chapter 1

Antimicrobial Pharmacokinetics and Pharmacodynamics

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The goal of antimicrobial therapy is to effectively eradicate pathogenic organisms while minimizing drug toxicities. Various factors affect the treatment outcomes of infectious diseases including host defense mechanisms, the site of infection, the virulence of the pathogen, and the pharmacologic properties of the antimicrobial agent used to treat the infection. The factor under the greatest control of the clinician, however, is related to the choice and dosing of antimicrobial agents. Various pharmacologic factors govern the design of an optimal antimicrobial regimen. These factors are conventionally divided into two distinct components: (1) pharmacokinetics and (2) pharmacodynamics. Examination of pharmacokinetic and pharmacodynamic relationships have been undertaken for most antibacterial drug classes and more recently for a number of antifungal and antiviral drug classes. These analyses are being recognized as increasingly important in the design of optimal antimicrobial therapies.

ANTIMICROBIAL PHARMACOKINETICS

Pharmacokinetics deals with drug disposition in the body, including the absorption, distribution, and elimination of drugs. It is these factors that determine the time course of drug concentrations in serum and tissues for a given dosing regimen. With antimicrobial agents one is particularly concerned about concentrations at the site of infection.

Kinetics at Site of Infection

Many studies have attempted to correlate antibiotic concentrations in serum with those in various tissues or sites of infection. However, several problems arise in both the measurement and the interpretation of drug concentrations in tissues. In theory, tissue concentrations consist of vascular, interstitial, and intracellular compartments. Different antimicrobial agents can vary in their ability to accumulate within these three compartments. Because most infections occur in tissues and the common pathogens are extracellular, interstitial fluid concentrations at the site of infection should be the prime determinants of efficacy. Free-drug concentrations in serum are a much better surrogate of interstitial fluid concentrations than are tissue homogenate concentrations. The majority of studies, however, have used tissue homogenates to determine antibiotic concentrations in tissue." The relative distribution of an antibiotic within a tissue sample cannot be distinguished by this method. Tissue homogenates mix interstitial, intracellular, and vascular components together. Measurement of antibiotic concentrations in tissue homogenate tends to underestimate or overestimate interstitial fluid concentrations depending upon the ability of the antimicrobial to accumulate

intracellularly. For example, one would expect that antibiotics with poor intracellular penetration, such as the (3-lactams, would reach high concentrations in interstitial fluid. However, tissue homogenate methods suggest this class of drugs penetrates poorly into the interstitial space because of the dilution of samples with intracellular contents. Techniques that directly extract interstitial fluid, such as subcutaneously implanted cotton threads or more recently microdialysis methods, demonstrate high (3-lactam concentrations in this tissue compartment that are similar to free drug levels in senum. 3-5

On the other hand, since fluoroquinolones accumulate intracellularly, tissue homogenates can overestimate the concentration of drug in interstitial fluid. Not all pathogens, however, are located in the extracellular space. For example, pathogens such as *Legionella spp.* and *Chlamydia spp.* reside primarily in the intracellular space. One may then anticipate superior quinolone potency in the treatment of these infections. However, when one looks at the relationship between the amount of fluoroquinolone necessary for efficacy in the treatment of both intracellular and extracellular pathogens, no difference is seen (Fig. 1-1). 6 This may suggest that only a fraction of the amount of quinolone that is intracellular is available for antimicrobial activity. Furthermore, it is clear that not all drugs that accumulate intracellularly do so in similar intracellular compartments. For example, fluoroquinolones reside in the cytosol, whereas macrolides concentrate in phagolysosomes. 7 In the same manner, not all intracellular pathogens have the same subcellular distribution. *Legionella spp.* and *Chlamydia spp.* are found in phagosomes, *Listeria* and *Shigella* are found in the cytosol, and *Salmonella* in phagolysosomes. 7

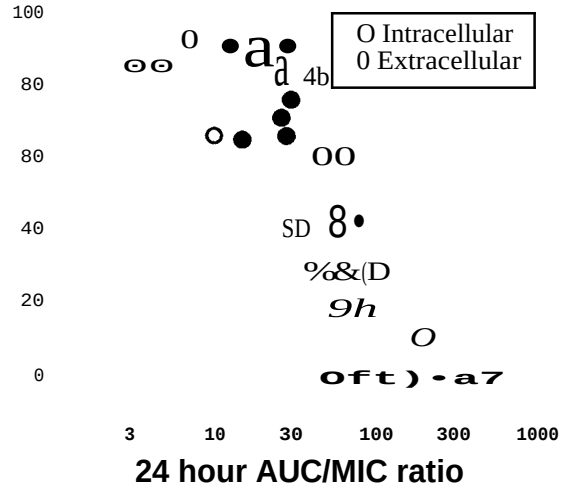

FIGURE 1-1. Relationship between the 24-hour area under the concentration curve (AUC)-to-minimum inhibitory concentration (MIC) ratio and mortality for extracellular (hollow circles) and intracellular (solid circles) pathogens in various experimental infection models in mice, rats, and guinea pigs treated with fluoroquinolones. (From Craig WA, Dalhoff A: Pharmacodynamics of fluoroquinolones in experimental animals. In Kuhlman J, Dalhoff A, Zeiler HJ, [eds]: Handbook of Experimental Pharmacology, vol 127: Quinolone Antibacterials. pp 207-232.)

Although for most antibiotics it appears that serum concentrations serve as an adequate surrogate of concentrations at the site of infection, there is growing controversy in regard to certain classes of compounds in the treatment of lower respiratory tract infections. For a few antimicrobial classes there is a large discrepancy between serum drug levels and levels in epithelial lining fluid (ELF). ELF is the fluid that bathes the respiratory epithelium, where it is believed most pathogens in bacterial pneumonia reside. For drugs such as clarithromycin and azithromycin, ELF concentrations can be 10- to 20-fold higher than in serum (Table 1-1)."° Some investigators suggest that for drugs with this degree of kinetic difference, the pharmacokinetics in ELF may be better for predicting therapeutic outcomes than those in serum. However, at this time there have not been either animal model or clinical trial data supporting or disproving this hypothesis.

Impact of Protein Binding

Various pharmacologic factors can alter the activity of an antimicrobial agent. In some circumstances, protein binding can have a detrimental effect, whereas in others it may enhance dosing efficacy. The antimicrobial activity of a drug is inversely related to the extent of protein binding. Protein binding of antimicrobials in serum can interfere with biologic activity, restrict tissue distribution, and delay elimination."," For example, a drug such as phenylbutazone, known to displace penicillins from albumin-binding sites, enhances its in vitro antimicrobial activity because it is only the unbound antimicrobial fraction that is available for penetration to the site of infection for antimicrobial activity. 13 In spite of numerous investigations documenting these effects, the clinical significance of protein binding remains controversial.

A common inaccurate assumption is that a given degree of protein binding will exert a similar pharmacologic effect on all antimicrobials. On the contrary, the effects of drug protein binding on the pharmacokinetics of an antimicrobial depend on how it is eliminated by the body. Excretion of drugs into the urine occurs either by glomerular filtration or tubular secretion. Protein binding reduces the rate of elimination only of drugs cleared by glomerular filtration. In contrast, tubular secretion is largely independent of protein binding. The diverging effects of binding on drugs depending upon their route of elimination is further illustrated in Fig. 1-2, which graphs the area under the serum concentration time curve (AUC) of both total and free levels of 16 R-lactams in serum and skin blister fluid based upon the degree of protein binding." In the left panel, one can see that the effect of increasing binding for drugs eliminated by tubular secretion is a progressive decline in free drug AUC in both serum and blister fluid. On the other hand, for the compounds eliminated by glomerular filtration the right

TABLE 1-1 m Comparison of Clarithromycin and Azithromycin Kinetics in Serum and ELF

	Clarithromycin		Azithromycin	
Time (hours)	Serum (gg/ml)	ELF (gg/ml)	Serum (gg/ml)	ELF (lag/ml)
4	2.0	34.5	0.08	1.0
8	1.6	26.1	0.09	2.2
12	1.2	15.1	0.04	1.0
24	0.2	4.6	0.05	**1.2**
24-h AUC	25	391	1.3	28

ELF, epithelial lining fluid.

AUC, area under the serum concentration-time curve;

panel demonstrates the progressive rise in AUC for total drug and the relatively constant AUC of free drug over a wide range of binding. The effect of protein binding on drugs with primarily hepatic elimination is less clear. If the drug has a low hepatic extraction ratio, however, the effect of protein binding would tend to slow elimination. On the other hand, for drugs with high extraction ratios, protein binding would affect elimination very little.

For drugs eliminated predominantly by tubular secretion or rapid hepatic extraction, the peak senun concentration level (C.), the AUC, and the duration of time the serum levels exceed the minimum inhibitory concentration (1VIIC) expressed as the percentage of the dosing interval (T >MIC) of highly bound drugs would be reduced by high protein binding. One might predict that binding of greater than 80% would be necessary to reduce unbound free drug levels in the body enough to adversely affect antimicrobial activity. For example, in a Staphylococcus aureus murine peritonitis model seven penicillin antibiotics with similar in vitro activity and pharmacokinetic profiles (all eliminated by tubular secretion) with the exception of protein binding were evaluated. The amount of drug necessary to cure 50% of the mice was directly related to the degree of protein binding. [12] The higher the binding, the larger the total dose required.

For drugs eliminated predominantly by glomemlar filtration, increasing binding reduces the peak level of free drug, but has no major effect on the AUC, and prolongs the duration of time free drug levels would exceed the MIC of sensitive organisms. Thus, if peak level was the important determinant of efficacy, protein binding might have a detrimental effect. On the other hand, if the duration of time serum levels exceeded the MIC were important, higher protein binding could have a beneficial effect. [14]

Pharmacokinetic Impact of Dosing Regimen Design

The pharmacokinetic parameters that characterize the time course of antibiotic concentration in serum and at sites of infection include several measures of exposure including the AUC, C.X, and the T >MIC (Fig. 1-3). When a drug's half-life is constant, each of these kinetic parameters will change with the dose magnitude and the frequency of drug administration. For a given total daily dose of drug the 24-hour AUC will be relatively constant regardless of the dosing regimen. Administration of large infrequent doses will result in high peak concentrations and shorter duration of time serum levels exceed a

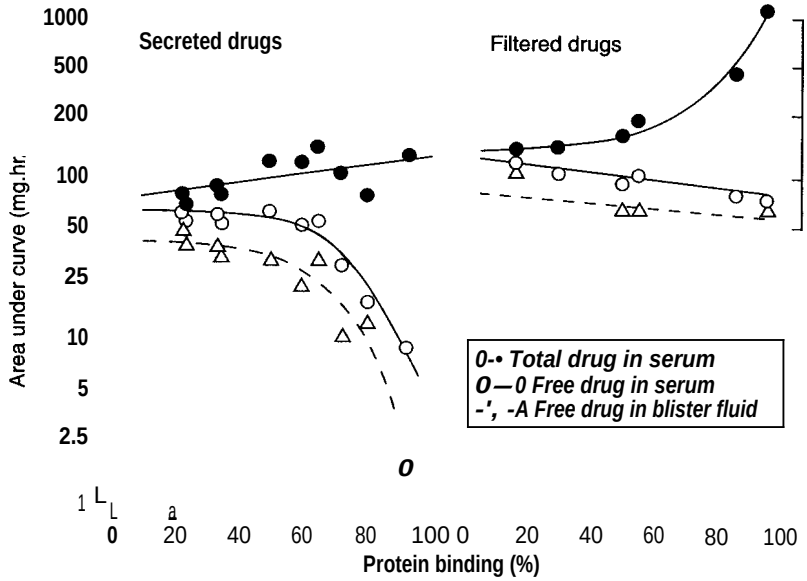

FIGURE 1-2. Relationship of the area under the concentration curve of total and free drug in serum and free drug in blister fluid with the percentage of protein bound drug for 16 R-lactams. Drugs eliminated primarily by secretion are shown in the left panel and those eliminated primarily by filtration are shown in the right panel. (From Craig WA, Suth B: Protein binding and the antimicrobial effects: Methods for the determination of protein binding. In Lorian V [ed]: Antibiotics in Laboratory Medicine, 4th ed. Baltimore, Williams & Wilkins,1996, pp 367-402.)

