

Pharmacokinetics/Pharmacodynamics for Critical Care Clinicians

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Since the advent of antimicrobial therapy, considerable controversy has existed as to the most appropriate method to administer antibiotics to maximize the killing of microorganisms, while minimizing toxicity to the patient, the emergence of bacterial resistance, and costs. Over the past decade, data gained from animal models of infection, *in vitro* pharmacokinetic (PK) and pharmacodynamic (PD) studies, volunteer studies, and clinical trials have enabled clinicians to establish the best mode of drug administration to achieve these goals. This article addresses these issues with particular attention to PK-PD concepts.

Pharmacokinetic and pharmacodynamic considerations

The study of the movement of a drug from its administration site to the place of its pharmacologic activity and its elimination from the body is called “pharmacokinetics.” Factors affecting the movement (kinetics) and fate of a drug in the body are (1) release from the dosage form; (2) absorption from the site of administration into the bloodstream; (3) distribution to various parts of the body, including the site of action; and (4) rate of elimination from the body by metabolism or excretion of unchanged drug. These processes are often referred to by using the acronym ADME: *A*bsorption, *D*istribution, *M*etabolism, and *E*xcretion. The ADME parameters of a drug are described by various terms, such as C_{max} (maximum concentration of the drug in serum); T_{max} (time to maximum concentration of the

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drug in serum after a dose); $T_{1/2}$ (half-life of a drug in serum); AUC_{0-24hr} or AUC_{∞} (area under the curve over 24 hours from the time of administration to infinity, representing the concentration of the drug in serum over time); and CL (clearance of the drug from the serum), which may include renal and nonrenal clearance.

Drug concentrations in interstitial fluid drive the antibiotic into the bacterium and, ultimately, to its binding site within the organism. Because interstitial fluid drug concentrations are proportional to and in rapid equilibrium with blood, antibiotic concentrations in serum are correlated with bacterial eradication. Although one cannot yet measure the drug's concentration directly at the site of attachment to the bacterium on the outside membrane of the organism, serum levels still allow one to determine the concentrations of the antibiotic that are necessary to inhibit (minimum inhibitory concentration [MIC]) or to be bactericidal (minimum bactericidal concentration [MBC]) to microorganisms. As a result, drug concentrations in the blood (plasma, serum) have been correlated with *in vivo* bacterial eradication.

Pharmacodynamics correlates the concentration of the drug with its pharmacologic or clinical effects. For an antibiotic, this correlation refers to the ability of the drug to kill or inhibit the growth of microorganisms. Antibiotics elicit their activity against bacteria by binding to a specific protein or structure in the organism.

For an antibiotic to eradicate an organism, three major factors must occur. First, the antibiotic must bind to its target sites in the bacterium. To reach the binding site is no easy matter. It must penetrate the outer membrane of the organism (penetration resistance); avoid being pumped out of the membrane (efflux pump resistance); and remain intact as a molecule (eg, avoid hydrolysis by β -lactamases). Once reaching its target, the antibiotic can still be frustrated if the binding site has changed its molecular configuration and now no longer allows the drug to attach. Until the antibiotic overcomes all these obstacles, there is no detrimental effect on the organism.

A range of different binding sites has been identified including ribosomes, penicillin-binding proteins, DNA topoisomerase-gyrase, and the cell membrane itself. The crucial binding site varies with the antibiotic class. These binding sites can be defined as points of biochemical reaction within the bacterium, which must be properly executed to continue the cell's life cycle. By binding to them, the antibiotic interferes with a crucial chemical reaction resulting in the death of the bacterium.

The second factor relates to concentration. The drug must not only attach to its binding target but also must occupy an adequate number of binding sites, which is related to its concentration within the microorganism. The third factor necessary for an antibiotic to work effectively is that it should remain at the binding site for a sufficient period of time for the metabolic processes of the bacterium to be sufficiently inhibited.

The two major determinants of bacteria killing include the concentration and the time that the antibiotic remains on its target binding sites. The

integration of how high (concentration [C]) and how long (time [T]) an antibiotic's level remains above a zero concentration over a dosing interval is referred to as the "area under the plasma concentration curve" (AUC). In essence, the AUC measures the concentration of the drug over a given time period and reflects the amount of exposure of the organism to the antibiotic over a dosing interval.

