

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., β -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.⁸ 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.^{9,10} 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 shown to date to apply 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. 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. β -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.

Combinations of antimicrobial agents may not always be beneficial. *Antagonism* between agents occurs when one agent diminishes the activity of another. β -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 β -lactam from exerting its bactericidal activity. In this case, the action of the β -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

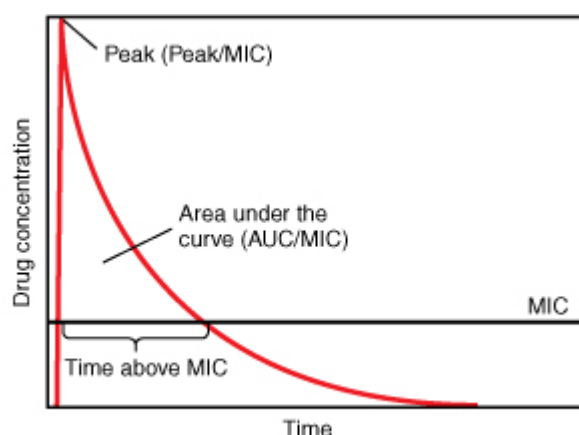
The traditional model used to study pharmacodynamic effects of anti-infective agents is the "hollow fiber model" system.¹² In this system, broth is used as a growth medium; bacteria are exposed to predetermined concentrations of antibiotics that are "eliminated" from the system in such a manner as to simulate pharmacokinetically determined excretion.¹³ 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, however, 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 colleagues¹⁴⁻¹⁶ 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.

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Figure 18-3 Common antibiotic pharmacokinetic and minimal inhibitory concentration (MIC) pharmacodynamic relationships.

Human Trials

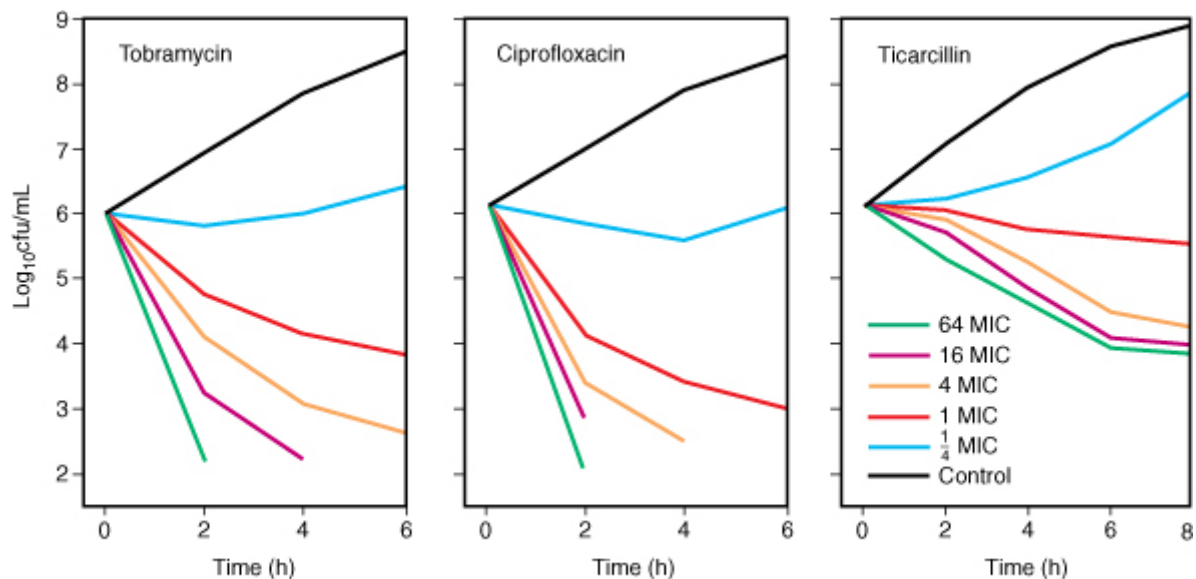
To date, most human trials¹⁷⁻²⁸ reported have been retrospective analyses of prospectively collected data, with only one study, that of Preston and co-workers,²⁹ being performed prospectively. These trials have used three measures of assessment to relate antimicrobial pharmacokinetics to pharmacodynamics: (1) clinical outcome (cure/fail or improved); (2) eradication of bacteria from the site of infection or reduction in virus concentration (load) in blood, 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}/MIC , AUC/MIC , or $T > MIC$ (Fig. 18-3). Few trials have focused on relationships of drug exposure to toxicity or on the development of resistance.