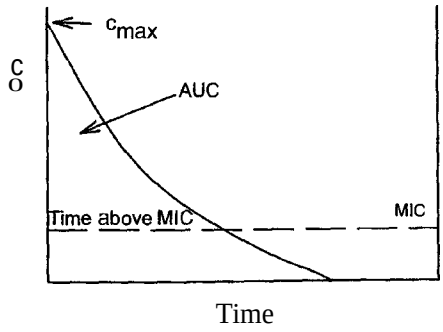

FIGURE 1-3. Antimicrobial pharmacokinetic parameters in relation to the minimum inhibitory concentration (MIC). AUC, area under the concentration curve.

threshold value such as the MIC. The converse will occur with lower drug doses administered more frequently.

PRE-PHARMACODYNAMIC DOSING TRADITIONS

Traditionally antimicrobial dosing regimens have been deduced from the relationship between some measure of drug potency in vitro such as the MIC or minimum bactericidal concentration (MBC) of an antimicrobial agent for important pathogens and the pharmacokinetics of the drug in serum. These parameters do not provide information regarding the time course activity of drugs, however. For example, the MIC does not provide information on the effect of fluctuating drug concentrations characteristically encountered in a patient, or on whether there are antimicrobial effects that can persist after drug exposure. Furthermore the MBC does not reveal the effect that higher drug concentrations have upon the extent or rate of killing. The persistent suppression of organism growth or regrowth after short antimicrobial exposures has been called the postantibiotic effect. [15] The effect of increasing concentrations upon the activity of an antimicrobial and the presence or absence of prolonged antimicrobial effects persisting after drug exposure give a much better description of the time course of activity than provided by the MIC or MBC.

The use of the MIC and MBC as predictors of antimicrobial success has led to two erroneous generalizations in dosing regimen design. One is that to achieve an optimal effect, drug concentrations must exceed the MIC for most of the dosing interval to prevent organism regrowth. Another dosing generalization has been that an increase in concentrations will invariably enhance antimicrobial efficacy.

ANTIMICROBIAL PHARMACODYNAMICS

Pharmacodynamics examines the relationships between the antimicrobial and organism over time (time course of activity), determining the effects of variations in drug kinetics on treatment outcomes. Various studies have demonstrated that the success of a drug and dosing regimen is dependent upon a measure of drug kinetics and a measure of drug potency against the infecting organism (e.g., MIC or MBC) (Fig. 1-4). Kinetic parameters, such as the C./MIC ratio, 24-hour AUC/MIC ratio, and time above MIC, have been shown to be major determinants of antimicrobial efficacy. Furthermore, studies examining the relationship between in vitro measurements (MIC and MBC) and the time course activity of various antimicrobials have demonstrated that drugs with different mechanisms of action vary in respect to the effect of increasing drug concentrations. These pharmacokinetic and pharmacodynamic analyses provide a better understanding of the relationship between drug dosing and effect. Understanding these relationships for various antimicrobial classes has proven valuable for (1) the design of appropriate dosing regimens in the treatment for both susceptible and multiply resistant pathogens, (2) the development of in vitro susceptibility breakpoints, and (3) the understanding how antimicrobial dosing relates to the emergence and spread of drug resistance.

Pharmacodynamic Determinants of Efficacy

The time course of antimicrobial activity is dependent on the drug's pharmacokinetics and two major

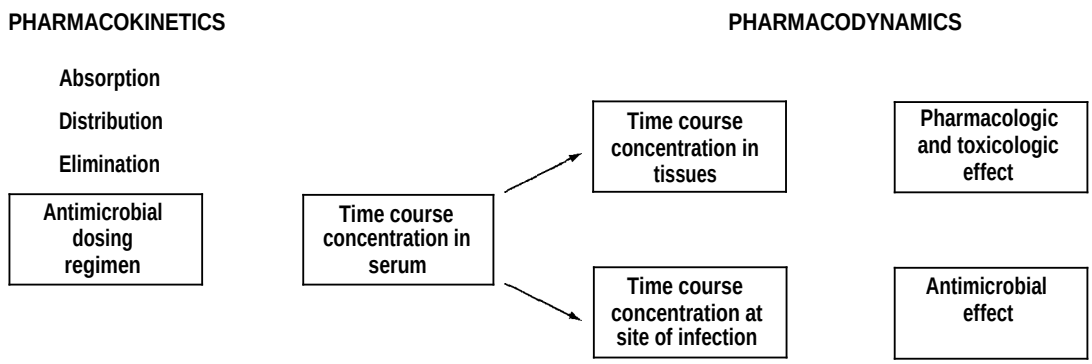

FIGURE 1-4. Overview of pharmacokinetics and pharmacodynamics in antimicrobial therapy. (From Craig WA: Pharmacokinetic/pharmacodynamic Parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-12.)

pharmacodynamic characteristics. The first is the rate of organism killing and whether increasing drug concentrations enhances the rate and extent of killing. The second is the absence or presence of inhibitory effects on organism growth that persist after drug levels have fallen below the MIC.

Concentration-Dependent vs. Time-Dependent Killing

it is clear that progressive escalation of antimicrobial concentrations above the MIC will not enhance organism killing for all antimicrobial drug classes. For example, the killing activity of the R-lactams, macrolides, glycopeptides, clindamycin, tetracyclines, oxazolidinones, triazoles, and flucytosine is saturable with respect to the effect of drug concentration upon the rate and extent of killing. [16-24] Maximal in vitro killing with (3-lactam compounds is usually observed at concentrations four to eight times the MIC. [11,21] Higher concentrations do not enhance drug activity and in fact have been demonstrated to be less active in some models (Eagle effect). [26] For agents with saturable killing with respect to drug concentration it is important to maximize the duration of time for which concentrations exceed the MIC rather than to enhance intensity of drug exposure.

On the other hand, there are a number of antimicrobial classes that do demonstrate concentration-dependent organism killing. With these drugs, higher concentrations result in more rapid and extensive organism killing. These killing characteristics have been observed with the aminoglycosides, fluoroquinolones, metronidazole, ketolides, the lipopeptide daptomycin, amphotericin B, and the new echinocandin class of antifungal. [6,15,1s,19,27-31] The pharmacologic goal of dosing regimens with these agents would be to maximize concentrations by administering the total daily dose infrequently.

Persistent Effects

Prolonged persistent effects are due to various phenomena referred to as postantibiotic effects (PAE), postantibiotic sub-MIC effects, and **postantibiotic-leukocyte effects.** [15,25,32-34] Sub-MIC concentrations of a number of antimicrobial classes have been shown to inhibit organism growth. [35] Sub-MIC concentrations can also prolong the duration of the PAR The postantibiotic leukocyte effect refers to the observation that organisms that have been exposed to antimicrobials are more susceptible to phagocytosis by leukocytes. This phenomenon can also prolong the duration of the PAR Persistent suppression of growth after limited exposure was initially reported in the 1940s with penicillin. [26] These phenomena have since been demonstrated both in vitro and in animal infection models for nearly all classes of antimicrobials. [11,21] Nearly all antibacterials appear to be capable of producing persistent effects with staphylococci. For example, although Cefazolin serum levels in mice remained above the MIC for only 1.6 hours, the growth of *S. aureus* in the thighs of treated animals was inhibited for several hours longer

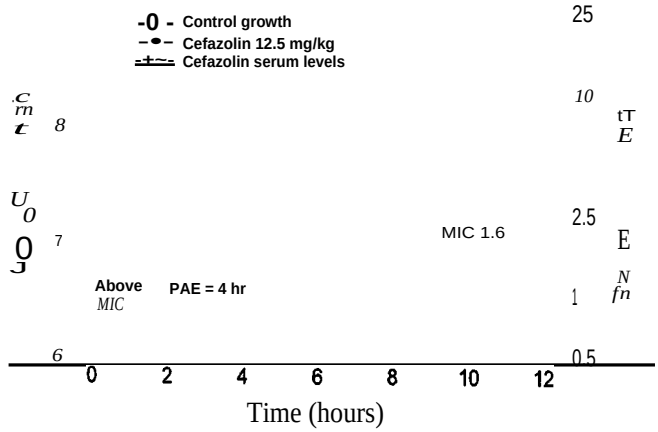

FIGURE tom. Cefazolin in vivo postantibiotic effect (PAE) with Staphylococcus aureus (American Type Culture Collection) (ATCC) 25923 in neutropenic murine thigh infection model following a 12.5 mg/kg dose. Hollow *circles* represent mean control in thighs from 3 mice. *Solid circles,* growth in thighs of treated animals. Simultaneous serum cefazolin concentrations are also shown. CFU, colony-forming units; MIC, minimum inhibitory concentration. (From Craig WA, Gudmundsson S: Postantibiotic effect In Lorian V [ed]: Antibiotics in Laboratory Medicine, 4th ed. Baltimore, Williams & Wilkins,1996, pp 296-329.)

(PAE 4 hours) (Fig. 1-5). [11] However, drugs that inhibit protein or nucleic acid synthesis such as the aminoglycosides, fluoroquinolones, tetracyclines, and rifampin also produce prolonged PAEs with gram-negative bacilli and streptococci. [11,25] In contrast, (3-lactams produce short or no PAEs with gram-negative bacilli. The only exception is with the carbapenems, primarily with strains of *Pseudomonas aeruginosa.*

Antifungal compounds have also been shown to have prolonged persistent effects. The most pronounced effects have been observed with the polyenes such as amphotericin B.[2'] The triazole compounds have not demonstrated PAEs in vitro but have demonstrated prolonged effects in vivo, probably representing significant postantifungal sub-MIC effects. [10,16,17] The pyrimidine analog flucytosine has been found to produce only modest persistent effects. [16] The new echinocandin class has also demonstrated prolonged in vitro PAEs [.3o]

The clinical significance of the pharmacodynamic observation of prolonged persistent effects following a limited drug-organism interaction is related to the potential to lengthen dosing intervals. If organism growth remains suppressed after drug levels fall below the MIC, then the dosing interval could be lengthened until the beginning of organism regrowth or the end of the PAE.