For certain classes of antibiotics, the major killing effect against an organism is produced by either the time or the concentration of the drug at the binding site. Of these two factors of bacterial killing, one may be so minimal in the killing process that it can be ignored in the prediction of a clinical response. For instance, certain antibiotics, like β -lactams (penicillins, cephalosporins, carbapenems, monobactams, and β -lactamase inhibitors), clindamycin, macrolides (erythromycin, clarithromycin), oxazolidinones (linezolid), and vancomycin, use mainly time at the binding site to eradicate organisms. Apparently, once the concentration exceeds a critical value, which seems to be about two to four times above the MIC for an organism, bacterial killing proceeds at a zero order rate, and increasing the drug concentration does not increase the microbial death rate.

As a result, these antibiotics are referred to as "concentration-independent" or "time-dependent" antibiotics (Box 1). For these drugs, the duration that the antibiotic's concentration remains above their MBC or MIC ($T > \text{MIC}$ or MBC) in any one dosing interval becomes the best predictor of clinical outcomes. For β -lactam antibiotics, the time above the MIC or MBC for the drug in serum is generally proportional to that in the fluid bathing the organism (ie, the interstitial fluid or wound fluid in tissues) because the antibiotic distributes to extracellular water, which is in dynamic equilibrium with serum.

Box 1. Mode of bacterial killing by anti-infective agents

Time-dependent

β -Lactams (eg, penicillins, cephalosporins, carbapenems, β -lactamase inhibitors, monobactams)

Clindamycin

Erythromycin

Clarithromycin

Linezolid

Vancomycin

Concentration-dependent

Fluoroquinolones

Aminoglycosides

Metronidazole

Amphotericin

Daptomycin

Certain classes of antibiotics, however, like aminoglycosides and quinolones, use mainly concentration at the binding site to eradicate organisms. Unlike concentration-independent killing antibiotics, the aminoglycosides and fluoroquinolones eliminate bacteria most rapidly when their concentrations are appreciably above their MICs for organisms and, hence, their type of killing is referred to as “concentration-dependent” or “dose-dependent” (see [Box 1](#)). For these drugs, the rate of bacterial eradication rises with increasing concentration up to a specific amount. After this specific concentration is achieved, increasing the concentration further does not increase the magnitude of bacterial killing (interestingly, even concentration-dependent antibiotics eventually behave like concentration-independent agents). If the concentration is high enough, most bacteria die within a short time. In these conditions, the effect of the duration of drug exposure is minimal. For concentration-dependent agents, the PD parameter of AUC/MIC or $C \times T/\text{MIC}$ can be simplified to peak or $C_{\text{max}}/\text{MIC}$ ([Fig. 1](#)).

These concepts have been even further refined. How long the concentration of a time-dependent antibiotic in serum should remain above its MIC or MBC for pathogens in any one dosing interval remains controversial. It is likely that this time may vary with different pathogens, the site of infection, and immunocompetence of the patients. Nevertheless, it seems from animal models of infection, *in vitro* PD models, volunteer studies, and clinical trials that β -lactam antibiotics levels should remain above their MIC or MBC for the target pathogen for at least 50% of the dosing interval to ensure the highest degree of bacterial eradication [1].

For agents with concentration-dependent killing, like aminoglycosides or fluoroquinolones, the best responses occur when the concentrations are greater than or equal to 10 times above the MIC for their target organisms at the site of infection [2]. For agents with concentration-dependent killing, it has also been shown that clinical responses can be predicted and the peak/MIC ratio by measuring the antibiotic’s AUC over the dosing interval and dividing that value by its MIC against the target organism [3]. In essence,

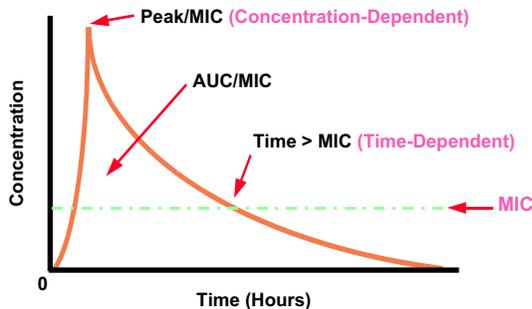


Fig. 1. Pharmacokinetic and pharmacodynamic parameters affecting antibiotic potency. AUC, area under the curve; MIC, minimum inhibitory concentration.

the AUC/MIC ratio becomes a default PD concept for the peak/MIC ratio for antibiotics with concentration-dependent killing.

