

## 20 – Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

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*Pharmacology* is the knowledge base of a compound concerning its history, source, physical and chemical properties, compounding, biochemical and physiologic effects, mechanisms of action and resistance, absorption, distribution, metabolism, excretion, and therapeutic and other uses.<sup>[1]</sup> *Pharmacokinetics* encompasses all the ways that the body manipulates a drug, including absorption, distribution, metabolism, and excretion. *Pharmacodynamics* describes the biochemical and physiologic effects of the drug and its mechanism of action (Fig. 20-1). The terms defined in this chapter are summarized in Table 20-1.

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**Figure 20-1** Overview of the interaction of pharmacokinetics and pharmacodynamics for anti-infective agents. Rights were not granted to include this figure in electronic media. Please refer to the printed book.

(From Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1-12.)

**TABLE 20-1 -- Quick Reference Pharmacologic Abbreviations and Their Definitions**

Type of Term	Abbreviation	Definition
<b>Pharmacokinetics</b>		
Absorption	F	Bioavailability; absolute bioavailability
	K <sub>a</sub>	Absorption rate constant
Distribution	V <sub>d</sub>	Volume of distribution
	V <sub>d</sub> /F	Apparent volume of distribution

Type of Term	Abbreviation	Definition
	$V_{ss}$	Volume of distribution at steady-state
	$V_{ss}/F$	Apparent volume of distribution at steady-state
	$CL_D$	Distributional clearance
	$CL_D/F$	Apparent distributional clearance
Metabolism	$K_m$	The drug concentration at which the rate that an enzyme system can metabolize a drug is half of $V_m$ (Michaelis-Menten type metabolism [saturable metabolism])
	$V_m$	Maximal metabolic capacity (Michaelis-Menten type metabolism [saturable metabolism])
	CYP	Cytochrome P-450 enzyme systems
Elimination	$CL_r$	Renal clearance
	$CL_{nr}$	Nonrenal clearance
	$CL_{nr}/F$	Nonrenal oral clearance
	$CL_T$	Total clearance
	$CL_T/F$	Total oral clearance
	$T_{1/2}$	Half-life
<b>Pharmacodynamics</b>		
	$MIC_{90}$	Minimal inhibitory concentration for 90% of isolates
	$EC_{50}$	Effective concentration for 50% of all isolates
	MPC	Mutant prevention concentration
	MSW	Mutant selection window
	$IC_{50}$	Inhibitory concentration for 50% of isolates
	$C_{max}/MIC$	Peak antimicrobial serum concentration-to-MIC ratio (concentration-dependent killers)
	$AUC/MIC$	24-hour area under the serum antimicrobial concentration versus time curve-to-MIC ratio
	AUIC	24-hour area under the inhibitory curve
	$T_{1/2}$	Half-life
	$T_{>MIC}$	Time that serum antimicrobial concentrations are above the organism's MIC (time-dependent killers)
	SBT	Serum bactericidal titer (concentration)
	IQ	Inhibitory quotient = ratio of rough serum concentration to $IC_{50}$
	PAE	Postantibiotic effect

## Pharmacokinetics

### PHARMACOKINETIC MODELING

Pharmacokinetic drug data may be analyzed by noncompartmental or compartmental methods. Noncompartmental analysis makes no assumption of the physiologic distribution or elimination of a drug. *Noncompartmental* analysis simply serves as a description of drug behavior in biologic fluids, most commonly serum or plasma. *Compartmental* analysis offers the potential to broaden the appreciation of the drug by providing more insight into physiologic distribution and potential elimination pathways. The latter may be linear, such as renal elimination, or nonlinear, such as hepatic elimination. Compartmental analysis can compensate best for errors in investigational procedures (i.e., sampling errors, missing values). Compartmental analysis is more amenable to population analysis, in which prior information about the pharmacokinetic and pharmacodynamic behaviors of a drug in the target population is incorporated into the analysis.

Compartmental modeling requires exploration of several candidate models (e.g., one-compartment model, two-compartment model), which can be selected initially after visual inspection of the plots of drug concentration versus time, but in the end, is defined by statistical guidelines. All models are defined by combinations of parameters depending on the route of administration, biologic fluids collected, chemical analyses performed, and other factors. The model that minimizes the statistical error in curve fitting ultimately is selected as the final model. The following sections describe commonly modeled parameters associated with the pharmacokinetics literature.

### ABSORPTION

Absorption of a drug into the systemic circulation occurs anywhere that it is administered except when it is

administered directly into a physiologic fluid compartment (e.g., bloodstream, cerebrospinal fluid). This definition includes intramuscular, subcutaneous, or topical administration and absorption from the gastrointestinal tract after oral, rectal, or tube administration. The amount of drug that reaches the systemic circulation is expressed as a percentage of the total amount that could have been absorbed. This percentage is defined as the drug's *bioavailability*, commonly described in the literature by the term *F*. It also may be reported as *absolute bioavailability*, a more accurate value that is determined by direct comparison of an intravenous form of the drug with the extravascularly administered form. By definition, most (but not all) intravenous forms of a drug are 100% bioavailable because all of the administered dose enters the bloodstream. Drugs that are not 100% bioavailable intravenously are often esters that need to be cleaved for activation, with elimination of the ester form of the drug from the body before it can be activated (generally by renal elimination). Many other pharmacokinetic values depend on bioavailability (e.g., clearance, volume of distribution) for drugs that need to be absorbed.

Absorption is a dynamic process. Depending on the dosage form, a drug's absorption and its bioavailability can vary. Oral absorption can be saturable or nonsaturable with factors such as acid degradation in the gut, gut metabolism by drug-metabolizing enzymes, efflux transporters such as p-glycoprotein inhibiting absorption, or concentration-dependent solubility determining the rate and extent of absorption. Other factors that can affect absorption and bioavailability are drug interactions with other compounds or food that may bind the drug and prevent it from being absorbed or a disease state that may affect adversely the site of absorption (i.e., diarrhea, parasites, ileus, ulcerative colitis).

In any case, the rate at which the drug is absorbed is termed the *absorption rate constant* ( $K_a$ ).

A factor commonly associated with a decrease in the bioavailability of a drug (i.e., the amount that gets into the systemic circulation) is the first-pass effect. Drugs that are absorbed from the small intestine can be affected by the first-pass effect of the liver because the circulation leading away from these sites (portal vein circulation) passes through the liver immediately. Drugs administered via other sites (e.g., rectally [variable], intramuscularly, intravenously) usually are not associated with a first-pass effect and can have higher bioavailability because they are not affected immediately by the liver's metabolic capacity.

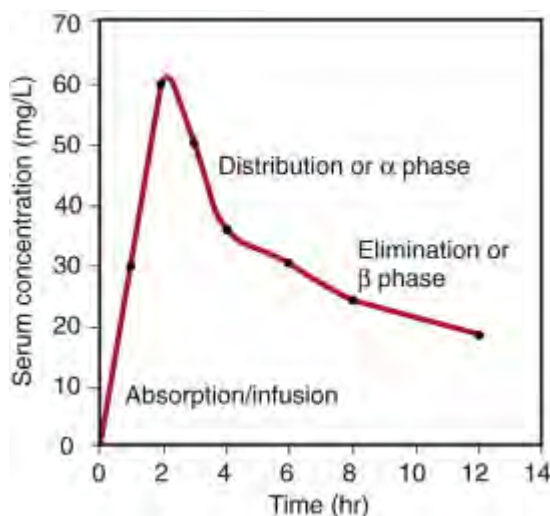
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## Distribution

Distribution of a drug is described most commonly by the *volume of distribution* ( $V_d$  or  $V_d/F$ ). The volume of distribution is not a real or physiologic volume, but rather a value that relates drug concentration in the system to the amount of drug present in that system. Factors that alter the volume of distribution include lipid solubility, partition coefficient of the drug between different types of tissues, blood flow to tissues, pH, and binding to biologic material (e.g., plasma proteins, cellular components).<sup>[2]</sup>

Drugs with small distribution volumes have limited distribution, whereas drugs with large distribution volumes are distributed extensively throughout the body. A drug with a 5-L volume of distribution in an adult would be restricted to the circulatory system. If the volume of distribution is between 10 and 20 L, the drug distributes into extracellular compartments. If the volume of distribution is on the order of 25 to 30 L, intracellular distribution is implied. Distribution volumes of approximately 40 L suggest distribution within whole-body fluid. In rare circumstances, distribution volumes may be measured in hundreds or even thousands of liters. These large volumes suggest either “deep” tissue deposition in peripheral compartments (e.g., fat) or extensive binding to biologic structures (e.g., tissue protein, organelles). When a steady state has been achieved after multiple doses of a medication, the *total volume of distribution* is referred to as the  $V_{ss}$ . This value represents the sum of the distribution volumes from each of the identified physiologic compartments.