Patterns of Activity

On the basis of these two time-course characteristics (effects of increasing drug concentrations and persistent effects), three patterns of antimicrobial activity have been observed. The first pattern of activity is characterized by marked concentration-dependent killing over a wide

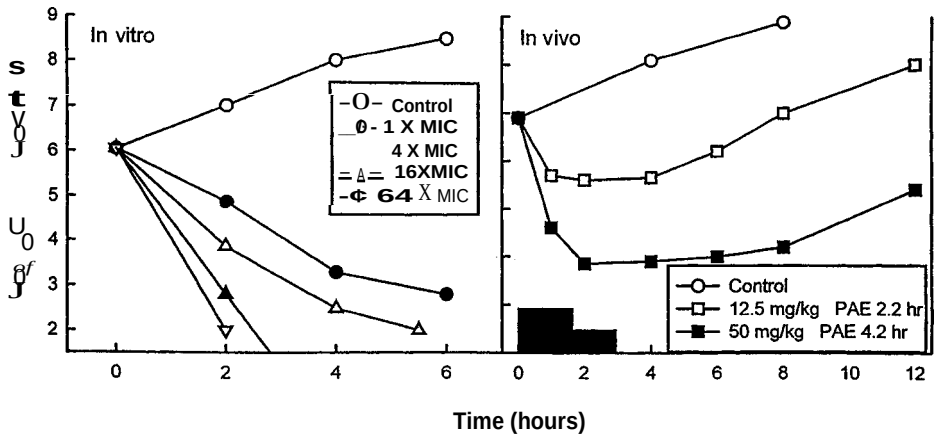

FIGURE 1-6. In vitro time-kill curves for tobramycin against *Pseudomonas aeruginosa* at escalating multiples of the minimum inhibitory concentration (MIC) *(left pane4* and bacterial counts of the same organism in vivo in neutropenic mice following single doses of tobramycin administered subcutaneously. Tobramycin MIC, 0.5 gg/mL. CFLJ, colony-forming units; PAE, postantibiotic effect. (From Craig WA, Gudmundsson S: Postantibiotic effect. In Lorian V [ed]: Antibiotics in Laboratory Medicine, 4th ed. Baltimore, Williams & Wilkins,1996, pp 296-329.)

range of concentrations and prolonged persistent effects. The higher the drug concentration, the greater the extent and rate of organism killing. This is illustrated in Fig. 1-6, where the activity of tobramycin against P. ***aeruginosa is*** examined in vitro and in vivo." In the left panel are seen marked concentration-dependent killing over a wide range of in vitro concentrations. In the right panel one can observe the prolonged dose-dependent growth suppression (PA-Es) in vivo. This pattern of killing and persistent growth suppression is observed with the aminoglycosides, fluoroquinolones, metronidazole, the ketolides, daptomycin, and the polyene antifungals.[6,18,24,27,29,3911] Since higher doses will lengthen the duration of antimicrobial effects, large infrequent doses of these agents maximizing the C./MIC ratio could enhance their activity. Furthermore, the prolonged persistent effects allow doses to be spread apart because organism regrowth will be suppressed when levels fall below the MIC.

The second pattern of activity is characterized by a saturation of the rate of killing at concentrations near the MIC and minimal-to-modest persistent effects. Thus high concentrations will not kill the organisms faster or more extensively than low concentrations. The duration of exposure rather than concentration is the major determinant of the extent of killing. This pattern of activity is called time-dependent killing and is the pattern that characterizes the activity of all of the (3-lactam antibiotics, most of the macrolides, clindamycin, the oxazolidinones, and flucytosme.[15-17,19,20,23,24,4013] For example, Figure 1-7 shows experimental data from both an in vitro and in vivo infection model with P. ***aeruginosa*** examining the activity of the P-lactam, ticarcillin.[38] In both the in vitro and in vivo studies, concentrations above four times the MIC did not appreciably increase the rate of killing. Furthermore, regrowth of organisms in vivo began immediately after serum levels dropped below the MIC (no persistent effect). With these drugs the frequency of administration and the dose are both important determinants of efficacy. Time above the MIC has been the major pharmacokinetic-pharmacodynamic (PK-PD) parameter correlating with efficacy of these drugs.

The final pattern of activity is not only characterized by time-dependent killing but also by prolonged persistent effects. This unique pattern of activity characterizes the azalide azithromycin, the tetracyclines, glycopepfdes, streptogramins, and the tfazole antifungals.[1,19,16] The dosing frequency is usually not a major factor in determining the efficacy of these drugs. The 24-hour AUC/MIC ratio is the primary parameter correlating with in vivo efficacy because the prolonged persistent effects prevent time above MIC from becoming important.

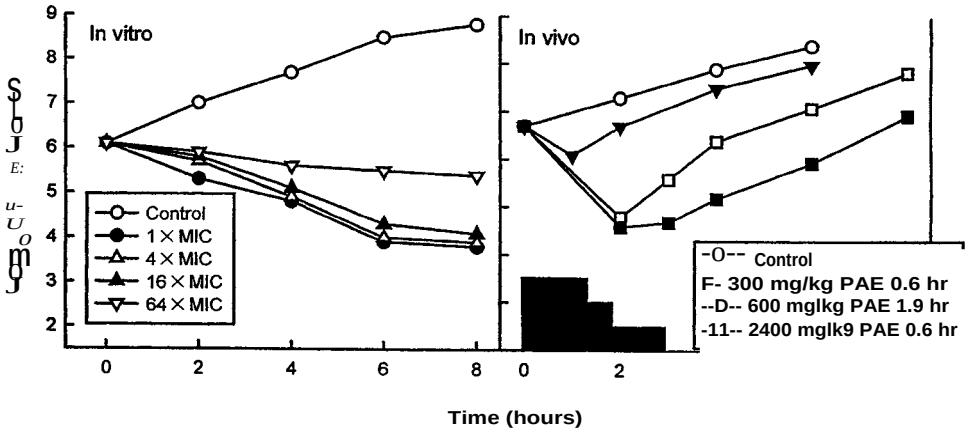

FIGURE 1-7. In vitro time-kill curves for ticarcillin against *Pseudomonas aeruginosa* at escalating multiples of the minimum inhibitory concentration (MIC) *(left panes* and bacterial counts of the same organism in vivo in neutropenic mice following single doses of ticarcillin administered subcutaneously. Ticarcillin MIC,16 gg/mL. CFU, colony-forming units; PAE, postantibiotic effect.

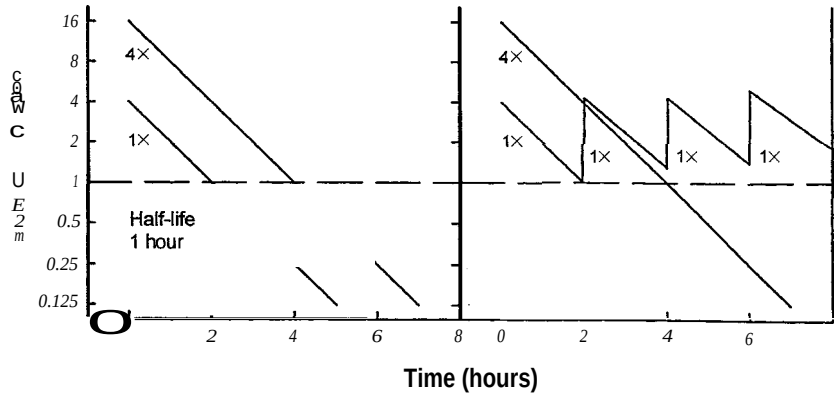

FIGURE 1-8. Effect of increasing the dose or changing the dosing interval of a hypothetical drug on the C..\,-to-minimum inhibitory concentration (MIC) ratio, area under the concentration curve (AUC)/MIC ratio, and the duration of time that serum levels exceed the MIC. (From Craig WA: Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect **Dis 1998;26:1-12.)**

DETERMINATION OF PHARMACOKINETIC-PHARMACODYNAMIC PARAMETERS PREDICTING EFFICACY

The specific parameters most commonly correlated with antimicrobial treatment outcome include the CmWC ratio, the 24-hour AUC/MIC ratio, and the T >MIC. These relationships have been examined primarily in in vitro and in vivo infection models. Investigation in human clinical trials to support or refute the observations from in vitro and animal models can be difficult because of the design of most clinical trials. Most studies are designed to determine the impact of higher doses of drug on efficacy with usually all regimens using the same dosing interval. As illustrated in the left panel of Figure 1-8, a four-fold higher dose results in a higher C/HVIIC ratio, a higher AUCMIIC ratio, and a longer duration of time above MIC. If a higher dose is associated with a better therapeutic outcome, it is difficult to determine which parameter is of primary importance, as all three increase to a similar extent. However, much of the interdependence among pharmacodynamic parameters can be eliminated with dosing regimens that use different dosing intervals. In the right panel of Figure 1-8 a dose administered every 2 hours is compared to a four-fold higher dose given every 8 hours, resulting in a lower C. level but a higher T >MIC. Over each 24-hour treatment regimen period the AUC/MIC ratio of the two regimens would be the same. With few exceptions, such study designs are most often not possible in human trials but are easily undertaken in animal infection models.

A study performed in the 1970s by Bodey et al did, however, vary dosing frequency comparing the efficacy of continuous vs. intermittent infusions of various antibiotics, including cefamandole, in febrile neutropenic patients." For those patients infected with susceptible pathogens, continuous infusion was more efficacious than intermittent administration. Two other studies have compared continuous and intermittent infusions of ceftazidime in the treatment of gram-negative infections.[45,46] These investigations found equivalent outcomes despite the fact that less total drug was used for continuous infusion (3-4 g vs. 6 g, respectively). Both dosing regimens, however, provided concentrations that exceeded the MIC for virtually all of the dosing interval.