Clinical application of concentration-dependent or dose-dependent killing antibiotics

Being a concentration-dependent drug, aminoglycosides eradicate organisms best when they achieve concentrations that are greater than or equal to 10 times above their MIC. In animal models of infection (including neutropenic animals), many more animals survive a potentially lethal challenge of bacteria if the aminoglycoside is given as a single daily dose than when given in divided doses on an every 8-hour basis [4]. To obtain this favorable ratio (the typical MIC of gentamicin and tobramycin against *Pseudomonas aeruginosa* is 2 µg/mL), the aminoglycoside should be given at a dose of 7 mg/kg once daily but may be given even less frequently in patients with renal dysfunction based on a nomogram [5]. This 7 mg/kg dose usually achieves a peak serum concentration of 20 µg/mL, thereby achieving the target of 10 times above the MIC for these aminoglycosides. In a meta-analysis comparing once-daily aminoglycoside with intermittent dosing in immunocompetent adults, once-daily dosing was equivalent with regard to bacteriologic cure, but showed a trend toward reduced mortality rates and reduced toxicity [6].

Compared with intermittent dosing, once-daily dosing of aminoglycosides has shown less rather than more damage of tissue, like the organ of Corti or the renal tubular cells, on pathologic examination [7,8]. The ototoxicity or nephrotoxicity of aminoglycosides correlates with tissue accumulation and not peak concentration in serum [4]. Further advantages of once-daily aminoglycoside dosing include reduction in supply and labor costs and the emergence of bacterial resistance [9]. This new once-daily dosing method for aminoglycosides based on the PD concepts mentioned previously has emerged as the preferred dosing method, except for patients with enterococcal endocarditis; pregnancy; ascites; renal dialysis; and burns (>20%).

Although fluoroquinolones also exhibit concentration-dependent killing of bacteria, excessively high serum concentrations of these agents can, unfortunately, be associated with seizures and other potentially serious central nervous system adverse reactions. This has been the major reason why quinolones cannot be dosed at very high concentrations. When peak/MIC ratios of greater than or equal to 10 cannot be reached without excessive toxicity, then time of exposure of the organism to the drug cannot be ignored, and bacterial eradication again becomes a function of concentration and time of exposure (ie, AUC/MIC).

Most of the currently available fluoroquinolones given at their usual dose, even orally, achieve urinary concentrations far above 10 times their MIC for even difficult organisms like *P aeruginosa*. Despite ciprofloxacin's slightly lower MIC against this bacterium compared with levofloxacin and

gatifloxacin, the patient outcomes are the same with all these fluoroquinolones because they all attain urine concentrations greater than or equal to 10 times their MICs against this bacterium. Interestingly, the only fluoroquinolone that was contraindicated for the treatment of *P aeruginosa* urinary tract infection was trovafloxacin, because of its very low urine concentrations (approximately 6 $\mu\text{g/mL}$) and its relatively high MIC (approximately 4 $\mu\text{g/mL}$) for this organism. Moxifloxacin is also an unwise choice because only 25% of active drug is eliminated in the urine. This is the reason why microbiology laboratories do not report the susceptibility of any urinary pathogens. The percentages of a dose of ciprofloxacin, levofloxacin, and gatifloxacin eliminated in the urine are 50%, 90%, and 90%, respectively. For evaluating the efficacy of fluoroquinolones, the PK-PD concept used for predicting outcomes in urinary tract infection is the concentration in urine/MIC greater than or equal to 10, whereas in systemic infection it is the AUC/MIC.

