a PAE, the duration of which is also concentration-dependent for aminoglycosides and fluoroquinolones; the higher the drug concentration, the longer the duration of the PAE for these drugs, and the less the residual bacterial population at the time of the next dose.

Indeed, effective dosing regimens for concentration-dependent antibiotics requires that either the 24-hour AUC:MIC be at least 100 to 125 for aminoglycosides or fluoroquinolones against gram-negative bacilli [16–18] and 25 to 30 for fluoroquinolones against *S pneumoniae* [19,20] or the  $C_{max}$ :MIC of the causative pathogen be greater than 10 [21,22]. For concentration-dependent drugs, dosing strategies that maximize the intensity of drug exposure, such as giving the total daily dose as a single dose every 24 hours rather than giving smaller divided doses, maximize the  $C_{max}$  and possibly allow for comparable efficacy at greater convenience and lower cost.

The AUC:MIC or the  $C_{max}$ :MIC ratios also can be used to compare the effectiveness of different concentration-dependent antibiotics. Drugs within a class having the greater potency (ie, lower MICs) have higher AUC:MIC or  $C_{max}$ :MIC ratios and are anticipated to have greater effectiveness. It is clear that an infection caused by susceptible pathogens with relatively high MICs may not be treated adequately with standard dosing of a concentration-dependent antimicrobial agent. For example, gentamicin-susceptible strains of *P aeruginosa* with MICs close to the breakpoint of gentamicin of 4  $\mu\text{g}/\text{mL}$  may respond suboptimally to standard dosing regimens that provide peak serum levels of gentamicin of 6  $\mu\text{g}/\text{mL}$ . Similarly, ciprofloxacin-susceptible strains of *P aeruginosa* with MICs close to the breakpoint of 2  $\mu\text{g}/\text{mL}$  may respond suboptimally to standard dosing regimens that provide peak serum levels of ciprofloxacin of about 3 to 4  $\mu\text{g}/\text{mL}$ , and levofloxacin-susceptible strains of *S pneumoniae* with MICs close to the breakpoint of 2  $\mu\text{g}/\text{mL}$  may respond suboptimally to standard dosing regimens that provide peak serum levels of levofloxacin of about 5  $\mu\text{g}/\text{mL}$ .

Higher rates of bactericidal action result in lower residual bacterial counts and longer intervals before significant regrowth occurs (see Fig. 5).

Maximizing serum concentrations of drugs that exhibit concentration-dependent bactericidal activity by increasing the dose maximizes the rate and extent of bactericidal activity, if adverse effects were not also concentration-dependent. Although dose-dependent toxicity was once thought to limit giving the total daily dose of an aminoglycoside as a single dose every 24 hours, data from both animal models of infection and human clinical trials suggest dosing regimens that provide very high peak aminoglycoside concentrations relative to the MIC and prolonged periods of subinhibitory aminoglycoside concentrations have not resulted in more nephrotoxicity than regimens that provide lower peaks but more persistent inhibitory concentrations [23], although the relationship between pharmacodynamic parameters and auditory and vestibular toxicity is unclear. Giving the total 24-hour dose as a single dose, rather than in smaller divided doses, and using extended dosing intervals has now become the standard in most clinical settings [18]. This strategy may be especially appropriate for treatment of many susceptible pathogens (eg, *P aeruginosa*) with MICs that are close to the breakpoint [24]. This same strategy, however, may not be appropriate for fluoroquinolones that likely have concentration-dependent toxicity.

All aminoglycosides have similar pharmacokinetics, but there is significant variation in pharmacokinetics in normal individuals and certain patient populations. For example, volume of distribution tends to be elevated in critically ill patients and clearance is elevated in children, in patients with cystic fibrosis, in pregnancy, and in the early postpartum period, and depressed in renal insufficiency. The C<sub>max</sub> is primarily affected by the volume of distribution and the AUC by both volume of distribution and clearance. Consequently, measurement of aminoglycoside levels is especially important early in the course of treatment and doses adjusted to achieve therapeutic levels [25].

### **Bacteriostatic activity**

The macrolides (erythromycin and clarithromycin), clindamycin, and the tetracyclines exhibit little if any concentration-dependent killing, but these drugs produce prolonged PAEs, which allows these drugs to be efficacious when concentrations exceed the MIC for less than 50% of the dosing interval [2]. The antimicrobial effects of the azalide, azithromycin, and the ketolides have been best characterized as concentration-dependent [26]. Persistence of resistant subpopulations of *S pneumoniae* and their subsequent emergence, however, may be encouraged by the presence of prolonged periods of sub-MIC concentrations of azithromycin in epithelial lining fluid.