Although it can be difficult to vary dosing regimens in clinical trials enough to reduce the inherent parameter interrelationships, studies in animal infection models do allow dosing regimen design to eliminate much of the parameter interdependence. As shown in Figure 1-9,

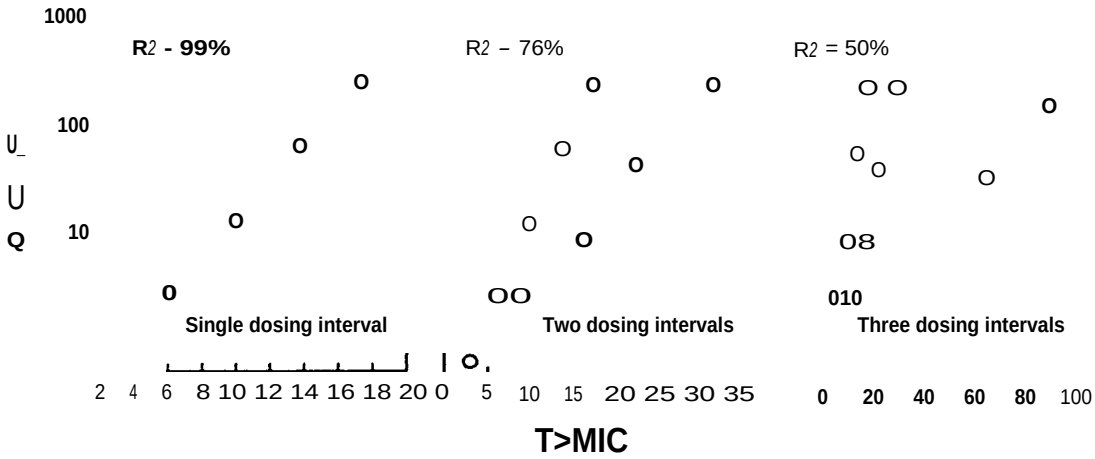

FIGURE 1-9. | nterrelationship among dosing interval number and the pharmacokinetic and pharmacodynamic parameters. AUC, area under the concentration curve; MIC, minimum inhibitory concentration; Rz, percentage of variation in bacterial numbers that could be attributed to differences in each of the pharmacodynamic parameters; T > MIC, percentage of time serum concentrations exeed the MIC.

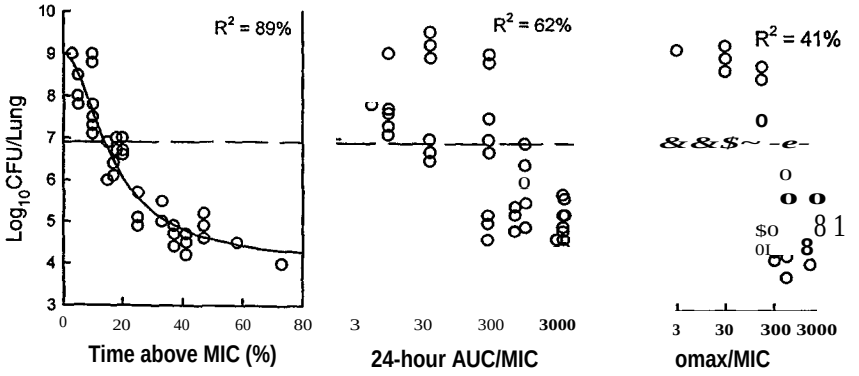

FIGURE 1-to. Relationship between three pharmacodynamic parameters (percentage of time serum levels are above minimum inhibitory concentration [MIC], the 24-hour area under the concentration curve [AUC], and the Cm JMIC ratio) and the number of *Pseudomonas aeruoinosa* organisms in the thighs of neutropenic mice after 24 hours of therapy with meropenem. Each point represents two mice (mean of four thighs). The dotted line reflects the number of bacteria at the initiation of therapy. The 02 value represents the percentage of variation in bacterial numbers that could be attributed to differences in each of the individual pharmacodynamic parameters. CFU, colony-forming unit

with only a single dosing interval (frequency) there is a strong correlation between the AUC/MIC ratio and the T >MIC. With two dosing intervals the interrelationship is less significant and is even less so with three or more dosing intervals. In these experimental designs, several total daily doses and dosing intervals are used to vary the drug AUC, $_{Cmax,}$ and T >MIC. Subsequent analysis of treatment endpoints in relation to each of the parameters then allows one to determine which parameter(s) best predicts antimicrobial activity.

Time above the MIC has consistently been the only PK-PD parameter that correlates with the efficacy of the (3-lactams.I1 For example, Leggett et al demonstrated that the cumulative dose of several (3-lactams necessary to produce 50% of the maximum bacteriologic effect (ED_{50}) increased significantly with longer dosing intervals.21 In similar animal infection models, others have found continuous R-lactam infusion regimens to be more efficacious than those intermittently dosed." Figure 1-10 illustrates the relationship between the treatment efficacy of the carbapenem meropenem against P. ***aeruginosa*** and each of the pharmacokinetic (PK) and pharmacodynamic (PD) parameters. Pairs of neutropenic mice were treated with multiple dosage regimens of meropenem that varied both in the total dose and dosing interval. Changes in organism burden after 24 hours of therapy are correlated with the Cm./MIC ratio, the 24-hour AUC/MIC ratio, and the percentage of time that serum levels exceed the MIC. Regression of the data with both the AUC/MIC ratio (coefficient of determination = R2 = 62%) and the Clna„/MIC (R2 = 41 %) demonstrate only a modest relationship. However, regression in the percentage of time serum levels remain above the MIC (R2 = 89%) demonstrates a strong relationship. Time above the MIC is also the parameter that correlates with the efficacy of most of the macrolides, clindamycin, oxazolidinones, and flucytosine. [16,17,19,20]

For aminoglycosides, fluoroquinolones, ketolides, streptogramins, glycopeptides, daptomycin, azithromycin, amphotericin B, and fluconazole the AUC/MIC or Cmd/MIC ratio has been the parameter that correlate with efficacy in animal infection models.` Figure 1-11 demonstrates the relationship between levofloxacin efficacy and each of the PK and PD parameters in a neutropenic murine thigh infection model due to Streptococcus ***pneumoniae.*** The strongest parameter correlation is seen with the 24-hour AUC/MIC ratio (AUC/MIC R2 = 88%, T >MIC R2 = 50%, C../MIC R2 = 45%). Several other studies have demonstrated the importance of the concentration-dependent PK and PD parameters for these drugs [12,13] For example, Blaser et al demonstrated superior efficacy with single compared with multiple aminoglycoside and quinolone exposures, suggesting that achieving a high peak concentration is important 2' These observations from both in vitro and in vivo models have demonstrated

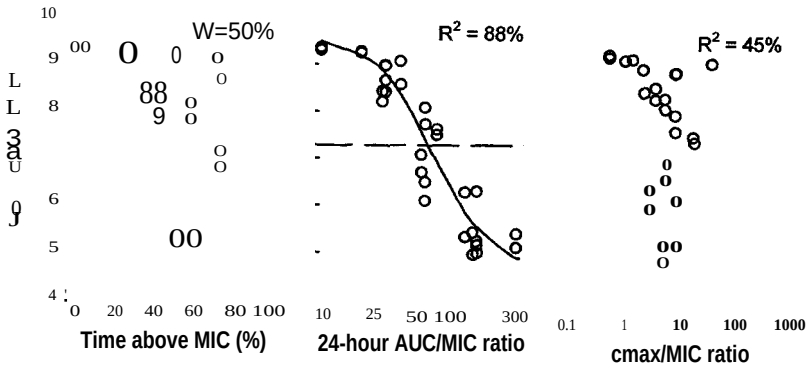

FIGURE 1-11. Relationship between three pharmacodynamic parameters (percentage of time serum levels are above minimum inhibitory concentration [MIC], the 24-hour area under the concentration curve [AUC], and the C m./MIC ratio) and the number of Streptococcus *pneumoniae* organisms in the thighs of neutropenic mice after 24 hours of therapy with levofloxacin. Each point represents one mouse (mean of two thighs). The dotted line reflects the number of bacteria at the initiation of therapy. The R2 value represents the percentage of variation in bacterial numbers that could be attributed to differences in each of the individual pharmacodynamic parameters. CFU, colony-forming unit.

'References 6,19,20,22-24,27,29,36,37,39,40,43,50,51.

that the AUC and C. level are the most important dosing parameters as long as the dosing interval is not extended beyond the T >MIC and the postantibiotic effect. In these studies the major contribution of higher peak concentrations was the prevention of regrowth of resistant subpopulations.[39,54] Furthermore the toxicodynamics of the aminoglycosides would also favor optimizing the C. level.[57,58] The aminoglycoside uptake kinetics at both of the end-organ sites of toxicity (renal tubule and organ of Corti) are saturable. Experimental animal models and human data have demonstrated that the renal cortical uptake of aminoglycosides is less with once-daily dosing than with more frequent administration (Figure 1-12).[59] Similar animal model data have also examined aminoglycoside kinetics in relation to ototoxicity.[57]

Although the glycopeptides, tetracyclines, azalides, and azoles do not exhibit concentration-dependent killing, the AUC/MIC ratio has been the major parameter correlating with therapeutic efficacy of these drugs.[19,20,36] This parameter correlation is likely related to the prolonged PAEs produced by these drug classes. For example, Louie et al demonstrated that fluconazole efficacy in a murine candidiasis model was dependent upon the total dose of drug (AUC) and not the dosing interval.[60] Subsequent evaluation demonstrated prolonged in vivo persistent effects (postantifungal effects) and confirmed the importance of the AUC in describing the activity of the azoles.[16]

Antivirals

Pharmacodynamic analysis with antivirals has been more difficult because of the lack of reproducible, standardized in vitro susceptibility testing. Various studies, however, have demonstrated the impact of dose and dosing interval upon antiviral effect and drug toxicity.[61] Drusano et al have successfully examined the effect of a variety of dosing intervals upon antiviral efficacy using an in vitro hollow fiber model.[61,62] For example, these investigations found the protease inhibitors are most efficacious when administered by continuous infusion, suggesting that the duration of time concentrations remain above a threshold level may be the most important PK-PD determinant for these compounds.[63] This same group of investigators found a similar dosing strategy to be important for the efficacy of zidovudine in a murine encephalitis model[65] On the other hand, the nucleoside analog stavudine was more efficacious when dosed intermittently in the hollow fiber model.[66] Analysis of foscarnet dosing in two cytomegalovirus retinitis clinical trials have demonstrated that both efficacy and toxicity are driven by total drug exposure or the AUC .[67,61] Most recently, clinical trial analysis has demonstrated that the time to clearance of influenza is related to the AUC of the neuraminidase inhibitor.[69]

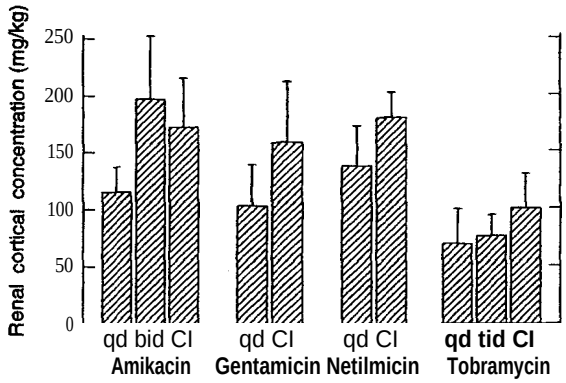

FIGURE 1-12. Renal cortical concentrations (mg/kg) of amikacin, gentamicin, netilmicin, and tobramycin following 24 hours of drug administration by continuous infusion, once daily, twice daily, or thrice daily. Cl, renal clearance. (From Urban A, Craig WA: Daily dosing of aminoglycosides. Curr Clin Top Infect Dis 1997;17:238-255.)