An indexing of the AUC with the MIC to predict clinical response has been used mainly with the respiratory quinolones. For instance, certain organisms require modest AUC/MIC ratio for their prompt eradication. *Streptococcus pneumoniae* are typically rapidly killed by quinolones at an AUC/MIC_{24hr} ratio of 30 to 35, whereas others, like *P aeruginosa* and most other aerobic gram-negative bacteria, require much greater exposure to quinolones (AUC/MIC_{24hr} ratios ≥ 100 –125) to be eradicated. The term “target attainment” is often used to determine the likelihood of an antibiotic to attain these ratios. The necessary dose and dosing interval of an antibiotic can be calculated to achieve these ratios that have been correlated with favorable outcomes. Unfortunately, for some antibiotics, particularly those with high MICs against a bacterium, these target ratios either cannot be achieved or only in a small percent of the time. These ratios should be reported as 24-hour unbound or free drug AUC/MIC and not as total drug because only the unbound drug is in equilibrium with its targets binding sites in the organism [10]. It should also be emphasized that it is only the unbound or free concentrations of an antibiotic that can cross biologic membranes (human and bacterial) and interact with target sites leading to a biologic effect (efficacy or toxicity). For an antibiotic to reach its target site in an organism it must first penetrate through the organism’s outer membrane. Because typically only molecules of less than 1000 d can pass through the channels (porins) in the outer membrane, and because albumin has a molecular weight of about 40,000 d, an antibiotic bound to albumin has no chance of reaching its binding site.

Clinical application of concentration-independent or time-dependent killing antibiotics

For antibiotics with time-dependent or concentration-independent killing, like β -lactams, the often mentioned advice in package inserts is that

the drug should be given in larger and more frequent doses for infections considered to be “severe” as compared with those that are deemed “mild” or “moderate.” This dosing concept makes little, if any, PD or pharmacoeconomic sense, except possibly for infections located in body areas (eg, cerebrospinal fluid, vitreous humor of the eye) where the higher serum concentrations may improve drug penetration. It should be remembered the high serum levels of β -lactam antibiotics do not drive more drug intracellularly or into “tissue” because these agents exhibit insignificant intracellular penetration. The higher serum levels merely result in similar levels in the interstitial fluid that surround the cells and the same PK-PD concepts that apply to serum levels also apply to interstitial concentrations. Although there typically exists a slight lag period before interstitial and serum levels attain equilibrium, there is a close parallel with β -lactam antibiotics between their concentrations in serum and interstitial fluid compartments. The poor intracellular penetration of β -lactam antibiotics is the explanation why these agents do not eradicate intracellular pathogens like *Chlamydia* sp, *Mycoplasma* sp, and *Legionella* sp.

There are five major ways to prolong the duration of a β -lactam concentration above its MIC for bacteria in any dosing interval: (1) use another drug (eg, probenecid) that interferes with its elimination; (2) dose frequently; (3) increase the dose of the antibiotic; (4) replace with another therapeutically equivalent antibiotic with a longer serum half-life; and (5) administer by constant infusion.

Although probenecid blocks the renal tubular secretion of most β -lactam antibiotics, it may do the same for other drugs, resulting in unexpected adverse reactions. Moreover, if a patient develops a hypersensitivity reaction it is difficult, if not impossible, to determine whether the reaction was caused by probenecid or the antibiotic.

Dosing frequently or increasing the dose is usually unacceptable in today's medical era of fiscal restraints because of excessive cost from high drug acquisition costs and ancillary service time. Moreover, doubling the dose of a β -lactam antibiotic is generally inefficient, yielding an increase in T greater than MIC of only one half-life.

Using an antibiotic with a longer half-life is sensible as long as the one with the longer half-life is therapeutically equivalent and is not appreciably more expensive. Examples of this type of interchange include replacing cephalothin with cefazolin, cefoxitin with cefotetan, and cefotaxime with ceftriaxone.

There has been a renewed interest in administering β -lactam antibiotics by a 24-hour constant infusion because this represents an easy way using the least amount of drug, supply, and labor costs to maintain drug concentrations above the antibiotic's MIC for the entire day or 100% of the dosing interval.