After intravenous administration of a drug, the concentration rapidly reaches a peak before beginning to decline. Distribution and elimination are two factors that affect the extent of the peak concentration and the rate of decay. Usually distribution is completed sooner than elimination. This situation results in two phases in the concentration versus time plot (Fig. 20-2). The first phase, or  $\alpha$  phase, is usually short and represents mixing of the drug throughout the circulatory system and distribution into rapidly equilibrating tissues. The second phase, or  $\beta$  phase, is usually a reflection of terminal elimination and is the phase from which the terminal half-life ( $T_{1/2}$ ) is calculated. Occasionally, more than two phases may be observed; this usually indicates further distribution into slowly equilibrating tissues. An understanding of distribution and elimination is important when applying pharmacokinetics to therapeutic drug monitoring. An example is aminoglycosides. In the use of single daily dose therapy, nomograms and rules have been constructed to assist in dosing. These nomograms and rules were devised, however, using assumptions of distribution of the drugs based on smaller doses. With the use of larger doses of aminoglycosides, distribution time is increased, and many popular nomograms and rules for dosing these agents once a day are subsequently in error because the original assumptions do not apply to high doses.<sup>[3]</sup>



**Figure 20-2** A graphic example of the serum concentration versus time profile of a typical two-phase or two-compartment drug during the absorptive-infusion, distributive, and elimination phases.

The rate at which a drug moves from the blood to tissues is described by the *distributional clearance* ( $CL_D$  or  $CL_D/F$ ). Just as total body clearance describes the volume of blood from which a drug is eliminated per unit of time, distributional clearance describes the volume of blood from which a drug is transferred into a tissue or compartment per unit of time. Distributional clearance is a bidirectional process reflecting the equilibrium in movement from blood to tissue and from tissue to blood. When the drug has moved into a tissue compartment, the local tissue concentration is a function of the amount of drug located in the tissue and the tissue volume of distribution, also known as the *volume of the peripheral compartment* ( $V_p$ ). These volumes can be estimated only by mathematical modeling because it is unusual to be able to collect biologic specimens from peripheral compartments and assay the drug concentration.

Many drugs bind to serum proteins, especially albumin or  $\alpha_1$ -acid glycoprotein. Similar to other classes of drugs, antimicrobial agents range from highly to poorly protein bound. Theoretically, protein binding is an important consideration for antimicrobial agents because only unbound drug is available to exert antimicrobial activity.<sup>[4]</sup> Changes in the unbound fraction of drug may be caused by displacement from other drugs, changes in serum protein concentrations, or accumulation of endogenous substances, such as free fatty acids. Changes in the unbound fraction typically do not lead, however, to significant changes in free drug concentration due to various equilibrium processes. Although changes in protein binding may alter pharmacokinetic behavior of an antimicrobial agent, it is unlikely that substantial changes in pharmacodynamics would occur.<sup>[5]</sup>

## METABOLISM AND BIOTRANSFORMATION

Drugs and other compounds are metabolized by a variety of reactions. Although traditionally drug metabolism was thought to occur in the liver, other organs also have the ability to metabolize drugs.

Because drug metabolism requires the presence of enzymes, the principles of Michaelis and Menten can be applied to drug metabolism. Michaelis and Menten showed approximately 90 years ago that enzyme systems have a finite capacity to metabolize substrate. Although all routes of drug metabolism are saturable, if the doses and concentrations at the site of metabolism do not exceed the maximal rate of metabolism ( $V_{max}$ ), the metabolic system appears to follow linear pharmacokinetics. If the dose exceeds the amount that can be metabolized, drug accumulation can occur, leading to high serum tissue concentrations. These high concentrations can result in toxic side effects. If a daily dose is given that is lower than what the body can eliminate, low concentrations may be seen. These *dose-dependent kinetics* (also called *Michaelis-Menten*, *zero-order*, or *saturation kinetics*) mean that when saturation of the ability to metabolize or otherwise eliminate the drug in a 24-hour period is reached, small dosage increases may produce large, disproportionate increases in serum concentrations. Conversely, if a daily dose is higher than what can be metabolized in 24 hours and results in high serum concentrations, small reductions in the dose may cause large reductions in the serum concentration.

Drug metabolism reactions are classified as either phase I or phase II reactions. *Phase I reactions* can inactivate, activate, or convert an active substrate into another active substrate with activity that is higher, lower, or equal to that of the parent compound. Generally, phase I reactions cause inactivation of substrate, with the resulting compound being more polar than the parent. Making the metabolite more polar facilitates its elimination from the body. Phase I reactions include dealkylation, hydroxylation, oxidation, and deamination. Generally, phase I reactions are governed by the cytochrome P-450 system.

*Phase II reactions* involve conjugation of the parent compound with larger molecules, which increases the polarity of the parent to ready it for excretion. Although phase II reactions generally lead to inactivation of the parent compound, occasionally conjugation increases the potency of the parent compound. When the conjugated compounds are secreted into the intestine, enzymatic cleavage may occur with release and reabsorption of the active parent compound, a phenomenon called *enterohepatic recirculation*. Conjugation reactions include glucuronidation, sulfation, and acetylation.

## CYTOCHROME P-450 SYSTEM

Phase I reactions generally are under the control of the *cytochrome P-450 (CYP) system*. CYP enzymes are heme-containing proteins that are localized in the endoplasmic reticulum of a variety of cell types, most abundantly in the liver. CYP enzymes are controlled by a superfamily of genes that are classified into families according to their amino acid sequences. Each family is divided further into subfamilies. The term *CYP3A4* designates a mammalian enzyme (CYP) family 3, subfamily A, gene 4. Fourteen families of CYPs have been found in mammals, including 26 subfamilies, of which 20 have been mapped in the human genome. Currently, data exist to describe 33 human CYP enzymes in 20 families.<sup>[6]</sup>



CYP enzymes are affected by many factors that stimulate or inhibit their ability to metabolize drugs. Genetic factors have been shown to result in a phenomenon called *polymorphism*. Simply put, polymorphism means that individuals vary in their genetically determined ability to metabolize CYP substrate. For some CYP enzymes, such as CYP2D6, distinct “poor” and “extensive” metabolic patterns exist in a population; in a white population, 4% to 6% are poor metabolizers, and the rest are extensive metabolizers. CYPs such as CYP2C9, CYP2C19, CYP2A6, and CYP2B6 also show genetic polymorphism. These CYPs are important in drug metabolism. For other CYPs, such as CYP3A, genetic polymorphism has been described; however, the significance of this continues to be confusing. These phenomena have important implications for anti-infective agents, for which efficacy against infecting organisms and toxicity to the host are determined by the pharmacokinetics of the agent and its resultant pharmacodynamic effect.

Other factors that have been investigated for their effects on CYP enzymes include sex, disease state, age, and menstrual cycle. In general, clinically significant differences related to sex and menstrual cycle (i.e., mid-follicular versus mid-luteal phase) have not been observed. Age and disease state effects are not clear. In infections, cytokines released during acute infection can cause inhibition of CYP activity. This may be the case with acute and chronic infections, such as human immunodeficiency virus (HIV) or with infections in hospitalized patients.<sup>[7]</sup>

Clinically, drug, food, disease, and herbal effects on the CYP system may translate into inhibition, activation, or induction of metabolism. Induction of CYP results in increased production of the protein and a resultant increase in the ability to metabolize specific compounds. An example is the induction by rifampin of CYP3A with a subsequent increase in the metabolism of protease inhibitors. Many inducers of CYP enzymes also induce phase II conjugation reactions and transporters. In addition, a phenomenon called *allosteric activation of drug-metabolizing enzymes* has been described. At present, it is unclear if classic inducers of drug-metabolizing enzymes also cause allosteric activation to increase the efficiency of these enzymes. The implication for increased substrate metabolism as it applies to anti-infective therapy is the development of resistance.

Inhibition of CYP activity occurs through reduction of enzyme production or competition for CYP substrate. Generally, persons with increased enzyme activity exhibit a greater inhibition of the CYP system with an inhibiting agent than do persons with less activity. Enzyme inhibition may result in increased pharmacodynamic effect, with the potential not only for greater efficacy but also for greater toxicity. This inhibitory process may be used in the clinical setting advantageously. Ritonavir can be used to decrease the activity of CYP3A in the gut, allowing greater absorption of other protease inhibitors such as tipranavir and darunavir (through a reduction in the first-pass effect) and reducing the overall cost of therapy. Clinically, a combination of ritonavir and lopinavir has been marketed to take advantage of this beneficial drug interaction.