Concentration-Dependent Killing Agents

Concentration-dependent killing agents (e.g., fluoroquinolones, aminoglycosides, macrolides, azalides, ketolides, metronidazole[®]) 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 18-4 for tobramycin[®] and ciprofloxacin against *Pseudomonas aeruginosa*.³⁰ 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}/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.¹⁷⁻²⁹ 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.³¹⁻³³ 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.

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 18-4. Generally, when the concentration at the bacterial site is more than four times higher than the MIC, the additional killing that occurs is modest.



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Figure 18-4 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.)

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.^{10,25} 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. 18-5).³⁴ An additional report of many animal studies with *S. 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.^{10,35} Time-dependent killing agents include the penicillins, cephalosporins, aztreonam[®], vancomycin, carbapenems, macrolides, linezolid[®], and clindamycin[®].

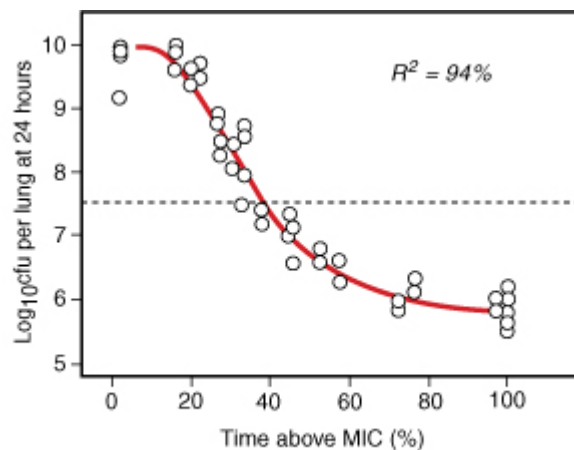
Ratio of Maximal Serum Concentration to Minimal Inhibitory Concentration

The C_{max}/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}/MIC ratio has been used in vitro to predict the development of bacterial resistance.¹³

There have been five studies in humans using the C_{max}/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 colleagues¹⁷ 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 colleagues²⁰ often is quoted as the basis for use of a C_{max}/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}/MIC ratio increased, with a mean ratio of 6.6±3.9 in patients who responded and 4.6 ±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}/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.



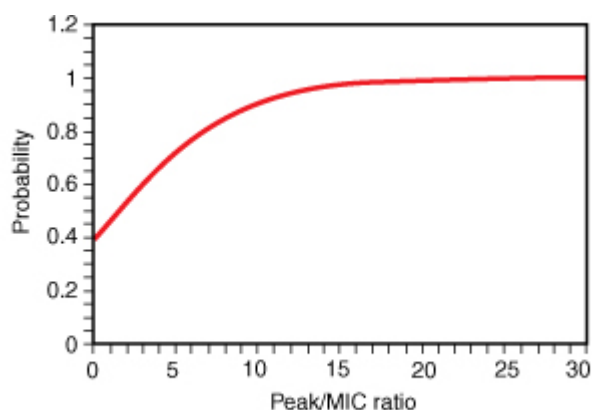
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Figure 18-5 The relationship of time above the minimal inhibitory concentration (MIC) and the reduction in bacterial count in a neutropenic mouse model of *Klebsiella pneumoniae* for cefotaxime. (From Craig WA. *Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins*. *Diagn Microbiol Infect Dis*. 1995;22:89-96.)

Deziel-Evans and associates²¹ examined a variety of pharmacodynamic predictors in 45 adult patients treated with aminoglycosides. In this trial, a Cmax/MIC ratio greater than 4 was noted to improve clinical response.

A more recent study by Kashuba and co-workers²⁶ described the relationship between Cmax 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 Cmax/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 18-6](#), a strong relationship was noted between Cmax/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 Cmax/MIC ratio yields an earlier and greater chance of surrogate marker normalization; this does not take into account the probability of toxicity with higher Cmax/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.