For the antipseudomonas β -lactams, constant infusion dosing methods are an alternative dosing approach because most of these agents have

a relatively short half-life. For instance, the recommended dose in the package insert of piperacillin-tazobactam to treat nosocomial pneumonia is 4.5 g every 4 to 6 hours. To optimize clinical outcomes, minimize toxicity, and reduce costs in view of the PK-PD considerations mentioned previously, piperacillin-tazobactam could be administered by constant infusion once daily. In the constant infusion program at Hartford Hospital, 12 g a day is used for a patient with suspected or proved pseudomonas infection; 9 g a day in patients not suspected to have pseudomonas infection; and an even lower infusion dose (based on a nomogram) if the patient has renal impairment [11]. Moreover, in a study [12] comparing intermittent with constant infusion ceftazidime with nosocomial pneumonia, similarities were noted in clinical outcomes but a major reduction in costs associated with constant infusion.

Further clinical outcomes studies are needed to confirm whether this constant infusion dosing method will become the preferred dosing approach for those β -lactam antibiotics that have relatively short half-lives and require high daily dose (eg, oxacillin, nafcillin, ceftazidime, piperacillin-tazobactam, ticarcillin-clavulanic acid).

Volume of distribution

One of the simplest models in PK describes the body as a single homogeneous compartment into which the drug seems to dissolve. The volume of this compartment measured in liters per kilogram, called the apparent volume of distribution, rarely relates to physiologic volumes but serves as a proportionality constant between the dose of drug administered and the observed plasma or serum concentration just after the intravenous administration of a bolus dose.

This concept can be more easily understood using a hydrodynamic or "bathtub" model. In the bathtub model, one adds a known amount of dye to a bathtub of known volume. Clearly, a large bathtub yields a smaller concentration than a small bathtub if the same quantity of dye is placed in each one. Drugs that distribute widely through the body tend to have large volumes of distribution and low serum concentrations; drugs that remain only in the blood volume typically have small volumes of distribution and high serum concentrations. In general, drugs with a high level of serum protein binding penetrate to a lesser extent into the interstitial spaces, produce higher peak serum concentrations, and exhibit a slower rate of elimination from the body, especially if the major elimination mode is by glomerulofiltration. An inverse relationship exists between protein binding and volume of distribution. There is no relationship between renal tubular secretion and protein binding.

The value of volume of distribution for the clinician is that this term roughly describes whether or not the antibiotic will be widely distributed

in tissue. Drugs that have poor tissue penetration (eg, β -lactam antibiotics) typically have low (<20 L) volumes of distribution at steady state, whereas agents with widespread tissue distribution (eg, fluoroquinolones) have high (> 100 L/kg) volumes of distribution at steady state. Drugs with low volume of distribution indicate their distribution is limited, mainly to extracellular fluids and not into tissue.

Clearance

Drug concentrations decline in the body as a result of elimination, usually from the kidneys or liver, or both. The term “clearance” is used to describe the intrinsic ability of the body to remove drug. Clearance represents a theoretic volume of blood or plasma that is cleared or completely removed of drug within a period of time. It is expressed as units of volume per time. The clearance volume for a drug is generally constant during a dosing interval. The amount of drug removed per unit of time can be determined if one recalls that concentration and volume are related. Because the clearance of a drug remains constant after distribution is complete, but the serum concentrations decline as drug is removed from the body, the amount of drug removed per unit of time is highest when the serum concentration is highest (ie, just after administration of a dose).

Half-life and steady-state

In the one-compartment PK model, which most antibiotics follow, drug distribution is assumed to be instantaneous, and elimination from the body follows first-order (log linear) decline. A semilogarithmic plot of drug concentration versus time yields a linear graph. This type of plot can be used to determine the half-life of a drug, which refers to the amount of time required for the drug concentration to decrease by 50%. A simple rule for drugs that follow a one-compartment model is to multiply the half-life by 5, and that predicts the time the serum concentrations decline to their lowest or trough concentration. Antibiotics with very short half-lives (eg, penicillin, nafcillin, oxacillin, cephalothin) require very frequent dosing, such as every 4 hours, because their half-lives are only 30 minutes. Now there are many antibiotics with long half-lives, like the respiratory quinolones (eg, levofloxacin, gatifloxacin, and moxifloxacin), ceftriaxone, and azithromycin, legitimizing once-daily dosing.