Quantification of CYP activity has been performed through the use of genotyping and phenotyping. Genotyping identifies the alleles present in the DNA of an individual patient. From this allele identification, a prediction of genetically determined CYP activity can be made. Because genetically determined CYP activity also is affected by exogenous influences (e.g., drugs, environmental pollutants, cigarette smoke), phenotyping has shown more promise for determining individual CYP activity. A relatively innocuous agent is administered as a single dose to a subject, and urine, blood, or breath analysis ensues. These techniques, although still under development, are beginning to be used in the clinical setting in an attempt to optimize drug dosing. Phenotyping of many drug-metabolizing enzymes can be performed simultaneously using a multidrug cocktail.<sup>[8]</sup>

To date, most drugs that are metabolized by phase I enzymes have been shown to be metabolized by five primary CYP enzymes. In decreasing order of potency for drug metabolism, they are CYP3A, CYP2D6, CYP2C, CYP1A2, and CYP2E1. Although a complete discussion of the CYP system is beyond the scope of this chapter, many of the newer anti-infectives, particularly antiretroviral agents, can induce or inhibit CYP enzymes, and in many cases they are substrates for CYP enzymes and are affected by changes in CYP activity. A thorough understanding of the CYP system is important to optimize efficacy and minimize toxicity of these agents.

As mentioned, the liver is not the only place in the body where metabolism occurs. Metabolism and detoxification of foreign substances can occur in most other organ systems.

## ELIMINATION

Elimination of a foreign substance from the body occurs via two main mechanisms of excretion. *Renal clearance* ( $CL_r$ ) describes the rate at which the body eliminates a substance via the kidneys, through various methods, including glomerular filtration, tubular secretion (an energy-dependent process), and passive diffusion. Different compounds are eliminated by one or more of these processes, and the degree to which a process is used may depend on the saturation of another process by the compound. Tubular secretion by the kidney is a saturable process, and dose-dependent pharmacokinetics can be shown for substances that undergo tubular secretion as their primary route

of elimination. Recent data suggest that transporters such as P-glycoprotein play an important role in tubular secretion of some drugs. Elimination through a dialysis procedure (hemodialysis or peritoneal dialysis) also can be construed as a form of renal elimination because these processes are acting as an artificial kidney.

*Nonrenal clearance* ( $CL_{nr}$  or  $CL_{nr}/F$ ) is a generic term that describes the sum of clearance pathways that do not involve the kidneys. These mechanisms may involve the biliary tree (e.g., ceftriaxone) or the intestine (e.g., azithromycin). Other, uncommon mechanisms can be used, such as elimination of alcohol through the skin and lungs (respiration) and ionization, DNA chelation, and inactivation of aminoglycosides by the sputum in cystic fibrosis patients with elimination through expectoration.

Renal and nonrenal clearance rates are combined to determine the rate at which a drug is eliminated from the body, known as *total body clearance* ( $CL_T$ , or  $CL_T/F$  for *total oral clearance*). Clearance also affects the *half-life*. The half-life of a compound is the amount of time required for the blood concentration of the compound to decrease by half. This time can be minutes or a day or more. Most pharmacologists consider that a *steady-state concentration* of a drug has been achieved when the patient has been taking the drug for a period equal to at least five to seven half-lives (e.g., 5 to 7 days for a drug with a half-life of 24 hours). Similarly, a drug is thought to have been eliminated almost completely when the time span of five to seven half-lives has passed since the final dose of the drug. Half-lives vary from patient to patient and often are reported as ranges. Changes in end-organ function or protein binding also can alter the half-life of a drug.

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## Pharmacodynamics

### ANTIMICROBIAL ACTIVITY

An antimicrobial agent may inhibit growth and replication (*static*) or cause bacterial cell death (*cidal*). Interference in the development of a bacterial cell wall or membrane (e.g.,  $\beta$ -lactams, vancomycin) results in cell lysis and death from intolerably high internal osmotic pressure or destruction by autolytic enzymes. Antimicrobials that inhibit nucleic acid (e.g., quinolones) or protein synthesis (e.g., aminoglycosides, macrolides-azalides) also lead ultimately to cell death. In contrast, changes in bacterial physiology, such as inhibition of folic acid synthesis (e.g., sulfonamides), may cause only inhibition of bacterial growth.

Another factor that affects whether a drug is bacteriostatic or bactericidal is the antimicrobial concentration at the site of action. Antimicrobials may be bacteriostatic at low concentrations but bactericidal at high concentrations. These inhibitory and bactericidal concentrations have been used to quantitate the activity of an agent against an organism. Most commonly, the *minimal concentration that is inhibitory for 90% of all isolates* of a bacterial species ( $MIC_{90}$ ) and the *inhibitory or effective concentration for 50% of all isolates* of a strain of virus ( $IC_{50}$  or  $EC_{50}$ ) have been used. Although these parameters are helpful, they do not provide information on the time course of activity. In addition, they do not provide information on the potential for persistent anti-infective activity after the concentration at the site has decreased below the inhibitory level or on the interaction of the immune system with the drug.

A more recent concept in microbiologic testing is being discussed increasingly in the literature. The concept of the *mutant prevention concentration* and *mutant selection window* has been used to investigate the relationship of drug exposure to the development of resistance.<sup>[9]</sup> Mutant prevention concentration indicates the concentration that prevents bacterial mutation that leads to the development of resistance. Mutant prevention concentration appears to be different for different organisms and different drugs. Mutant selection window is the period of exposure that is below the mutant prevention concentration of the organism but above the MIC. It is thought that the time in the mutant selection window can determine the development of resistance for an organism to an antibiotic.<sup>[10,11]</sup> To date, much of this work has been performed with the concentration-dependent killing drugs in the fluoroquinolone class. Although interesting, these concepts have not been applicable to the clinical setting. Antimicrobial agents are given in combination for several reasons, including severe or life-threatening infections, empirical therapy when the pathogen is unknown, avoidance of resistance, and the desire for synergistic activity.<sup>[12]</sup> Data on avoidance of resistance or the improved outcome in the use of antibiotic combinations are conflicting, however. *Synergism* is defined as activity of two antimicrobials given together that is greater than the sum of activity had the two agents been given separately.  $\beta$ -Lactams commonly are given in combination with aminoglycosides to take advantage of synergy against *Pseudomonas* or *Enterococcus* spp. Trimethoprim and sulfamethoxazole are combined to provide synergy through inhibition of sequential steps in folic acid synthesis. For antiretroviral therapy, targeting multiple sites leads to a reduction in viral resistance and a faster decline in viral load. This concept is being applied to the new hepatitis C drugs under development.

Combinations of antimicrobial agents may not always be beneficial. *Antagonism* between agents occurs when one agent diminishes the activity of another.  $\beta$ -Lactams require a normally growing bacterium to inhibit cell wall synthesis. Concomitant administration with a bacteriostatic agent (e.g., a tetracycline) that inhibits cell growth prevents the  $\beta$ -lactam from exerting its bactericidal activity. In this case, the action of the  $\beta$ -lactam has been antagonized. Most antimicrobial combinations result in little or no change in activity of the two agents, an interaction termed *indifference*.

### METHODOLOGY FOR THE STUDY OF PHARMACODYNAMIC EFFECTS OF ANTI-INFECTIVE AGENTS

#### In Vitro Models

The traditional model used to study pharmacodynamic effects of anti-infective agents is the "hollow fiber model" system.<sup>[13]</sup> In this system, broth is used as a growth medium; bacteria are exposed to predetermined concentrations of antibiotics that are "eliminated" from the system in such a manner as to simulate pharmacokinetically determined excretion.<sup>[14]</sup> Although these models offer control over bacterial inoculum and drug exposure (in terms of concentration



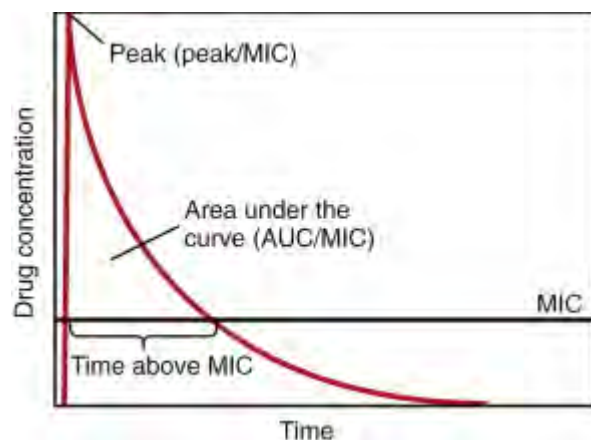
and time), they do not assess the effects of the immune system on organism killing or growth inhibition. They do assess the relationship of free drug concentrations to effect, assisting in the development of relationships of protein-bound drug in humans.