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Figure 18-6 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.)

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To date, one study has addressed the use of the Cmax/MIC ratio with the quinolone [levofloxacin](#)[®]. Preston and co-workers²⁹ 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}/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}/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}/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.

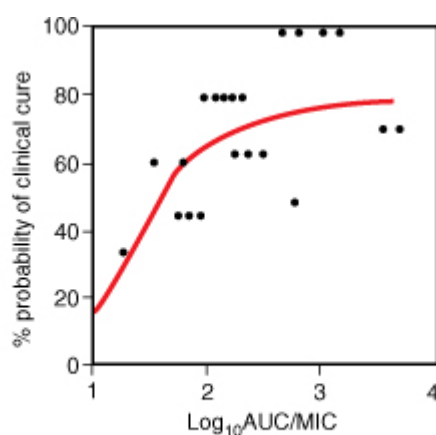
These retrospective analyses of prospective data illustrate the potential importance of the C_{max}/MIC ratio for concentration-dependent killing agents. Because none of the four trials with aminoglycosides used single daily dosing of these agents, however, it is not possible to extrapolate these data to support this mode of administration.³⁶

In terms of prevention of bacterial resistance, only in vitro data using the hollow fiber model exist relating the C_{max}/MIC ratio to resistance. The study of Blaser and co-workers¹³ examined the C_{max}/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 associates³⁷ using ciprofloxacin noted the development of resistant *P. aeruginosa* when the organism was exposed to a C_{max}/MIC ratio of 6 compared with no resistance when the C_{max}/MIC ratio was 12, even though both regimens showed adequate rates of bacterial killing. These in vitro data suggest that C_{max}/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}/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

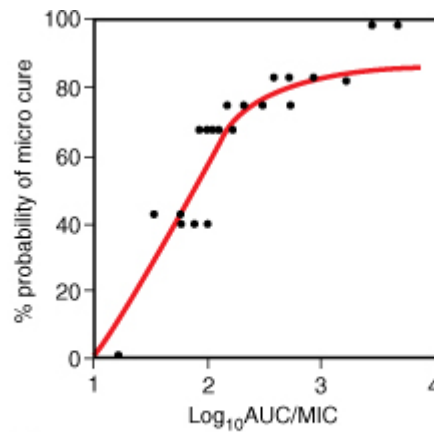
The AUC/MIC ratio is a measure of total exposure of bacteria to an antimicrobial agent. The AUC/MIC ratio encompasses peak concentration and prolonged exposure, which may be vital for drugs with a long half-life. C_{max}/MIC and AUC/MIC ratios are difficult to separate in a scientifically designed clinical 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.



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Figure 18-7 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.)

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 ($\text{SIT}^{-1} \cdot \text{T}$), was identified as the factor most predictive of clinical and microbiologic success (Fig. 18-7). At an AUC/MIC ratio lower than $125 \text{ SIT}^{-1} \cdot \text{hr}$ ($\log^{10} = 2.1 = 125 \text{ SIT}^{-1} \cdot \text{hr}$), the probabilities of clinical and microbiologic cure were 42% and 26%, whereas at values greater than $125 \text{ SIT}^{-1} \cdot \text{hr}$, the probabilities were 80% and 82%. At an AUC/MIC ratio lower than $125 \text{ SIT}^{-1} \cdot \text{hr}$, between 125 and $250 \text{ SIT}^{-1} \cdot \text{hr}$ ($\log^{10} = 2.4 = 250 \text{ SIT}^{-1} \cdot \text{hr}$), and higher than $250 \text{ SIT}^{-1} \cdot \text{hr}$, the median time to eradication was more than 32 days, 6.6 days, and 1.9 days.²³ A similar analysis was performed for a small number of patients experiencing an acute exacerbation of chronic bronchitis treated with grepafloxacin.²⁸ At an AUC/MIC ratio less than $75 \text{ SIT}^{-1} \cdot \text{hr}$, the probability of clinical cure was 71%, whereas with AUC/MIC ratios greater than $175 \text{ SIT}^{-1} \cdot \text{hr}$, the probability of cure was 98%. Clear conclusions cannot be drawn from this study, however, because of the limited sample size.