If the half-life of a drug is known, one can predict the time required to reach steady-state when all the peak and trough concentrations are the same after the dose. Fifty percent of the final steady-state concentration accumulates during each half-life, so that after five half-lives, approximately 97% of the final steady-state concentration has been achieved. For example, an antibiotic with a half-life of 2 hours (eg, ceftazidime) takes about 10 hours

to attain steady-state, whereas an agent with an 8-hour half-life (eg, ceftriaxone) reaches steady-state in about 40 hours.

The longer the half-life of a drug, the longer it takes to achieve a steady-state concentration. This can be particularly important for patients receiving drugs that have long half-lives and narrow therapeutic ranges of serum concentrations. In these patients often a loading dose is used to achieve rapidly therapeutic drug concentrations.

Postantibiotic effect

The postantibiotic effect (PAE) describes the persistent suppression of bacterial growth after exposure of a microorganism to an antibiotic. The term should not be confused with the effects of bacterial suppression caused by antibiotic subinhibitory concentrations. Antibiotics that kill bacteria by interfering with protein synthesis (eg, aminoglycosides, chloramphenicol, macrolides, tetracyclines) or DNA replication (eg, quinolones) usually demonstrate prolonged PAEs (eg, 1–5 hours) against gram-negative bacteria, whereas agents that kill bacteria by interfering with cell wall synthesis (eg, β -lactam antibiotics, glycopeptides) have little, if any, PAE against these types of organisms. The one major exception is the carbapenems (eg, imipenem, meropenem) that exhibit fairly long PAEs against *P aeruginosa*. Against gram-positive bacteria, both types of antibiotics typically exhibit short PAEs of about 1 hour. The clinical relevance of the PAE is related to its use in establishing dosage regimens that are directed against a specific pathogen. The PAE has been one of many explanations for the success of intermittent dosing with drugs that exhibit short half-lives.

Bioavailability

The degree of absorption or bioavailability of an antibiotic has become an extremely important PK and pharmacoeconomic property of an antibiotic because it often allows for inexpensive and the effective treatment of an infection without the use of injectable agents or hospitalization. Moreover, there are many other advantages to replacing an intravenous antibiotic rapidly with an oral formulation. Probably the greatest advantage is the avoidance of so-called “intravenous line sepsis,” the major source for hospital-acquired bacteremias and fungemia. Proactive programs converting patients rapidly from intravenous to oral therapy is often designated as sequential, transitional, or switch therapy. To replace an intravenous antibiotic with an oral formulation, the oral drug should have a high degree of bioavailability, preferably over 90%. In this situation, the concentrations of the oral antibiotic in tissue or serum can rival the levels that are obtained if the patient is kept on the intravenous formulation. **Box 2** records the oral antibiotics that exhibit greater than or equal to 90% bioavailability.

Box 2. Oral anti-infectives with greater than or equal to 90% bioavailability

Levofloxacin (Levaquin)^a, gatifloxacin (Tequin), moxifloxacin (Avelox)

Metronidazole (Flagyl), clindamycin, TMP-SMX (Bactrim), rifampin^a

Minocycline^a, doxycycline, fluconazole (Diflucan)^a, voriconazole (Vfend), linezolid (Zyvox)^a

Cephalexin, cefadroxil, cefprozil

^a 100% bioavailable.

Replacing intravenous antibiotic with an oral drug is probably unwise for those oral agents with less than 50% bioavailability.

Common mistakes in the interpretation of pharmacokinetic and pharmacodynamic concepts

For decades, it has been traditional to view an antibiotic with bactericidal activity against a pathogen as a preferable choice over one that exhibits bacteriostatic activity. It is now well recognized that antibiotics cannot be categorized in such a simplistic manner, because their type of activity varies against different pathogens and under different conditions. Antibiotics with bacteriostatic activity may be as efficacious as ones with bactericidal activity against an organism even in difficult infections (eg, meningitis, endocarditis, osteomyelitis, the febrile neutropenic patient) where it has been customary to recommend a drug that exhibits bactericidal action against the target pathogen. It now probably makes sense for clinicians to avoid using this concept in selecting one antibiotic over another.