## Animal Models

Animal models have used a variety of species, often with the animals rendered neutropenic before infection. Craig and colleagues<sup>[15-17]</sup> showed that the presence of neutrophils may affect antibacterial activity with fluoroquinolones, penicillin, clindamycin, and doxycycline. Animal infectious disease models have been developed to mimic human infections. Animal models allow for frequent sampling of blood and tissue and allow a broad dosage range to be investigated along with a wide range of organism inocula, allowing investigators to study the effects of variation in a single parameter at a time. Problems with animal models include lack of standardization of inocula size (often large inocula are required to produce infection) and the faster rate of drug elimination in animals compared with humans, which leads to the use of unusual dosing regimens in an attempt to mimic human drug exposure. Recently, the use of immunocompetent animals has been applied to attempt to develop more realistic guidelines for pharmacodynamic targets in infected patients, many of whom are not neutropenic.

## Human Trials

To date, most human trials<sup>[18-29]</sup> reported have been retrospective analyses of prospectively collected data, with only one study, that of Preston and co-workers,<sup>[30]</sup> being performed prospectively. These trials have used three measures of assessment to relate antimicrobial pharmacokinetics to pharmacodynamics: (1) clinical outcome (cure/fail or improved); (2) eradication of bacteria from the site of infection or reduction in virus concentration (load) in blood or other sites, or both; and (3) improvement in surrogate markers of infection, such as temperature or leukocyte count. The disadvantage of these types of trials is the retrospective nature of their analyses; prospective trials using all three criteria are needed. Most retrospective trials that have been published have used one of three antimicrobial pharmacodynamic outcome parameters (defined and discussed later):  $C_{\max}/\text{MIC}$ ,  $\text{AUC}/\text{MIC}$ , or  $\text{T} > \text{MIC}$  (Fig. 20-3). Many trials have not reported free drug pharmacodynamic indices. Because free drug is active drug, correction for protein binding is important unless the binding is very low. Few trials have focused on relationships of drug exposure to toxicity or on the development of resistance.

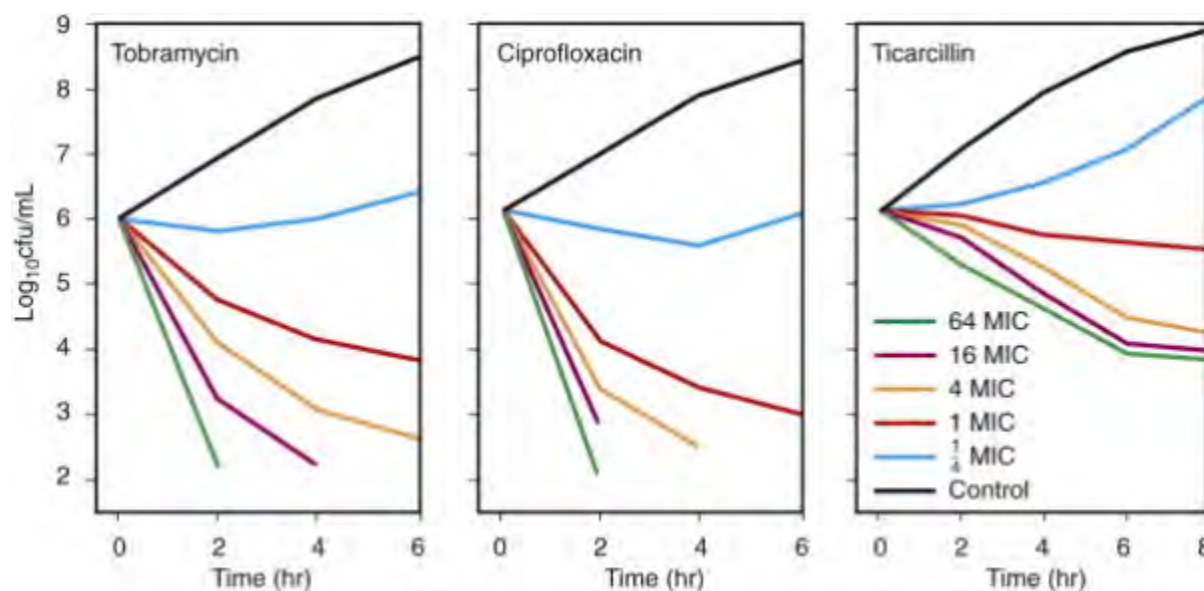


**Figure 20-3** Common antibiotic pharmacokinetic and minimal inhibitory concentration (MIC) pharmacodynamic relationships.

## Concentration-Dependent Killing Agents

Concentration-dependent killing agents (e.g., fluoroquinolones, aminoglycosides, macrolides, azalides, ketolides, metronidazole, daptomycin, and oritavancin) eliminate bacteria when their concentrations are well above the MIC of the organism. When the ratio of the concentration at the site of infection to the MIC is increased further, greater killing occurs. This concept is illustrated in Figure 20-4 for tobramycin and ciprofloxacin against *Pseudomonas aeruginosa*.<sup>[31]</sup> As the ratio of drug concentration to MIC increases from 0.25 to 64, bacterial killing continues to increase. In addition, these agents exhibit postantibiotic effect (PAE) (discussed later): Growth inhibition continues for a varying period after the concentration at the site of the bacteria has decreased below the MIC for the antimicrobial agent. In vivo the  $C_{\max}/\text{MIC}$  ratio—the maximal serum concentration of the drug ( $C_{\max}$ ) divided by the MIC—is the clinical correlate used as the pharmacodynamic predictor for outcome for concentration-dependent killing agents. In

clinical trials, the AUC/MIC ratio—the area under the 24-hour serum concentration versus time curve (AUC) divided by the MIC—also has been correlated with improved outcome.<sup>[18-30]</sup> This finding is not surprising because  $C_{max}$  and AUC are covariates: When  $C_{max}$  increases, AUC increases also. More recent data have suggested that for drugs such as fluoroquinolones, different goals for AUC/MIC ratios are required for gram-positive pathogens compared with gram-negative pathogens.<sup>[32-34]</sup> In general, free drug AUC/MIC ratios of 30 are desired for maximal kill of *Streptococcus pneumoniae*, whereas AUC/MIC ratios of greater than 100 are desired for gram-negative pathogens.



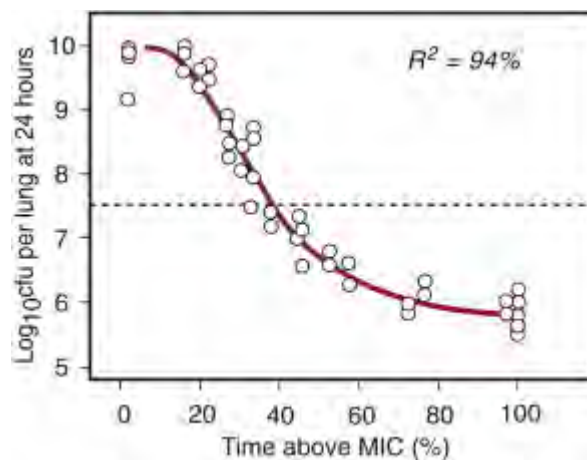
**Figure 20-4** Time-kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration (MIC).

(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. *Scand J Infect Dis*. 1991;74:63-70.)

### Time-Dependent (Concentration-Independent) Killing Agents

Time-dependent killing agents kill gram-negative bacteria only when the concentration at the site of the bacteria is higher than the MIC of the organism; this is shown for ticarcillin against *P. aeruginosa* in Figure 20-4. Generally, when the concentration at the bacterial site is more than four times higher than the MIC, the additional killing that occurs is modest.

Some authors have attempted to use the time during which the serum drug concentration is greater than the MIC (time above MIC [ $T > MIC$ ]) as the dynamic parameter to predict efficacy for these anti-infectives.<sup>[11,26]</sup> One study in the neutropenic mouse model using *Klebsiella pneumoniae* lung infection and treatment with cefotaxime suggested a strong correlation of 0.94 in terms of reduction of bacterial colony counts versus  $T > MIC$  (Fig. 20-5).<sup>[35]</sup> An additional report of many animal studies with *Streptococcus pneumoniae* in which treatment was performed with penicillins or cephalosporins showed that when  $T > MIC$  was 20% or less of the dosing interval, mortality was 100%. In contrast, a mortality rate of 0% to 10% occurred when serum concentrations were above the MIC for longer than 40% to 50% of the dosing interval.<sup>[11,36]</sup> Time-dependent killing agents include the penicillins, cephalosporins, aztreonam, vancomycin (for which AUC/MIC is predictive), carbapenems, macrolides, linezolid, tigecycline, doxycycline, and clindamycin.