MAGNITUDE OF PHARMACOKINETIC-PHARMACODYNAMIC PARAMETER REQUIRED FOR EFFICACY AND CLINICAL IMPLICATIONS

Because PK-PD parameters can correct for differences in pharmacokinetics among species and intrinsic antimicrobial activity, it has been shown that the magnitude of these parameters necessary for efficacy is similar in different animal species including humans.[9,39,70-72] This should not be surprising since the receptor for the antimicrobial is in the pathogen and therefore is the same in both animal models and humans. Studies show that the magnitude of the PK-PD parameter required for efficacy of a drug is similar for different dosing regimens, for different drugs within the same class providing free drug concentrations are used, and for different sites of infection.[19] Furthermore, treatment of infections due to organisms with reduced susceptibility to penicillins, macrolides, and quinolones and with resistance mechanisms due to reduced target affinity also appear to require similar parameter magnitudes for efficacy.[10,73,74] Thus the results from these studies in animal infection models have been useful in the design of dosing regimens in humans.[75,16] This has been particularly helpful for the design of dosing regimens for antimicrobials under development and also for those drugs already available in clinical situations in which it is difficult to accumulate sufficient patient data, as is the case for the treatment of emerging resistant pathogens. Most recently this type of analysis has been used in the development of antimicrobial treatment guidelines for otitis media, sinusitis, and community-acquired pneumonia.[75,77-79]

(3-Lactams

Studies in animal infection models and humans have demonstrated that antibiotic concentrations do not need to exceed the MIC for the entire dosing interval to exert sufficient antimicrobial activity.[43,80] For a variety

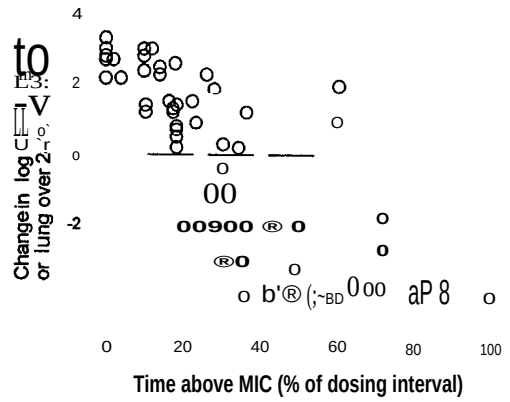

FIGURE 1-13. Relationship between time above minimum inhibitory concentration (MIC) and change in bacterial number for numerous strains of Streptococcus *pneumoniae* at 24 and 48 hours in the thighs and lungs, respectively, of neutropenic mice following treatment with amoxicillin or amoxicillin-clavulanate. CFU, colony-forming unit. (From Andes D, Craig WA: In vivo activities of amoxicillin and amoxicillin-clavulanate against Streptococcus *pneumoniae:* Application to breakpoint determinations. Antimicrob Agents Chemother 1998;42:2375-2379.)

of (3-lactams, in vivo bacteriostatic efficacy in animal infection models has been observed when serum levels are above the MIC for 20% to 40% of the dosing interval, and maximal organism reductions are seen when levels are above the MIC for 60% to 70% of the interval.[19,42,70,80] Similar times above the MIC have been observed for a variety of (3-lactams in several infection models and at several infection sites providing free drug levels in serum were used for comparison. Data in Figure 1-13 represent a compilation of two amoxicillin in vivo studies against ***S. pneumoniae*** in a thigh and lung infection model .[70] In general, the percentages of time above the MIC are slightly lower for the penicillins (30% to 40%) than for the cephalosporins (40% to 50%) and are lower yet for the carbapenems (20% to 30%).[19] These differences appear to reflect differences in the rate of killing, which is fastest with the carbapenems and slowest with the cephalosporins.

Drug kinetics in the central nervous system (CNS) are different from those in any other compartment of the body. The fluid surrounding the brain parenchyma is an ultrafiltrate of serum. Despite these clear differences in kinetics, one would expect that the patterns of antimicrobial activity predictive of efficacy outside of the CNS would also be observed in meningitis. However, the poor penetration of most antibiotics across the blood-brain barrier and the long elimination half-lives observed in cerebrospinal fluid (CSF) compared with those in serum often result in much less fluctuation in drug concentrations than is observed in other infection sites. Furthermore the goal of complete sterilization in the CSF to prevent disease relapse is with few exceptions not necessary in other infections. In general, however, the pharmacodynamic activity and relationships for the various classes of antimicrobials do hold true in this protected site.[81-85] Here, however, it is clear that CSF levels are a much stronger predictor of efficacy than serum levels. In addition, because of the significant differences in rates of organism replication in the CSF and the lack of factors present in serum that can often contribute to prolonged PAEs, the in vitro measure with which drug kinetics are best correlated is the MBC rather than the MIC.[83] For example, the (3-lactams in serum saturate killing rates with levels exceeding the MIC four or five times, whereas in the CSF maximum bactericidal activity is not observed until levels exceed the MBC by 10 to 30 times." Lutsar et al found maximal killing in a rabbit meningitis model when ceftriaxorie levels exceeded the MBC for 75% to 100% of the dosing interval.[85] Likewise, study of ampicillin in pneumococcal meningitis models fractionated into 8-, 12-, and 24-hour regimens showed it was successful as long as CSF ampicillin levels exceeded the MBC for about 50% of the dosing interval, similar to the relationship observed in nonmeningitis models.[79]

Although studies in animal infection models lend themselves to easily determining parameter magnitudes necessary to achieve a variety of treatment endpoints, there are obvious limitations to making similar observations in clinical trials. For prospective clinical trials there is the ethical issue regarding the design of treatment regimens thought to be potentially inferior (R-lactam regimen with T >MIC less than 40% of dosing interval). For retrospective analysis there may not be enough MIC (pathogen resistance) or drug concentration variation to produce sufficient parameter magnitude variations. However, one clinical study type that is being recognized as increasingly important for predicting pharmacodynamic outcomes in humans is the clinical trial simulation using population pharmacokinetics.[86] These investigations determine antimicrobial pharmacokinetics in patient populations representative of those who would receive antimicrobial treatments in various clinical scenarios using optimal sampling techniques. Large clinical trials of patients with varying pharmacokinetics are simulated to determine the frequency with which a specific dosing regimen would achieve a pharmacodynamic target against most (e.g., MIC90) of the pathogens one would expect to encounter. This pharmacodynamic target is based upon results from animal model studies. The data from these studies is then related to the distribution of MICs of the target pathogens. For example, (3-lactams have been shown to be effective when dosing regimens produced serum levels above the MIC for 40% to 50% of the dosing interval.

A few clinical trial investigations have lent themselves to pharmacodynamic analysis. Several investigators have performed treatment trials in acute otitis media in children and acute maxillary sinusitis in adults in which fluid at the site of infection has been sampled before and after antimicrobial therapy to determine bacteriologic cure rates.[72,a 7-92] Furthermore, because of the

emergence of resistant S. *pneumoniae,* recent studies of this type have provided MIC fluctuation of sufficient degree to produce pharmacodynamic magnitude variation. As one would expect, the primary therapeutic agents used in these respiratory tract treatment trials have included a variety of R-lactams and macrolide antibiotics. One can estimate the time above MIC for the various antimicrobial agents based upon human pharmacokinetic data and the MICs of the organisms recovered and examine the relationship between bacteriologic treatment success and the magnitude of the T >MIC. In Figure 1-14 one sees bacteriologic cure rates in the range of 85% to 100% when R-lactam and macrolide serum levels exceeded the MIC for 40% to 50% of the dosing interval.[72] This is similar to the time above the MIC found to produce bacteriologic efficacy of (i-lactam in animal models. Ambrose et al observed a similar association in the treatment of community-acquired pneumonia.[93] This study of cefuroxime therapy compared continuous infusion of 1.5 g/day (T >MIC 100%) to a lower total dose administered thrice daily (750 mg = T >MIC 50% to 60%) and found no difference in clinical endpoints. These results suggest again that serum drug levels need not exceed the MIC for the entire dosing interval and that a T >MIC magnitude of 40% to 50% may be a suitable target.

Continuous infusion is the most efficient approach for achieving serum levels above the MIC of an infecting organism. This regimen design can be convenient in the outpatient setting because of the reduction in the number of manipulations necessary. In addition, less total drug is necessary to achieve the pharmacodynamic goal. Since the rate and extent of killing with (3-lactams saturates at concentrations around four times the MIC, one could choose this as a target steady state concentration for continuous infusion dosing. One could estimate the dose and rate of infusion with a simple calculation. One need only consult a common reference book to find the estimated volume of distribution and elimination half-life of the drug. Factoring in the body weight of the patient, the rate of infusion would equal (R):

$$R = (Css)\ (VD)\ (BW)\ (0.693)$$
$$(t/O$$

Where R is the rate of infusion (mg/h), C', is the desired steady state concentration (mg/L), O is the volume of distribution (L/kg), BW is the body weight (kg), and t_{ii2} is the elimination half life in hours. In addition to the therapeutic advantage of continuous infusion, the ability to use less total drug to achieve one's dosing goal may also reduce the incidence of dose-related adverse effects such as neutropenia. For example, a 2 g dose of ceftazidime administered every 8 hours would achieve a steady state level of 25 mg/L. On the other hand, a 3 g ceftazidime dose administered via continuous infusion would achieve a level of 29 mg/L.[45,46] Continuous infusion is best suited for R-lactam drugs with short elimination half-lives and stability at room temperature for at least 12 hours.

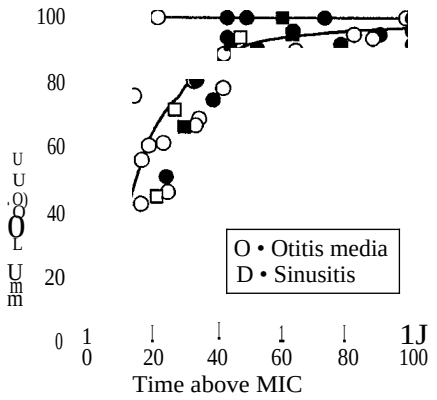

FIGURE 1-14. Relationship between the time above minimum inhibitory concentration (MIC) and bacteriologic cure for various P-lactams and macrolides against ***Streptococcus pneumoniae*** and ***Haemophilus influenzae*** in patients with otitis media and sinusitis.