A retrospective analysis by Ambrose and colleagues³⁸ 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 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 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.

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 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.³⁹ An in vitro study by Fazili and associates⁴⁰ 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-workers⁴¹ 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.

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.⁴² 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. β -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[®].¹⁰ Human studies are sparse, however, in defining this parameter as an important one. The study of Bodey and colleagues¹⁸ 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 associates¹⁹ also noted for cefmenoxime that T>dynamic response concentration (DRC) (analogous to T>MIC) correlated better than the AUC/DRC ratio (analogous to 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. Turnidge⁴³ 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 β -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 Andes²⁵ 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 β -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 are available for staphylococcal infections and vancomycin in pediatric patients. Schaad and colleagues⁴⁴ noted that a peak serum bactericidal titer of 1:8 or greater was associated with cure in 16 of 20 patients. Louria and co-workers⁴⁵ 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.

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. β -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 β -lactams. As in the in vitro studies, β -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.⁴⁶ 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⁺ 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.⁴⁷

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Large interindividual variability exists in the pharmacokinetics of protease inhibitors. Concentration-effect relationships have been shown, however, for indinavir,^{48,49} saquinavir[®],⁵⁰⁻⁵² nelfinavir,⁵³ amprenavir[®],⁵⁴ and lopinavir.^{55,56} Adverse effects have been linked to concentrations of indinavir⁵⁷ and amprenavir[®].⁵⁴ Pharmacokinetic-pharmacodynamic relationships also have been established for the nonnucleoside reverse transcriptase inhibitors nevirapine[®]⁵⁸ (efficacy and toxicity), delavirdine,⁵⁹ and efavirenz[®].⁶⁰

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^{61,62} result in plasma parent drug concentrations that do not correlate well with intracellular drug concentrations.⁶³ Plasma concentration-effect relationships have been shown, however, in a few patients for zidovudine[®]⁶⁴ and didanosine[®].⁶⁵ Concentration-toxicity relationships have been shown for zidovudine[®]⁶⁶ and didanosine[®].⁶⁷ One investigation showed significant positive correlations between the rate of HIV-1 RNA decline and change in CD4⁺ T lymphocytes and intracellular concentrations of zidovudine[®] and lamivudine[®] triphosphate.⁶³

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,⁶⁸ 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 IC₅₀, IC₉₀, IC₉₅, or IC₉₉, with or without the presence of plasma proteins. The IC₅₀ 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),⁶⁹ virtual inhibitory quotients (vIQ), or normalized inhibitory quotients (nIQ) currently is being evaluated⁷⁰ 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: $C_{\text{trough}}/IC_{50}$. 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 data base): $C_{\text{trough}}/IC_{50} \cdot \text{virtual phenotype}$. The nIQ is the ratio of C_{trough} to the fold change of the virtual phenotype ($C_{\text{trough}}/\text{fold-change in } IC_{50}$), 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 $C_{\text{trough}}/\text{fold-change resistance cutoff}$).⁷¹ 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[®].⁷² The vIQ has been shown to be a significant predictor of virologic response in patients treated with indinavir/ritonavir⁷³ and amprenavir/ lopinavir.⁷⁴ In one preliminary investigation, the nIQ for amprenavir[®] correlated with change in plasma HIV RNA in patients receiving a multiple antiretroviral drug regimen.⁷⁵ 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.²⁹ 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*. Pneumococcal isolates globally continue to show increasing incidences of resistance to all antibiotics that typically are used to treat pneumococcal infections, including penicillin (β -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.⁷⁷⁻⁸¹ The answers to why this occurs most likely do lie within the indices described in this chapter. For β -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 β -lactams for the treatment of pneumococcal infections, including resistant ones and ones in difficult-to-reach physiologic spaces.⁸²⁻⁸⁴ 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_{max} achieved with steady-state intravenous levofloxacin[®] is 8 mg/L⁸⁵ and the average levofloxacin[®] pneumococcal MIC is 1 mg/L, and the desired ratio of the two for optimal activity is 12,²⁹ 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.h/L⁸⁶ 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 not only for resistant pneumococcal isolates, but also 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.h/L, that inside of a neutrophil is approximately 1500 mg.h/L.⁸⁶ 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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




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