**Figure 20-5** The relationship of time above the minimal inhibitory concentration (MIC) and the reduction in bacterial count in a neutropenic mouse model of *Klebsiella pneumoniae* for cefotaxime.

(From Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn Microbiol Infect Dis.* 1995;22:89-96.)

### Ratio of Maximal Serum Concentration to Minimal Inhibitory Concentration

The  $C_{\max}/\text{MIC}$  ratio has been used in animal studies and retrospective analyses of clinical trials to predict the outcome of antimicrobial therapy. This pharmacodynamic parameter applies to concentration-dependent killing agents, such as aminoglycosides and fluoroquinolones. In addition to the prediction of efficacy, the  $C_{\max}/\text{MIC}$  ratio has been used in vitro to predict the development of bacterial resistance.<sup>[14]</sup>

There have been five studies in humans using the  $C_{\max}/\text{MIC}$  ratio to predict outcome, four with aminoglycosides and one with levofloxacin. These trials used either clinical response (measured by improvement with therapy or by improvement of surrogate markers) or cure/fail as the outcome measure.

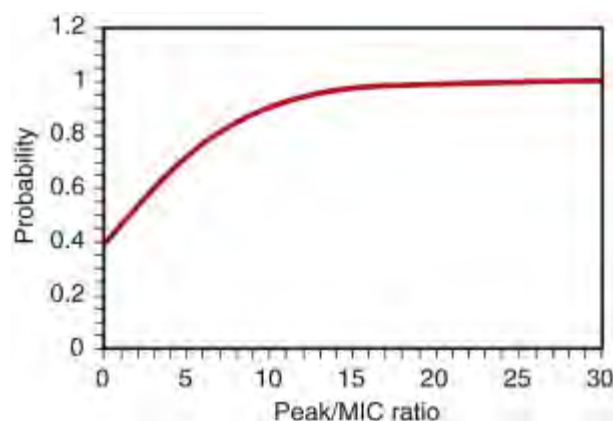
The trial by Keating and colleagues<sup>[18]</sup> examined neutropenic cancer patients. In this trial, patients were assigned randomly to receive continuous infusions of one of three aminoglycoside antibiotics plus carbenicillin. When the ratios of aminoglycoside concentration to MIC were examined, a relationship was noted for response rate. For mean ratios of 1 to 4, 4 to 10, and greater than 10, response rates were 57%, 67%, and 85%.

The study by Moore and colleagues<sup>[21]</sup> often is quoted as the basis for use of a  $C_{\max}/\text{MIC}$  ratio target of 10 or greater in the clinical setting. In this retrospective analysis of prospectively collected data, the investigators examined 236 patients with a variety of gram-negative infections treated with aminoglycoside antibiotics on an every-8-hour basis. They found that the odds ratio for improved clinical response increased as the  $C_{\max}/\text{MIC}$  ratio increased, with a mean ratio of  $6.6 \pm 3.9$  in patients who responded and  $4.6 \pm 3.6$  in patients who did not respond. This trial had a majority of patients with urinary tract infections (approximately 60%), however. Because aminoglycosides are known to concentrate 5-fold to 100-fold in the urine, the relationship of  $C_{\max}$  to MIC in this study may be meaningless. It was impossible to separate patients with other disease states to determine the optimal  $C_{\max}/\text{MIC}$  ratio needed to elicit response. In addition, the authors did not consider concurrent antibiotic therapy in their model, so it is difficult to assess the contribution of other antimicrobial agents to the response rate.

Deziel-Evans and associates<sup>[22]</sup> examined a variety of pharmacodynamic predictors in 45 adult patients treated with aminoglycosides. In this trial, a  $C_{\max}/\text{MIC}$  ratio greater than 4 was noted to improve clinical response.

A more recent study by Kashuba and co-workers<sup>[27]</sup> described the relationship between  $C_{\max}$  and MIC in 78 patients with documented gram-negative pneumonia. The authors examined cure or failure along with two surrogate markers of infection, temperature and leukocyte count. There was a high cure rate for well-documented gram-negative pneumonia (92%), and no pharmacodynamic variable could be correlated with cure/fail, probably because of the small number of failures. The researchers did examine the  $C_{\max}/\text{MIC}$  ratio, however, in relation to the time required for the patient to become afebrile ( $\leq 37.9^\circ\text{C}$ ) and the time to normalization of the leukocyte count. As shown by the probability graph in Figure 20-6, a strong relationship was noted between  $C_{\max}/\text{MIC}$  ratio and time to normalization of fever. A ratio of 10 or greater gave a 90% probability of normalization of temperature by day 7. Similar graphs can be constructed for

earlier and later days into therapy. Generally, these probability graphs show that an increased  $C_{\max}/\text{MIC}$  ratio yields an earlier and greater chance of surrogate marker normalization; this does not take into account the probability of toxicity with higher  $C_{\max}/\text{MIC}$  ratios. One strength of this trial is that the authors statistically analyzed concurrent antibiotic therapy, which was not a significant variable for prediction of surrogate response or cure/fail.



**Figure 20-6** Probability graph for temperature normalization for peak antimicrobial serum concentration-to-minimal inhibitory concentration (peak/MIC) ratio for aminoglycosides in 78 patients with culture-proven, nosocomial gram-negative pneumonia.

(Adapted from Kashuba ADM, Nafziger AN, Drusano GL, et al. *Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother.* 1999;43:623-629.)

To date, one study has addressed the use of the  $C_{\max}/\text{MIC}$  ratio with the quinolone levofloxacin. Preston and co-workers<sup>[30]</sup> prospectively examined 134 evaluable patients with bacterial infections of the respiratory tract, the urinary tract, or the skin who were treated with levofloxacin monotherapy. All 134 patients had serum concentrations obtained along with identified microorganisms with an MIC determined. In terms of clinical outcome,  $C_{\max}/\text{MIC}$  ratio and AUC/MIC ratio were found to be the most important predictors of outcome; the correlation of these two pharmacodynamic parameters was 0.942. The investigators did not find any failures in patients with urinary tract infections, illustrating that the  $C_{\max}/\text{MIC}$  ratio may not be a valid predictor in patients receiving drugs that concentrate in the urine. In terms of microbiologic response, the  $C_{\max}/\text{MIC}$  ratio was the most important predictor of bacterial eradication. In this study, 26% of infections were due to gram-positive organisms, however, and outcomes for gram-positive and gram-negative organisms were not separated. As shown by in vitro studies, breakpoints of pharmacodynamic indices for efficacy seem to be pathogen specific. AUC/MIC ratios that correlate to efficacy are higher for gram-negative organisms compared with gram-positive organisms. As noted subsequently (AUC/MIC section), another study has correlated fluoroquinolone exposure as measured by AUC/MIC ratios to efficacy and bacterial eradication.

These retrospective analyses of prospective data illustrate the potential importance of the  $C_{\max}/\text{MIC}$  ratio for concentration-dependent killing agents. Because none of the four trials with aminoglycosides used single daily dosing of these agents, however, it is not possible to extrapolate these data to support this mode of administration.<sup>[37]</sup>

In terms of prevention of bacterial resistance, only in vitro data using the hollow fiber model exist relating the  $C_{\max}/\text{MIC}$  ratio to resistance. The study of Blaser and co-workers<sup>[14]</sup> examined the  $C_{\max}/\text{MIC}$  ratio for enoxacin and netilmicin against various gram-negative organisms. Regrowth of organisms occurred in all cultures when enoxacin or netilmicin attained ratios lower than 8. On redosing of these antibiotics after bacterial regrowth, no killing was seen because of the development of resistance. A similar study by Marchbanks and associates<sup>[38]</sup> using ciprofloxacin noted the development of resistant *P. aeruginosa* when the organism was exposed to a  $C_{\max}/\text{MIC}$  ratio of 6 compared with no resistance when the  $C_{\max}/\text{MIC}$  ratio was 12, even though both regimens showed adequate rates of bacterial killing. These in vitro data suggest that  $C_{\max}/\text{MIC}$  ratios may be influential in determining the development of bacterial resistance for aminoglycosides and quinolones. A disadvantage of these trials, however, is that they do not account for the role of the immune system in “cleaning up” small numbers of resistant bacteria before they can become pathogenic.