Macrolides

When one looks at various macrolide antibiotics, animal infection models have suggested that efficacy is achieved when serum levels are above the MIC for 50% of the dosing interval.[19,20] As with a number of P-lactams, macrolides have also been examined in double-tap otitis media trials.[12] Data in Figure 1-14 also include a number of macrolide trials. As with P-lactams, when serum levels of the macrolides exceeded the MIC 40% to 50% of the dosing interval, high rates of bacteriologic eradication are observed. For example, treatment against susceptible *S. pneumoniae* was successful in 93% and 100% of patients treated with erythromycin and clarithromycin, respectively (Table 1-2). One would anticipate this high success rate, with macrolide levels above the MIC for much more than 50% of the dosing interval. On the other hand, when examining treatment outcome against *Haemophilus influenzae* one would anticipate bacteriologic failures, as macrolide dosing would achieve levels above the MIC for far less than 50% of the dosing interval. In these trials, both erythromycin and clarithromycin resulted in bacteriologic success rates similar to those that would be observed with placebo (50% or less).

Azithromycin and Ketolides

For the azalide azithromycin and the new ketolide class of antimicrobial, the 24-hour AUC/MIC ratios have correlated best with treatment outcome. The magnitude of the azalide 24-hour AUC/MIC ratio associated with treatment efficacy in both in vivo infection models and clinical trials is near 25.[2°] The clinical trial data available for azithromycin is similar to the otitis media data for the (3-lactams and other macrolides. In treatment of

TABLE 1-2 n Bacteriologic Cure in Otitis Media with Macrolide Based upon Pharmacodynamic Parameter Magnitude

	Streptococcus pneumoniae			*Haemophilus influenzae*		
Drug	***Susceptibility***	***PK-PD Parameter magnitude***	***Bacteriologic cure***	***Susceptibility***	***PK-PD Parameter magnitude***	***Bacteriologic cure***
Erythromycin	S	T>MIC = 88%	14/15(93%)	R	T>MIC = 0%	3/2005%)
Clarithromycin	S	T>MIC = 100%	12/12 (100%)	S?	T>MIC = 0%	3/15(20%)
Azithromycin	S	AUC/MIC = 50	15/16(94%)	S?	AUC/MIC < 2	13/35(37%)
	R	AUC/MIC < 0.1	1/3(21%)			

AUC (area under the serum concentration-time curve)/MIC (minimum inhibitory concentration) ratio; PD, pharmacodynamic; PK, pharmacokinetic; R, resistant; S, susceptible; T>MIC, percentage of time serum concentrations exceed the MIC.

azithromycin-susceptible S. *pneumoniae,* when the 24-hour AUC/MIC ratio exceeded 25, bacteriologic success was observed in 94% of patients (Table 1-2). In the treatment of resistant S. *pneumoniae* and H. *influenzae,* however, 24-hour AUC/MIC values are low (<O.1 and 2, respectively), and treatment success rates were similar to what one would expect from placebo alone (21% and 37%, respectively)." For treatment of pathogens in pneumonia, if ELF concentrations (24-hour AUC/MIC 25 = MIC 2 gg/mL) are more important than serum pharmacodynamics (24-hour AUC/MIC 25 = MIC 0.12 gg/mL), then one would predict being able to successfully treat infections due to organisms with MICs 16-fold higher than has been demonstrated in otitis media (Table 1-1).[10] Again, however, no studies thus far have answered this important question. Similar 24-hour AUC/MIC magnitudes may apply to the ketolides.

Fluoroquinolones

Studies against gram-negative bacilli in animals and humans have suggested that the fluoroquinolone 24-hour AUC/MIC ratio must exceed 100 to 125 to obtain high rates of bacteriologic efficacy and clinical cure.[16,24] Analyses from a variety of animal models including pneumonia, endocarditis, meningitis, and thigh infection demonstrate that the magnitude of the AUC/MIC ratio is similar regardless of the infection site.[6,19,39,40,43] Data shown in Figure 1-15 demonstrate maximal survival in a variety of gram-negative in vivo infection models when the 24-hour fluoroquinolone AUC/MIC ratio approaches a value of 100. A 24-hour AUC/MIC ratio of near 100 is essentially like maintaining serum concentrations four times above the MIC during the 24-hour dosing period. Forrest et al found a relationship between a ciprofloxacin 24-hour AUC/MIC ratio of greater than 125 and satisfactory clinical outcomes in an intensive care unit population (Fig. 1-16).[2] Lower parameter magnitudes resulted in treatment failures in nearly 50% of patients. Preston et al have also analyzed a clinical trial using levofloxacin population pharmacokinetics and demonstrated that a Cmax/MIC ratio of greater than 12 or a 24-hour AUC/MIC ratio of 100 was predictive of treatment success.[86] However, studies using in vitro kinetic models,

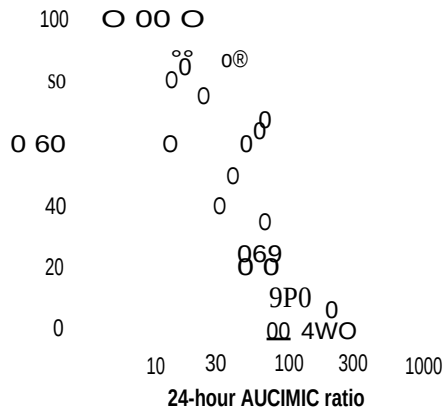

FIGURE 1-15. **Relationship between the 24-hour area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) ratio and mortality in various experimental infection models treated with fluoroquinolones. *Solid circles,* data from neutropenic murine thigh and lung infection models. Hollow *circles,* data from the literature using pneumonia, peritonitis, and sepsis models in mice, rats, and guinea pigs. (From Craig WA, Dalhoff A: Pharmacodynamics of fluoroquinolones in experimental animals. In Kuhlman J, Dalhoff A, Zeiler HJ [eds]: Handbook of Experimental Pharmacology, vol 127: Quinolone Antibacterial. pp 207-232.)**

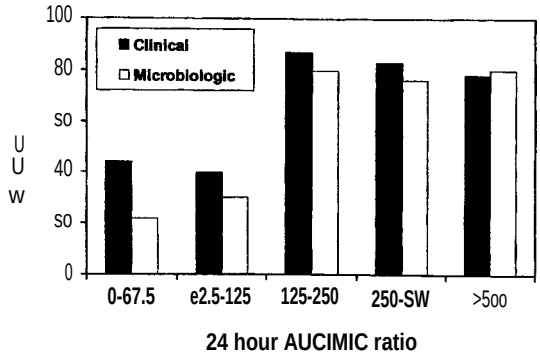

FIGURE 1-16. **Relationship between the 24-hour area under the curve (AUC)/minimum inhibitory concentration WIC) ratio and the microbiologic and clinical efficacy of ciprofloxacin in patients with serious bacterial infections. (From Craig WA: Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-12.)**

animal survival studies in nonimmunocompromised animals, and clinical trials suggest that the magnitude of the 24-hour AUC/MIC ratio necessary for efficacy of the quinolones in treatment of pneumococcal infections is more in the range of 25 to 35, or essentially like having levels average 1 time the MIC for the 24-hour dosing period.[6,13,39a] For example, Lacy et al studied both levofloxacin and ciprofloxacin in an in vitro kinetic model of S. *pneumoniae* and observed maximal organism killing with quinolone AUC/MIC ratios of approximately 30.[9] This is also supported by studies in non-neutropenic pneumococcal infection models with a number of fluoroquinolones in which maximal survival has been observed when the 24-hour AUC/MIC ratio magnitude approaches 25 to 30 (Fig. 1-17). More recently, Ambrose et al examined the relationship between the fluoroquinolone AUC/MIC ratio and treatment outcomes in patients with pneumococcal lower respiratory tract infections. In this randomized, double-blind evaluation a fluoroquinolone 24-hour AUC/MIC ratio of 50 was associated with a 90% probability of bacterial eradication.[96] This AUC/MIC magnitude is similar to that seen in experimental models and offers an explanation for the good efficacy of the newer fluoroquinolones against S. *pneumoniae*.

Aminoglycosides

Several investigators have found a C_{min}/MIC ratio of 8 to 10 in both in vitro and in vivo models to be associated with efficacy and the prevention of the emergence of resistant subpopulations.[28,29,80,114] Recent analysis of multiple aminoglycoside animal model studies found a strong relationship between the AUC/MIC ratio and bacteriologic efficacy in meningifs.[12] In this analysis a maximal reduction in bacterial numbers was observed when the aminoglycoside AUC/MIC ratio exceeded 50. One clinical nosocomial pneumonia trial also reported a clinical response rate (reduction in fever and leukocytosis) in more than 90% of patients when the C_{max}/MIC ratio reached 8 to 10.[97] Of further interest is the fact that most patients did not achieve this dosing goal with the empiric use of 5 mg/kg/day of the aminoglycoside. Moore et al found a similar association between C_{max}/MIC ratio and survival in the treatment of bacteremia.[98] Once-daily aminoglycoside administration is the most efficient and reliable strategy to achieve high peak concentrations. A number of other investigations have studied the impact of dosing regimens on the efficacy of aminoglycosides in clinical trials.[99,100] The results of these studies have been examined in 7 meta-analyses and suggest a small, nonsignificant trend toward better efficacy in 5 of 7 analyses and a 26% reduction in nephrotoxicity in the largest analysis with the once-daily administration of aminoglycosides.[41,101-107] Other clinical studies have demonstrated that the onset of nephrotoxicity is delayed for several days (3 vs. 7 days) when these drugs are administered once-daily rather than in multiple-daily doses.[108-111] However, once-daily dosing may not be best in all situations. Animal models of enterococcal endocarditis have demonstrated a more significant reduction in vegetation organism counts when aminoglycosides were administered in multiple rather than single daily doses.[112]

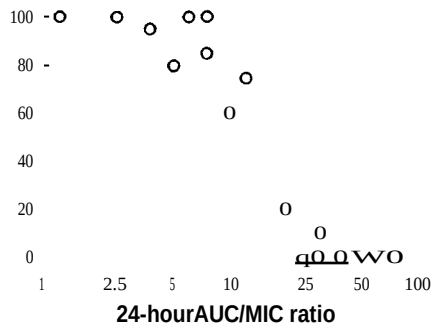

FIGURE 1-17. Relationship between the 24-hour area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) ratio and survival in the neutropenic murine thigh and lung infection models infected with S. pneumoniaetreated with fluoroquinolones.

Oxazolidinones

Although the distribution of linezolid MICs have thus far been narrow, animal model studies suggest that efficacy with these compounds is observed when dosing regimens achieve serum levels above the MIC for 50% of the dosing interval." The studied dosage regimen of this drug provides serum levels above an MIC of 8 gg/mL for 50% of the dosing interval and has proven effective in various comparative clinical trials.