Craig [3] has recently reviewed the pharmacodynamics of linezolid. In animal models, the 24-hour AUC:MIC correlated best with efficacy of this drug [27], although both percent of time above MIC and 24-hour AUC:MIC

were found to correlate with efficacy in clinical trials [28]. Chance of success with bacteremia, lower respiratory tract infection, and skin and skin structure infections were greater when linezolid plasma concentrations remained in excess of the MIC for the entire dosing interval. Although bactericidal against *S pneumoniae* [29], it is mainly bacteriostatic against *S aureus*. In the rabbit *S aureus* endocarditis model, linezolid was bactericidal if the levels were maintained above the MIC constantly by continuous infusion, and only bacteriostatic when administered by intermittent infusion [30]. Linezolid penetrates epithelial lining fluid better than vancomycin, being threefold higher than simultaneous serum levels [31].

### Prevention of resistance

Subpopulations with reduced susceptibility to antibiotics are a normal feature of dense populations of some bacterial species, especially *P aeruginosa* and *S aureus*. The likelihood that resistant subpopulations will emerge on antimicrobial therapy depends on the propensity for resistance within the population (eg, spontaneous mutation rate for antibiotic resistance); the ability of host defenses to control the growth of the resistant subpopulation; and the magnitude of the antimicrobial drug levels at the site of infection. It is thought that drug levels should at least exceed 8 to 10 times the MIC to prevent emergence of resistant subpopulations, which could be accomplished by single daily dosing of aminoglycoside, or using the most potent fluoroquinolone, or high doses of a  $\beta$ -lactam. In vitro and animal models of infection have identified the peak to MIC ratios and free drug 24-hour AUC:MIC ratios for fluoroquinolones that are required to prevent emergence of resistant subpopulations. The minimal prevention dose, which has been shown to vary among bacterial species, is higher for denser bacterial populations, and is often higher than ratios required for efficacy [32].

### Use of pharmacodynamic breakpoints for antimicrobial susceptibility testing

For time-dependent drugs, the minimal serum concentration of free drug that is present for 40% to 50% of the dosing interval is the important parameter for predicting efficacy and can be determined if the peak serum level of free drug after a particular dose regimen and serum half-life of the drug are known. This concentration is the so-called “pharmacodynamic breakpoint” for time-dependent drugs. If the MIC of the drug for a particular pathogen, or the MIC<sub>90</sub> of the drug against a group of common pathogens causing a particular infection, is below this breakpoint, the drug is likely to be clinically useful (sensitive), and if above this breakpoint the drug may not be useful (resistant). For example, a 500-mg dose of amoxicillin given every 8 hours or 875 mg every 12 hours yields a concentration of at least 2  $\mu$ g/mL for 40% to 50% of the dosing interval,

and the MIC<sub>90</sub> for amoxicillin against *S pneumoniae* in the United States is currently below this breakpoint, predicting clinical success with these dosing regimens of amoxicillin. The same calculations can be done with other time-dependent drugs to determine pharmacodynamic breakpoints [33].

For concentration-dependent drugs, the optimal effect is reached at the 24-hour free AUC:MIC ratio of 25 for streptococci and 100 for gram-negative bacilli or peak serum level of free drug:MIC ratio greater than 10 to 12. In clinical practice AUC:MIC and C<sub>max</sub>:MIC are difficult to separate with limited ranges of dosing schedules. The pharmacodynamic clinical breakpoint MIC can be calculated by the following formula: for *S pneumoniae*, AUC/25, and for gram-negative bacilli, AUC/100, when the average AUC from the dosing regimen is known [33]. Similarly, the pharmacodynamic clinical breakpoint MIC can be calculated by the following formula: peak serum level of free drug/10. For ciprofloxacin, the peak serum level is about 4 µg/mL and the pharmacodynamic breakpoint MIC is 0.4 µg/mL; strains of *S pneumoniae* having MIC greater than 0.4 µg/mL are considered resistant, and those with MIC less than or equal to 0.4 µg/mL are considered sensitive.

## Summary

The importance of pharmacodynamic factors in developing optimal treatment strategies has been confirmed in many studies in *in vitro* models and in models of infection in experimental animals that simulate human infections, and in clinical studies. The requirement for bactericidal therapy for endocarditis and meningitis, for synergistic combinations to treat enterococcal endocarditis or to shorten the course of antimicrobial therapy, for obtaining C<sub>max</sub>/MIC ratios that are greater than 10 or AUC:MIC ratios that are greater than 100 to 125 for concentration-dependent agents against gram-negative bacilli and 25 to 30 against *S pneumoniae*, and for percent of time above the MIC that is at least 40% to 50% of the dosing interval for time-dependent agents are a few important pharmacodynamic concepts demonstrated in animal models that have successfully guided therapy of human infections. Pharmacodynamics can also optimize dosing to prevent emergence of resistance and be used to rationalize determination of antimicrobial susceptibility.

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