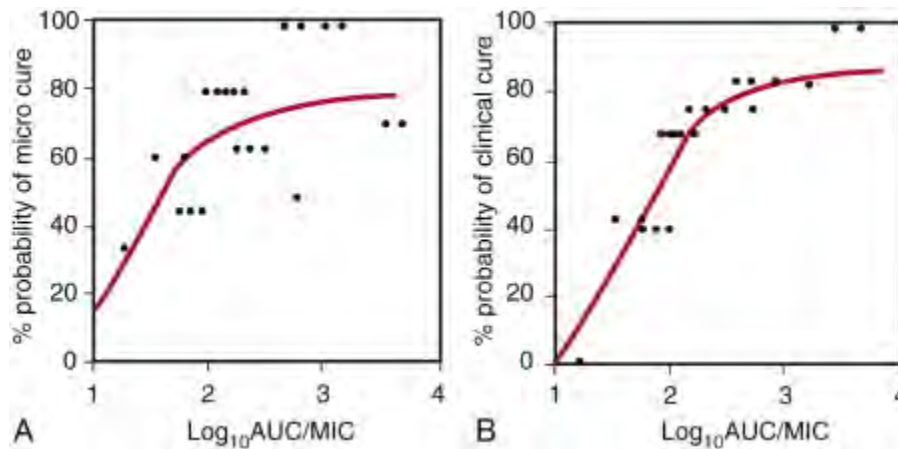
Although the  $C_{\max}/\text{MIC}$  ratios for aminoglycosides and quinolones may be useful, no data to date have examined drug toxicity with higher exposures. A prospective trial to evaluate efficacy and toxicity with pharmacodynamic dosage adjustments is needed.



## Ratio of Area under the 24-Hour Serum Concentration Curve to Minimal Inhibitory Concentration

The AUC/MIC ratio is a measure of total exposure of bacteria to an antimicrobial agent. The AUC/MIC ratio encompasses peak concentration and prolonged exposure, which may be vital for drugs with a long half-life.  $C_{max}/MIC$  and AUC/MIC ratios are difficult to separate in a scientifically designed clinical trial because when the  $C_{max}/MIC$  ratio is high, the AUC/MIC ratio usually is high as well. Both would be found to be statistically predictive of outcome and indistinguishable in terms of which is of primary importance.

Several studies have defined the role of the AUC/MIC ratio as a predictor of bacterial or clinical success. Various pharmacodynamic predictors of outcome were evaluated in 74 acutely ill patients, mostly with nosocomial pneumonia, who were treated with ciprofloxacin. The AUC/MIC ratio, which represents the inverse serum inhibitory titer over time ( $SIT^{-1} \cdot T$ ), was identified as the factor most predictive of clinical and microbiologic success (Fig. 20-7). At an AUC/MIC ratio lower than  $125 SIT^{-1} \cdot hr$  ( $\log_{10} = 2.1 = 125 SIT^{-1} \cdot hr$ ), the probabilities of clinical and microbiologic cure were 42% and 26%, whereas at values greater than  $125 SIT^{-1} \cdot hr$ , the probabilities were 80% and 82%. At an AUC/MIC ratio lower than  $125 SIT^{-1} \cdot hr$ , between 125 and  $250 SIT^{-1} \cdot hr$  ( $\log_{10} = 2.4 = 250 SIT^{-1} \cdot hr$ ), and higher than  $250 SIT^{-1} \cdot hr$ , the median time to eradication was more than 32 days, 6.6 days, and 1.9 days.<sup>[24]</sup> A similar analysis was performed for a small number of patients experiencing an acute exacerbation of chronic bronchitis treated with grepafloxacin.<sup>[29]</sup> At an AUC/MIC ratio less than  $75 SIT^{-1} \cdot hr$ , the probability of clinical cure was 71%, whereas with AUC/MIC ratios greater than  $175 SIT^{-1} \cdot hr$ , the probability of cure was 98%. Clear conclusions cannot be drawn from this study, however, because of the limited sample size. Because ciprofloxacin is approximately 40% protein bound, the data in this study convert to a desired AUC/MIC ratio of 75.



**Figure 20-7** Relationship between 24-hour area under the serum antimicrobial concentration versus time curve-to-minimal inhibitory concentration ratio (AUC/MIC) and clinical (A) or microbiologic (B) cure in 74 patients with nosocomial pneumonia.

(From Forrest A, Nix DE, Ballow CH, et al. *Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother.* 1993;37:1073-1081.)

One study examining levofloxacin in nosocomial pneumonia demonstrated that a total-drug AUC/MIC value greater than 87 correlated with the eradication of gram-negative bacilli ( $P = 0.01$ ). Levofloxacin is approximately 30% protein bound, translating to a free drug AUC/MIC equal to 62. In this study a free drug AUC/MIC greater than 62 resulted in a 90% bacterial eradication rate versus 43% for an AUC/MIC less than 62.<sup>[39]</sup>

A retrospective analysis by Ambrose and colleagues<sup>[40]</sup> in patients with community-acquired pneumonia due to *S. pneumoniae* noted microbiologic response in 64% with free drug AUC/MIC ratios less than 33.7 and in 100% at ratios greater than 33.7. This finding is consistent with in vitro studies with *S. pneumoniae*. In addition, these researchers reported clinical cure of 70% when the free drug AUC/MIC ratio was less than 40 and 92% when the AUC/MIC ratio was greater than 40. No patient-specific pharmacokinetic measures were obtained, however, and fluoroquinolone exposure was determined by using population-derived estimates of clearance.

Response to telithromycin was evaluated in patients with community-acquired pneumonia. The response rate was 91% in patients with an AUC/MIC value greater than 3.375 and 76% in patients with lower AUC/MIC values (OR, 5.9;  $P = 0.002$ ).<sup>[41]</sup> A study examined the relationship of AUC/MIC and response to therapy for *Enterococcus faecium* and methicillin-resistant *S. aureus* (MRSA) bacteremia. In this study 98% of patients in whom total-drug AUC/MIC values

were 185 had favorable clinical outcomes, whereas in those with lower ratios, 79% responded favorably. Additional data from this study in patients with complicated skin and skin structure infections suggested that an AUC/MIC ratio of 110 or greater resulted in a better outcome.<sup>[42]</sup>

Data for tigecycline (a time-dependent killing antibiotic for which AUC/MIC is the predictive pharmacodynamic parameter) have been reported for skin and skin structure infection as well as intra-abdominal infection. In complicated skin infections, with *S. aureus* or group A streptococcal infections, an AUC/MIC ratio of greater than 17.9 was associated with a 100% positive response rate. The response rate below this cutpoint was 50%.<sup>[43]</sup>

In gram-negative intra-abdominal infections an AUC/MIC of greater than 3.1 was associated with an 89% response rate while lower AUC/MIC ratios resulted in a 50% response rate.<sup>[44]</sup>

At this time, it is clear that for different organisms, different free drug AUC/MIC ratios are desirable. Attempts to standardize exposure to one AUC/MIC ratio are erroneous.

The use of the AUC/MIC ratio for the prevention of bacterial resistance is limited to in vitro and animal data. An in vitro study with gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, and trovafloxacin linked AUC/MIC ratios less than 31.7 with significant regrowth and resistance of ciprofloxacin-resistant *S. pneumoniae* strains.<sup>[45]</sup> An in vitro study by Fazili and associates<sup>[46]</sup> showed that an initial population of ciprofloxacin-sensitive *S. pneumoniae* became resistant to ciprofloxacin after 12 hours on ciprofloxacin treatment and after 48 hours on gatifloxacin treatment. Resistance was suppressed when gatifloxacin at an AUC/MIC ratio greater than 50 was used. Because different AUC/MIC ratios correlate with efficacy for gram-negative and gram-positive organisms, breakpoints for resistance with gram-negative organisms are generally higher compared with gram-positive organisms. In an in vitro study with garenoxacin, Tam and co-workers<sup>[47]</sup> showed that AUC/MIC ratios greater than 200 were needed to suppress resistance with *P. aeruginosa*, and ratios greater than 100 were needed with *K. pneumoniae*. AUC/MIC ratios less than 200 and less than 100 for *P. aeruginosa* and *K. pneumoniae* were selected for resistant subpopulations at 48 hours to garenoxacin and ciprofloxacin. In vitro studies with fluoroquinolones evaluating the emergence of resistance showed consistent results that suboptimal dosing of antibiotics may select resistant subpopulations to grow. A study by Jumbe and colleagues<sup>[48]</sup> suggested that for levofloxacin, an AUC/MIC ratio of 157 was necessary for suppression of resistant mutants. However, in this study, the authors using Monte Carlo simulation showed that almost 40% of patients getting ciprofloxacin (400 mg every 8 hours) or levofloxacin (750 mg once daily) would not achieve these suppressant levels.