Fluconazole

Although in vitro susceptibility testing with antifungals has only recently been standardized, data from a number of animal model studies and clinical trials suggest that triazole MICs correlate reasonably well with treatment outcomes. For fluconazole, study in animal models has found treatment success associated with 24-hour AUC/MIC ratios near 25 over a wide range of MICs.[36] This, 24-hour AUC/NIIC ratio correlates closely with the dose-MIC relationship recently established by the NCCLS (National Committee for Clinical Laboratory Standards).'" As shown in Table 1-3, a fluconazole dose of 200 mg/day would produce a 24-hour AUC/breakpoint MIC (8 gg/mL) ratio of near 20. With dose escalation to 400 or 800 mg/day, a similar ratio would be seen at the susceptible-dose-dependent breakpoints (16-32 pg/mL), again similar to the parameter magnitude observed in animal infection models.

Flucytosine

Andes and van Ogtrop found maximal reduction in *Candida* burden in the kidneys of mice when flucytosine serum levels were above the MIC of the organism for

TABLE 1-3 • Comparison of Fluconazole AUC/MIC Ratio to Results from Clinical Trials

NCCLS breakpoint (mg/L)	Dose (mg/day)	AUC (mg/hr/L)	AUCBreakpoint MIC ratio	Clinical success
R >>-64	800	475	7	**54**
S-DD 16-32	**400-800**	**240-475**	15	86
S<- 8	200	134	17	81

AUC, area under the serum concentration-time curve; MIC, minimum inhibitory concentration; NCCLS, National Committee for Clinical Laboratory Standards; R, resistant; S, susceptible; S-DD, susceptible-close-dependent breakpoints.

50% of the dosing interval." These studies, however, included only a single pathogen. If, however, this parameter magnitude is relevant for other organisms, it would suggest that we are currently overdosing this compound with a narrow therapeutic window. Current administration of 100 to 150 mg/kg/day in four divided doses would provide time above the MIC_{90} of commonly treated pathogens for more than 100% of the dosing interval, even if the interval were to be doubled.

PHARMACODYNAMICS OF COMBINATION ANTIMICROBIAL THERAPY

Combination therapy has been used to enhance the antimicrobial activity of two or more drugs whose activity together is either additive or synergistic. In addition, various drug combinations have also been used to reduce the emergence of resistance to one or both of the compounds and to reduce drug toxicity by occasionally allowing the administration of lower doses of drugs with a narrow therapeutic index.

A large number of in vitro studies have used a variety of techniques to examine the effects of different antimicrobial classes in combination.[91.11Φ116] Despite the extensive fund of pharmacodynamic knowledge available for an antimicrobial used alone, however, few studies have analyzed the in vivo pharmacodynamics of these agents used in combination. Thomas et al suggested that adding the AUC/MIC ratio of an aminoglycoside or fluoroquinolone to the AUC/MIC ratio of a (3-lactam was an appropriate way to estimate their pharmacodynamic activity in combination.[117] Mouton et al however, recently demonstrated that the in vivo pharmacodynamics predictive of efficacy of R-lactams, aminoglycosides, and fluoroquinolones when used in combination is similar to that predictive of efficacy when these compounds are used alone."' Thus the PK-PD parameter and parameter magnitude predictive of efficacy for individual drugs are class dependent when used in combination and are similar to when they are used as single agents.

TREATMENT OF RESISTANT ORGANISMS

Studies with a number of antimicrobial classes against multiply resistant pathogens have observed similar treatment outcomes when dosing regimens are able to produce pharmacodynamic parameter magnitudes equal to those shown to be successful in the treatment of susceptible pathogens. For example, in vivo pharmacodynamic studies with amoxicillin and amoxicillin-clavulanate against a large number of strains of S. *pneumoniae,* including strains classified as penicillin-susceptible, -intermediate, and -resistant, with amoxicillin MICs varying 60-fold, demonstrated that the magnitude of the T >MIC parameter required to produce various microbiologic outcomes (static dose, ED_{50-801} and mortality) was similar for all of the organisms (Fig. 1-18).[1°] Maximal killing over 24 hours was observed when serum levels remained above the MIC for 50% to 60% of the dosing interval for both susceptible and resistant S. *pneumoniae.* In subsequent studies involving a longer course of therapy (4 days), 100% survival was achieved when dosing resulted in serum levels above the MIC for at least 40% of the dosing interval. Analysis of cefprozil therapy in this model has demonstrated similar results.[119]

In the past 5 years the NCCLS has begun to review susceptibility breakpoints for oral P-lactams. Various types of data have been factored into breakpoint determi nations, including the population distribution of organism MICs, the activity of the antimicrobial in question against organisms with known mechanisms of resistance, the correlation of clinical outcome with susceptibility results, and, more recently, pharmacodynamic predictions from in vivo infection models.

In situations in which there is insufficient clinical data with various compounds against less susceptible pathogens such as R-lactam-resistant pneumococci, the NCCLS is relying upon PK-PD parameter magnitudes defined in animal infection models.[12°] For example, a pharmacodynamic template for (3-lactams can be based upon a pharmacodynamic goal of maintaining serum levels above the MIC of the infecting pathogen for 40% of the dosing interval. Thus susceptibility breakpoints (MICs) for various antimicrobial-organism combinations can be based upon the highest MIC that would produce levels above the MIC for 40% of the dosing interval. Table 1-4 lists the current susceptibility breakpoints for a number of oral and parenteral (3-lactams and the highest MIC for which serum levels would still remain above the MIC for 40% of a standard dosing regimen. One can see that often times the current breakpoint MIC is lower than the

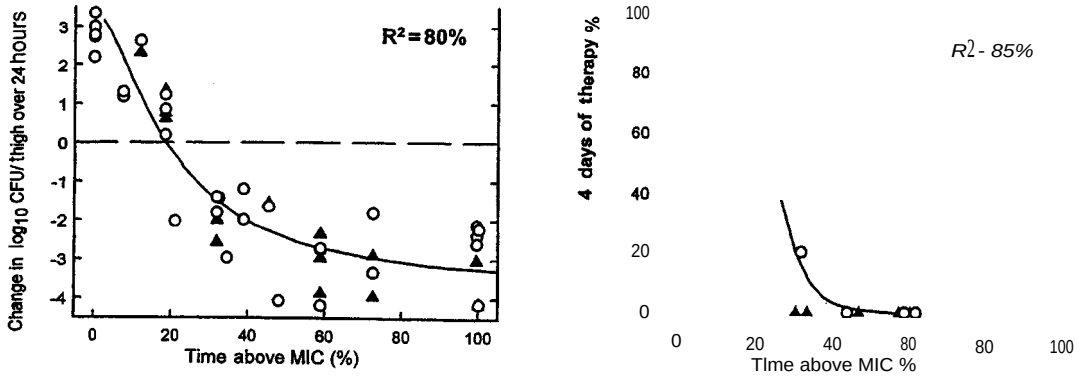

FIGURE 1-18. Left Panel, Relationship between change in log,, colony-forming units (CFU) per/thigh over 24 hours and duration of time that serum levels exceed the minimum inhibitory concentration WIC) following doses of 2, 7, and 20 mg/kg of amoxicillin every 8 hours and doses of 7 mg/kg of amoxicillin-clavulanate every 8 hours. Each value represents the mean for two thighs. *Right* Panel, Relationship between mortality and duration of time that serum levels exceed the MIC following doses of amoxicillin at 2, 7, and 20 mg/kg and amoxicillin-clavulanate at 7 mg/kg every 8 hours. Each value represents the mean for 5 mice. R 2, percentage of variation in bacterial numbers that could be attributed to differences in each of the pharmacodynamic parameters. (From Andes D, Craig WA: In vivo activities of amoxicillin and amoxicillin-clavulanate against Streptococcus pneumoniae: Application to breakpoint determinations. Antimicrob Agents Chemother 1998;42: 2375-2379.)

TABLE 1-4 a Accepted and Pharmacodynamic in Vitro Susceptibility Breakpoint of Selected R-Lactams

Drug-Dosing regimen	Susceptibility breakpoint MIC (gg/mL)	Pharmacodynamic breakpoint MIC (gg/mL) (T>MIC 40%)
Amoxicillin 500 mg PO tid (40 mg/kg)	2.0*	2.0
Amoxicillin 1 g PO tid (80 mg/kg)	2.0*	4.0
Cefaclor 500 mg PO tid	1.0*	0.5
Cefuroxime 500 mg PO bid	1.0*	1.0
Cefprozil 500 mg PO bid	1.0*	1.0
Cefpodoxime 200 mg PO bid	0.5*	0.5
Cefixime 400 mg PO bid		0.5
Loracarbef 400 mg PO bid		1.0
Penicillin G 2 MU IV qid	<0.1	4.0
Ampicillin 1 g IV qid	<0.1	4.0
Nafcillin 2 g IV qid	1.0t	1.0
Ticarcillin-Clavulanate 3 g IV qid	8.Ot	16
Cefotaxime 1 g IV tid	0.5"	2.0
Cefuroxime 0.75 g IV tid	0.5*	4.0
Ceftriaxone 1 g IV qid	0.5*	2.0
Cefepime 1 g IV bid	0.5*	4.0
Meropenem 0.5 g IV tid	4.Ot	4.0
Imipenem 500 mg IV qid	4.Ot	4.0

MIC, minimum inhibitory concentration; T>MIC, percentage of time serum levels remain above the MIC.
**Streptococcus pneumoniae.*
'*Staphylococcus aureus.*

pharmacodynamic breakpoint, particularly for the parenteral agents. The susceptibility breakpoints for the parenteral compounds are almost always lower because that these values have been based upon the treatment of meningitis, where higher serum levels would be necessary to achieve adequate CSF levels. There are numerous case reports of meningitis treatment failures to support these breakpoints.[121,122] In most situations, however, these breakpoints would be too high to guide therapy of non-CNS sites such as pneumonia. A number of clinical trials in the literature have demonstrated successful outcomes when these agents have been used to treat these less susceptible pathogens in community-acquired pneumonia. Pallares et al were the first to address this issue. For a cohort of more than 500 patients with severe community-acquired pneumonia receiving both penicillins and third-generation cephalosporins, mortality rates were independent of the susceptibility of the pathogen (Table 1-5).[123] Most recently Feiken et al examined risk for mortality in more than 4000 patients with bacteremic pneumococcal pneumonia.[114] In this large analysis investigators were able to demonstrate a significant association between MIC elevation and mortality. As shown in Table 1-6 however, it was not until the penicillin MIC

TABLE 1-5 • Treatment Impact of Drug-Resistant Pneumococci on Mortality in Community-Acquired Pneumonia

Penicillin MIC (gg/ml)	Mortality/Patients in group (%) Penicillin/Ampicillin	Ceftotaxime/Ceftriaxone
S =<-0.06	24/12609)	32/127(25)
I = 0.12-1.0	4/14(24)	5/3305)
R = 2-4	6/24(25)	13/59(22)

I, penicillin-intermediate; MIC, minimum inhibitory concentration; R, penicillin-resistant; S, penicillin susceptible.