It must be emphasized that once target AUC/MIC ratios, peak concentration/MIC ratio and $t > \text{MIC}$ are achieved, there is no evidence that higher values result in more rapid bacterial killing or less emergence of bacterial resistance. Even concentration-dependent antibiotics eventually behave like a concentration-independent agent. For instance, if one compares the AUC/MIC ratios of the three respiratory quinolones (levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin) against *S pneumoniae*, all attain the target ratio of 30 to 35. Compared with moxifloxacin, gemifloxacin, and gatifloxacin, levofloxacin achieves somewhat lower ratios against this bacterium, yet, as predicted, has identical efficacy in infections, like community-acquired pneumonia, caused by this bacterium.

Excessive AUC/MIC ratios may produce unwanted adverse reactions by disrupting the normal gastrointestinal flora (collateral damage) and

producing organ dysfunction. For instance, it has recently been shown that AUC/MIC ratios greater than or equal to 60 with gatifloxacin have an association with hyperglycemia [13] and the high fecal concentration with moxifloxacin has been associated with an increase in gastrointestinal colonization with *Clostridium difficile*, vancomycin-resistant enterococci, and *Candida albicans* [14].

Another common mistake is to equate an antibiotic's potency against an organism solely by its MIC, assuming that the antibiotic with the lowest value has the greatest activity. It must be underscored that the MIC or MBC of an antibiotic against a pathogen is only one of many factors that determines the best or preferred drug to cure an infection. When determining the potency of an antibiotic against a bacterium, one must include other items, such as protein binding, PK, distribution into the site of infection, the adequacy of the patient's host defenses, and the amount of exposure an organism requires to an antibiotic for its eradication. Paradoxically, microbiologic reports that provide both MIC data along with susceptibility data may actually encourage a clinician to select the wrong antibiotic because of the tendency of clinicians to view potency only in terms of the MICs. Reporting systems that merely report the data in terms of sensitive, intermediate, or resistant are actually better for most clinicians because these values are determined by an integration of the microbiologic and PK properties of the antibiotic.

A common example of this type of mistake is the popular view by clinicians that ciprofloxacin has more activity or potency compared with levofloxacin against *P aeruginosa* based solely on its slightly lower MIC against this bacterium (ciprofloxacin, approximately 0.5 µg/mL; levofloxacin, approximately 1 µg/mL). This slightly lower MIC of ciprofloxacin is cancelled out by its lower serum concentration compared with levofloxacin resulting in no difference in potency of these two agents against this organism. At equivalent dosages for nosocomial pneumonia, levofloxacin, 750 mg intravenously every 24 hours, has a threefold higher peak serum level and AUC_{24h} than ciprofloxacin, 400 mg intravenously every 8 hours. As expected, national surveillance studies [15,16] performed over the last 7 years comparing the susceptibility of *P aeruginosa* to ciprofloxacin and levofloxacin have shown no difference. In a PD study [12] comparing the likelihood of either ciprofloxacin, 400 mg every 8 hours, or levofloxacin, 750 mg every 24 hours, achieving a target AUC/MIC in serum of greater than or equal to 125 against *P aeruginosa*, there was no significant difference (ciprofloxacin 61.8%; levofloxacin 61.2%). These low attainment values suggest that neither ciprofloxacin nor levofloxacin should be given alone to treat serious systemic *P aeruginosa* infection and that addition of another antipseudomonas agent is required. In a large multicenter, randomized, double-blind trial in the treatment of severe pneumonia that compared intravenous ciprofloxacin with imipenem-cilastatin, the incidence of failure to eradicate *P aeruginosa* and the development of bacterial resistance in this bacterium in

patients treated with monotherapy with ciprofloxacin was 67% and 38%, respectively [17].

Summary

The ultimate goal of antimicrobial therapy is to eradicate microbial pathogens at the specific site of infection. To accomplish this goal, the clinician must become familiar with PK and PD concepts because an understanding of this information establishes the basis for appropriate dosing strategies to optimize clinical efficacy and minimize toxicity, costs, and the emergence of bacterial resistance. Appreciation of these concepts results in dosing of antibiotics in a scientifically and economically sound fashion.

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