Clinical studies examining the emergence of resistance with AUC/MIC goals are limited. A retrospective study of 107 acutely ill patients with nosocomial lower respiratory tract infections examined resistance rates with the use of pharmacodynamics.<sup>[49]</sup> Bacterial isolates were separated into four groups: *Pseudomonas* spp., gram-negative organisms resistant to narrow-spectrum cephalosporins, gram-negative rods susceptible to cephalosporins, and a last group that contained the remainder of a diverse number of organisms. Five antimicrobial regimens were evaluated: ciprofloxacin, cefmenoxime, ceftazidime, ciprofloxacin plus piperacillin, and ceftazidime plus tobramycin. The likelihood of developing resistance was greater when ciprofloxacin was used to treat *P. aeruginosa* and at AUC/MIC ratios less than 100. The AUC/MIC ratio was applied to either monotherapy or combination therapy of antibiotics inappropriately, however.  $\beta$ -Lactams have been linked pharmacodynamically to  $T > MIC$ , and the use of a concentration-dependent pharmacodynamic index such as AUC/MIC may not be an accurate prediction of efficacy or resistance.

### Time above Minimal Inhibitory Concentration

$T > MIC$  is a pharmacodynamic parameter that measures how the time that serum drug concentrations stay higher than the MIC for the organism relates to outcomes. This definition usually refers to total drug concentration, although some authors have used free drug concentration in the definition. For intermittent bolus infusions, the parameters  $T > MIC$ , AUC/MIC ratio, and  $C_{max}/MIC$  ratio are interrelated: As  $T > MIC$  increases, AUC/MIC and  $C_{max}/MIC$  ratios do also. It may be difficult to separate the importance of these dynamic parameters, unless a study compares continuous versus intermittent infusions of antimicrobials.

Animal models have shown that  $T > MIC$  is an important pharmacodynamic predictor for penicillins, cephalosporins, carbapenems, monobactams, macrolides, and clindamycin.<sup>[11]</sup> Human studies are sparse, however, in defining this parameter as an important one. The study of Bodey and colleagues<sup>[19]</sup> examined the efficacy of intermittent versus continuous infusions of cefamandole plus intermittent infusions of carbenicillin in neutropenic patients. These investigators showed a slightly higher response rate in the continuous infusion group, but the difference was not significant. Analysis of a subset of patients with cefamandole-susceptible organisms revealed a significant benefit of continuous versus intermittent infusion, although the patient numbers were small.

Schentag and associates<sup>[20]</sup> also noted for cefmenoxime that  $T$  greater than dynamic response concentration (DRC)



(analogous to  $T > MIC$ ) correlated better than the AUC/DRC ratio (analogous to the AUC/MIC ratio) for bacterial eradication from the lung. The results of the retrospective and prospective portions of the study were combined, however. In the retrospective study, no dose adjustments to cefmenoxime were made during treatment, whereas in the prospective study doses were adjusted to achieve time to eradication by day 4. Turnidge<sup>[50]</sup> reanalyzed the data to separate the results of the retrospective study and showed that  $T > MIC$  is the best predictor of outcome compared with the AUC/MIC ratio for this  $\beta$ -lactam. Because presently defined  $T > MIC$  is being extrapolated from neutropenic animal studies and limited clinical studies, establishing the optimal  $T > MIC$  for gram-positive and gram-negative organisms clinically requires further research.

A retrospective analysis by Craig and Andes<sup>[26]</sup> attempted to correlate the pharmacodynamics of antibiotics in the treatment of otitis media. Using retrospective data and free drug calculations, the authors examined  $T > MIC$  and bacteriologic cure for  $\beta$ -lactams, macrolides, and trimethoprim-sulfamethoxazole. They concluded that an 80% to 85% efficacy rate was achieved when the  $T > MIC$  was 40% to 50% of the dosing interval.

Data for oritavancin have been reported. In patients in whom a free drug  $T > MIC$  value greater than 22% of the dosing interval was attained, 93% of patients responded favorably, whereas 76% responded favorably when lesser exposures were achieved (OR, 8.8).<sup>[51]</sup>

Data are available for staphylococcal infections and vancomycin in pediatric patients. Schaad and colleagues<sup>[52]</sup> noted that a peak serum bactericidal titer of 1 : 8 or greater was associated with cure in 16 of 20 patients. Louria and co-workers<sup>[53]</sup> noted cure of staphylococcal infections when the serum bactericidal titer was 1 : 8 or greater (six patients) and failure when the titer was less than 1 : 8 (three patients, although in one, cure was seen after dose escalation). Although animal and in vitro data suggest that for certain antibiotics  $T > MIC$  is an important pharmacodynamic predictor, few data in human studies exist to support this conclusion; it would appear that AUC/MIC is the predictive pharmacodynamic parameter for vancomycin.<sup>[54]</sup>

### Postantibiotic Effect

During in vitro testing of antimicrobials, there may be a delay before microorganisms recover and reenter a log-growth period. This phenomenon is termed the *postantibiotic effect* (PAE). The exact duration of the PAE is species and drug dependent. Aminoglycosides and fluoroquinolones produce in vitro PAEs against gram-negative bacilli of approximately 2 to 6 hours.  $\beta$ -Lactam antibiotics (except for imipenem) produce little or no PAE against gram-negative organisms under identical experimental conditions but generally induce 2-hour PAEs against gram-positive organisms. Other factors that affect the in vitro PAE include combinations of antimicrobials, antimicrobial concentration, duration of antimicrobial exposure, and pH. Potential factors that also may affect the PAE include size of inoculum, type of growth medium, and bacterial growth phase.

Studies in animal models have verified that PAE is not an artifact of in vitro testing. Investigational animal models that have been studied include a neutropenic mouse thigh model, a rabbit meningitis model, a rat endocarditis model, and a guinea pig pneumonia model. These studies showed that an in vivo PAE exists against gram-negative organisms for aminoglycosides, fluoroquinolones, erythromycin, clindamycin, and tetracycline, but not for  $\beta$ -lactams. As in the in vitro studies,  $\beta$ -lactam agents do produce abbreviated PAEs against gram-positive organisms.

The mechanism of the PAE is unknown. Possible explanations include nonlethal bacterial damage induced by the antimicrobial agent and persistence of the antimicrobial at the site of action. When fresh organisms are injected into animals during the PAE period, however, there is rapid and immediate growth, suggesting that the PAE is not caused by persistence of the drug in tissue.

The presence or absence of a PAE has been used to alter antimicrobial dosing schedules. Theoretically, an agent with a long PAE can be dosed less frequently than an antimicrobial lacking a PAE. Alternatively, an agent with little or no PAE may be most effective if it is given as a continuous infusion so that the serum concentration always exceeds the MIC. Dosing strategies such as these are theoretical and require clinical investigation in human studies of sufficient size before implementation into clinical practice.

### Antiretroviral Pharmacodynamics

Pharmacologic differences between patients is an important factor responsible for heterogeneity in the response to antiretroviral therapy. Although many antiretroviral agents are available, the number of treatment options is limited because these drugs generally are used in combinations of three or more. It has been shown that successive antiretroviral regimens do not perform as effectively or for as extensive a duration as the initial regimen. Optimizing success with the first regimen is crucial.

Many variables can confound the pure relationship between one antiretroviral drug and its pharmacodynamic response. Antagonism or synergy between antiretroviral agents, demonstrated in vitro cross-resistance, adherence patterns, and protein binding all can contribute to distort the true relationship between individual drugs and efficacy.<sup>[55]</sup> Despite these obstacles, numerous studies have shown correlations between antiretroviral drug exposure and outcome, as measured by changes in plasma HIV RNA concentrations or CD4<sup>+</sup> T-lymphocyte changes.