TABLE 1-6 w Risk for Mortality in Bacteremic Pneumococcal Pneumonia Based upon P-Lactam MIC

Drug MIC	Odds ratio (95% CI)
Penicillin G MIC >>-4.0	7.1 (1.7-30)
Penicillin G MIC = 2.0	0.7 (0.1-5.5)
Penicillin G MIC = 0.12-1.0	1.0 (0.3-3.0)
Penicillin G MIC <- 0.12	Referent
Cefotaxime MIC >- 2.0	5.9 (1.1-33)
Cefotaxime MIC = 1.0	1.5 (0.3-7.4)
Cefotaxime MIC <_ 1.0	Referent

CI, confidence interval; MIC, minimum inhibitory concentration.

reached 4 gg/mL and the cefotaxime MIC reached 2 gg/mL that the risk of death increased. In both of these circumstances, one would have predicted treatment failure for these patients, as dosing regimens would not produce the pharmacodynamic goal of T >MIC of 40%. Re-evaluation of susceptibility breakpoints for the parenteral (3-lactams in the treatment of non-CNS infections is under consideration.

Animal model studies with numerous fluoroquinolones, macrolides, and ketolides have likewise demonstrated that the pharmacodynamic parameter magnitude required to successfully treat infections due to pathogens with reduced susceptibility is most often the same as that needed against susceptible organisms .' [3,14] This has been the case for all organisms whose mechanism of resistance is due to changes in drug target affinity. This would include macrolide- and ketolide-resistant pathogens with methylase mutations and fluoroquinolone mutations in one of the gyrases. There has, however, been a general resistance mechanism for which the degree of in vitro resistance does not appear to predict the in vivo behavior. Pneumococci exhibiting resistance due to an efflux mechanism appear significantly more susceptible in vivo than the in vitro MIC testing would suggest. [73,74] For example, the magnitude of the AUC/MIC ratio required to produce a net bacteriostatic effect was twofold to sevenfold less than that required for either the susceptible organisms or those with altered ribosomal affinity (Table 1-7).[74] Similarly, in studies with the a new fluoroquinolone against susceptible organisms and those resistant because of GyrA, ParC, or ParE, a similar PK-PD parameter magnitude was required to achieve efficacy. [73] Studies with organisms overexpressing efflux pumps, however, were more susceptible than would be predicted. The magnitude of the AUC/MIC ratio necessary to achieve a bacteriostatic effect was twofold to fivefold less than that required for either the susceptible organisms or those with altered gyrase enyzmes. The reason(s) underlying this in vitro-in vivo differential with organisms expressing these efflux pumps remains unclear.

PHARMACODYNAMIC PARAMETER-AND MAGNITUDE REQUIRED TO PREVENT THE EMERGENCE OF RESISTANCE

Clearly a number of factors can contribute to the development or emergence of antimicrobial resistance, including the organism inoculum and the varying mutational rates of different microbial species. [67,125,126] However, there is also a clear association between antimicrobial exposure and the selection or development of resistance. A growing knowledge base from in vitro and animal infection models has been used to examine the relationships between antimicrobial PK-PD parameters for different antimicrobials and the emergence and prevention of resistant pathogens.

TABLE 1-7 • Bacteriostatic Dose and Corresponding AUC/MIC Ratio of New Ketolide and Fluoroquinolone against Various Susceptible and Resistant Streptococcus *pneumoniae* Strains

Drug	MIC (mg/L)	Resistance mechanism	Bacteriostatic dose (mg/kg/day)	AUC/MIC ratio
Ketolide	0.015	Susceptible	8-20	260-826
	0.06	Decreased affinity (MLSB)	73-96	660-883
	0.5	Drug efflux (Mef)	145-153	160-165
Fluoroquinolone	0.008-0.015	Susceptible	112-781	10-73
	0.06-0.5	GyrA, ParC, ParE	224-1222	10-56
	0.06-0.12	Efflux	192035-286)	11401-116)

AUC, area under the serum concentration time curve; MIC, minimum inhibitory concentration.

Resistance Mutations

In most clinical trials and in vivo animal infection models, analysis demonstrating the relationship between antimicrobial dosing and resistance mutations has been extraordinarily difficult because of the relatively low mutation rates. In a nosocomial pneumonia trial of ciprofloxacin therapy, however, in those patients infected with P. *aeruginosa, six* patients developed drug resistance during therapy. [121] In this small cohort of patients who developed resistance the ciprofloxacin Cma~MIC ratio was less than 8. In the group of four patients whose C./MIC ratio exceeded 8, however, only one developed resistance. Thomas et al similarly examined data from a larger cohort of 107 patients with pneumonia.'" In this cohort, 25% of patients developed drug resistance. The incidence of resistance was highest for P. *aeruginosa* and (3-lactamase (type I)-producing gram-negative bacilli (45% and 27%, respectively). The investigators calculated the 24-hour AUC/MIC ratios from patients' serum concentrations and the organisms' MIC. The authors then determined the relationship between the magnitude of the 24-hour AUC/MIC ratio and the development of resistance. They found that quinolone AUC/MIC ratios exceeding 100 and Cma,/M1C ratios of greater than 8 were associated with the emergence of resistance in 9% of cases, whereas resistance developed 82% of the time when these ratios were less than 100 and 8, respectively. It is not clear if the same magnitudes for the C./MIC and 24-hour AUC/MIC ratios apply to gram-positive cocci such as S. *pneumoniae,* as these studies had only a single case of infection with this organism.

In vitro models have been more successful in detecting resistant mutants following exposure to varying drug concentrations over time. [121,129] Several investigators have explored the concept of a mutation prevention concentration (MPC), defined as the lowest drug concentration in agar that prevents the growth of any colonies of resistant mutants for different organisms and for different drugs. [126] For example, the MPC_{90} for a variety of fluoroquinolones against S. *pneumoniae* has varied from 4 to 8 times the MIC_{90}. [130] One potential disadvantage of this testing system is that it only measures the effect of long-term exposure to a constant concentration and does not examine the effect of shorter term exposures to similar or higher concentrations. Further studies are necessary to examine the clinical relevance of these observations.

Selection of Resistant Mutants

Although it has been difficult for animal infection models to examine the relationship between the time course of antimicrobial exposure and the development of resistance mutations, these models have been useful for describing the relationship between antimicrobial pharmacodynamics and the selection of resistant subpopulations. For example, several animal and in vitro studies have suggested that a C.,/MIC ratio of at least 8 to 10 can significantly reduce the emergence of resistant subpopulations with fluoroquinolones and aminoglycosides. [28,39,s4]

Spread of Resistant Mutants

Along with eradicating the infecting pathogen from the site of infection, antimicrobial therapy for respiratory infections must aim to prevent the selection of resistant mutants, and be capable of minimizing the carriage of resistant strains in the nasopharynx. [131] The ability to achieve these pharmacologic goals depends to some extent on the PK-PD characteristics of the antibiotic and on the dosing regimen. For example, it has been theorized that long half-life drugs that provide sustained but sub-MIC concentrations may be more likely to promote selection of resistant pathogens.

Antibiotics vary in their ability to eradicate the pathogen from the nasopharynx. Times above MIC around 80% to 100% are required for (3-lactams to achieve eradication, which is only possible at higher doses than are currently used for most (3-lactams. Macrolides have been shown to reduce colonization in some studies, but more often macrolide therapy increases carrier status. [33,106,132-134] For example, Ghaffar et al recently examined carriage of pneumococci in the nasopharynx of children following therapy with the extra-strength formulation of amoxicillin-clavulanate and azithromycin. [13S] Both amoxicillin-clavulanate and azithromycin were successful in eradicating susceptible pneumococci (10/10 [100%] and 8/10 [80%], respectively). On the other hand, amoxicillin-clavulanate eradicated intermediate and resistant pneumococci in 82% (14/17) of patients, whereas azithromycin therapy cleared resistant organisms in only 36% (5/14) of patients. Overall amoxicillin-clavulanate was superior to azithromycin for eradicating the pneumococcal carrier state ($P = 0.04$). The fluoroquinolones are generally effective at eradicating organisms from the nasopharynx.

Clearly much more information is needed to determine which PK-PD parameter and its magnitude that is necessary to prevent the emergence of resistant organisms with commonly used antimicrobials.

SUMMARY

Pharmacokinetic and pharmacodynamic parameters are the major determinants of the efficacy of antimicrobial therapy. The ability of a drug to reach the magnitude of the parameter required for efficacy against common pathogens and emerging resistant organisms should be considered in drug and dosage regimen selection for empiric therapy (Table 1-8). Antimicrobial pharmacodynamic analyses have been useful for the development of (1) in vitro susceptibility breakpoints, (2) antimicrobial treatment guidelines, (3) new drug formulations (e.g., high-dose/ratio amoxicillin-clavulanate and extended

TABLE 1-8 a Pharmacodynamic Activity of Antimicrobials

	Pattern of activity		Pharmacodynamics	
Drug class	*Concentration dependent*	*Persistent effects*	*Parameter*	*Magnitude*
Antibacterials				
Penicillins	No	Minimal	T>MIC	40%
Cephalosporins	No	Minimal	T>MIC	50%
Carbapenems	No	Minimal	T>MIC	25%
Macrolides	No	Modest	T>M I C	40%-50%
Azithromycin	No	Prolonged	AUC/MIC	25
Oxazolidinones f inezolid)	No	Minimal	T>MIC	40%
Trimethoprim-Sulfamethoxazole	No	Minimal	T>MIC	ND
Clindamycin	No	Minimal	T>MIC	ND
Glycylcyclines	No	Modest	T>MIC	ND
Fluoroquinolones	Yes	Prolonged	AUC/MIC	25 (G +) 100 (G -)
Aminoglycosides	Yes	Prolonged	Cman/MIC	8-10
Tetracyclines	No	Prolonged	AUC/MIC	ND
Ketolides	Yes	Prolonged	AUC/MIC	25-50
Streptogramins (Synercid)	No	Prolonged	AUC/MIC	ND
Daptomycin	Yes	Prolonged	AUC/MIC	ND
Glycopeptides (vancomycin)	No	Prolonged	AUC/MIC	ND
Metronidazole	Yes	Prolonged	Cmajmic	ND
Antifungals				
Triazoles	No	Prolonged	AUC/MIC	25
Polyenes	Yes	Prolonged	Cmejmlc	ND
Flucytosine	No	Modest	T>MIC	25%-50%
Echinocandins	Yes	Prolonged	—	—
Antivirals				
Zidovudine (AZT)	ND	ND	Time > Threshold	ND
Stavudine (D4T)	ND	ND	AUC/Threshold	-ND
Protease inhibitors	ND	ND	Time > Threshold	ND
Foscamet	ND	ND	AUC/Threshold	ND
Neuraminidase inhibitors	ND	ND	AUC/Threshold	ND

AUC, area under the serum concentration-time curve; MIC, minimum inhibitory concentration; ND, no data; T>MIC, percentage of time serum concentration exceed the MIC.

release clarithromycin), and for (4) dose selection for clinical trials.

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