Drug exposure is an important determinant of virologic outcome, particularly with protease inhibitors. Plasma clearance, peak plasma concentration ( $C_{max}$ ), trough plasma concentration ( $C_{trough}$  or  $C_{min}$ ), and AUC all have been proposed as determinants of virologic response, and all correlate with each other. Although no study has compared directly all three pharmacokinetic parameters as individual predictors of treatment efficacy, most attention has been focused on the role of trough plasma concentrations in determining virologic outcome.<sup>[56]</sup>

Large interindividual variability exists in the pharmacokinetics of protease inhibitors. Concentration-effect relationships have been shown, however, for indinavir,<sup>[57,58]</sup> saquinavir,<sup>[59-61]</sup> nelfinavir,<sup>[62]</sup> amprenavir,<sup>[63]</sup> and lopinavir.<sup>[64,65]</sup> Adverse effects have been linked to concentrations of indinavir<sup>[66]</sup> and amprenavir.<sup>[63]</sup> Pharmacokinetic-pharmacodynamic relationships also have been established for the nonnucleoside reverse transcriptase inhibitors nevirapine<sup>[67]</sup> (efficacy and toxicity), delavirdine,<sup>[68]</sup> and efavirenz.<sup>[69]</sup> However, recent data have suggested that due to the large intraindividual variability in HIV treatment drugs, the application of therapeutic drug monitoring would be challenging.<sup>[70]</sup>

Defining concentration-effect relationships with nucleoside analogue reverse transcriptase inhibitors is more difficult because these drugs require intracellular phosphorylation to their active triphosphate moieties. Multiple intracellular rate-limited phosphorylation steps and potential cellular membrane efflux transporter activity<sup>[71,72]</sup> result in plasma parent drug concentrations that do not correlate well with intracellular drug concentrations.<sup>[73]</sup> Plasma concentration-effect relationships have been shown, however, in a few patients for zidovudine<sup>[74]</sup> and didanosine.<sup>[75]</sup> Concentration-toxicity relationships have been shown for zidovudine<sup>[76]</sup> and didanosine.<sup>[77]</sup> One investigation showed significant positive correlations between the rate of HIV-1 RNA decline and change in CD4<sup>+</sup> T lymphocytes and intracellular concentrations of zidovudine and lamivudine triphosphate.<sup>[73]</sup>

Generally, most of these pharmacodynamic relationships are linear, with no obvious concentration target. It is not rational, however, to use the same drug exposure for patients with drug-sensitive virus as for patients with drug-resistant virus. It follows that relating drug concentrations to an individual patient's viral isolate might be a better option for optimizing antiretroviral exposure.

First described by Ellner and Neu,<sup>[78]</sup> the inhibitory quotient has been proposed as a predictor of clinical outcomes in HIV and integrates drug exposure and viral susceptibility measures. Drug exposure can be defined as AUC,  $C_{max}$ , or  $C_{trough}$  (either as protein-unbound or as total drug concentration), and viral susceptibility can be expressed as the in vitro  $IC_{50}$ ,  $IC_{90}$ ,  $IC_{95}$ , or  $IC_{99}$ , with or without the presence of plasma proteins. The  $IC_{50}$  is used most commonly because it is associated with the least degree of error (due to the sigmoidal relationship between viral inhibition and drug concentration) and can be determined by a phenotypic assay or by the virtual phenotype.

The use of inhibitory quotients (IQ),<sup>[79]</sup> virtual inhibitory quotients (vIQ), or normalized inhibitory quotients (nIQ) currently is being evaluated<sup>[80]</sup> primarily for the protease inhibitors. IQ is defined as the ratio of the drug concentration at the end of the dosing interval ( $C_{trough}$ ) to the in vitro concentration of drug resulting in 50% inhibition of virus:  $C_{trough}/IC_{50}$ . Although  $C_{trough}$  may not be the optimal measure of drug exposure, it is logistically simple to obtain in ambulatory patients. The virtual IQ is defined as the ratio of  $C_{trough}$  to the  $IC_{50}$  of wild-type virus multiplied by the virtual phenotype (a calculated fold-increase in concentration-response relationships determined from the individual patient viral genotype and matched phenotype in a large database):  $C_{trough}/IC_{50} \cdot \text{virtual phenotype}$ . The nIQ is the ratio of  $C_{trough}$  to the fold change of the virtual phenotype ( $C_{trough}/\text{fold-change in } IC_{50}$ ), all divided by a fixed ratio of the mean antiretroviral  $C_{trough}$  in the population to the cutoff for resistance for the virtual phenotype (population  $C_{trough}/\text{fold-change resistance cutoff}$ ).<sup>[81]</sup> This ratio was derived to eliminate protein binding confounding, but it may be effective only in choosing targets for wild-type virus.

The benefits of these ratios still are primarily theoretical. The IQ has been shown to predict virologic response with saquinavir.<sup>[82]</sup> The vIQ has been shown to be a significant predictor of virologic response in patients treated with indinavir/ritonavir<sup>[83]</sup> and amprenavir/lopinavir.<sup>[84]</sup> In one preliminary investigation, the nIQ for amprenavir correlated with change in plasma HIV RNA in patients receiving a multiple antiretroviral drug regimen.<sup>[85]</sup> Investigations into the clinical utility of the IQ, vIQ, and nIQ are ongoing.

## CAUTIONARY NOTE ON PHARMACODYNAMIC INDICES

When studying an antibiotic and its pharmacodynamic properties when it is first introduced into development research

or the market, it is common to note that multiple pharmacodynamic dosing indices may apply to the drug and that the one to follow is chosen as the one most statistically correlated.<sup>[30]</sup> Multiple indices may be correlated positively because MICs tend to be very low for susceptible isolates, and many of the pharmacokinetic parameters that are used in the index equations are interrelated. Although the application of the chosen index may continue to validate the drug's use for a time, when MICs of previously susceptible organisms begin to rise, there will come a point at which the necessary index ratio breakpoint no longer is achieved. At this point, the index descriptions that have been discussed in this chapter would indicate that the drug would have to be abandoned because clinical and microbiologic outcomes no longer would be optimal. What has not been discussed, however, is how to interpret the worth of these indices if the drug continues to work despite higher or even resistant MICs being encountered in which the pharmacodynamic index ratios are far from optimal. Whether the indices are wrong or just being applied to the wrong biologic matrix (all currently are based on antibiotic serum concentrations) is as yet unclear.

The best example of this quandary exists with community-acquired respiratory tract infections caused by *S. pneumoniae*.<sup>[86]</sup> Pneumococcal isolates globally continue to show increasing incidences of resistance to all antibiotics that typically are used to treat pneumococcal infections, including penicillin ( $\beta$ -lactams in general), macrolides, and fluoroquinolones. Despite this show of resistance, the antibiotics all continue to prove successful clinically and continue to be recommended as first-line treatment options by a variety of treatment guideline groups throughout the world.<sup>[87-91]</sup> The answers to why this occurs most likely do lie within the indices described in this chapter. For  $\beta$ -lactams, whose extracellular, interstitial infection site concentrations would be in relative equilibrium with concurrent serum concentrations, the use of  $T > \text{MIC}$  for these drugs most likely is appropriate. Whether purposely or not, clinicians have continued to rely on this index and optimize it by using higher or more frequent doses of  $\beta$ -lactams for the treatment of pneumococcal infections, including resistant ones and ones in difficult-to-reach physiologic spaces.<sup>[92-94]</sup> The use of these higher doses keeps concentrations in the serum and in the interstitial space, where most of the pathogen load exists above the MIC of the pneumococcus for a greater portion of the dosing interval, optimizing their dynamics. For the fluoroquinolones and macrolides, the answer is less clear. Both classes of drugs have serum concentrations that are lower than either their interstitial fluid concentrations, especially those in an inflamed area, or the concentrations in the phagocytes that eventually clear the bacteria from the infection site. As a result, the use of serum concentrations in index ratio calculations most likely is flawed, as is evidenced by the following examples: (1) If the average  $C_{\text{max}}$  achieved with steady-state intravenous levofloxacin is 8 mg/L<sup>[95]</sup> and the average levofloxacin pneumococcal MIC is 1 mg/L, and the desired ratio of the two for optimal activity is 12,<sup>[30]</sup> intravenous, let alone oral, levofloxacin should never be curative for pneumococcal infections because the ratio that is achieved is only 8. (2) If the average 24-hour AUC that is achieved with a 500-mg oral dose of azithromycin is 2 mg·hr/L<sup>[96]</sup> and the average MICs of susceptible and resistant pneumococcal isolates are 0.25 mg/L and 32 mg/L and the desired ratio is greater than 30, azithromycin should never be curative for resistant pneumococcal isolates or for infections caused by susceptible isolates because the ratio that is achieved is only 8. Despite this index evidence to the contrary, both of these agents continue to work and be recommended on a regular basis at currently approved dosages. It may be postulated that although the index may be correct, the use of a different biologic matrix to determine the pharmacokinetic values for the index equations may be more appropriate. As an example, although the 24-hour serum AUC of azithromycin is only 2 mg·hr/L, that inside of a neutrophil is approximately 1500 mg·hr/L.<sup>[96]</sup> By applying this new value to the previous example, it may be possible to state that an MIC of 50 mg/L has the potential to be optimally treated. Whether this alteration of the equation to fit the distribution properties of the class of drugs and what the pathogen actually comes into contact with on its being cleared from the body turns out to be the appropriate manipulation of these index equations, or, whether a next generation of the pharmacodynamic model evolves that can actually use serum concentrations in all instances is something for further study.

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