

## STATE-OF-THE-ART CLINICAL ARTICLE

**Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men****William A. Craig***From the Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin*

The pharmacology of antimicrobial therapy can be divided into two distinct components (figure 1). The first of these components is pharmacokinetics, or the absorption, distribution, and elimination of drugs. These factors, combined with the dosage regimen, determine the time course of drug concentrations in serum, which in turn determine the time course of drug concentrations in tissues and body fluids. With respect to antimicrobials, the time course of drug concentrations at the site of infection is of special interest. Pharmacodynamics is the relationship between serum concentration and the pharmacological and toxicological effects of drugs. With respect to antimicrobials, the primary interest is in the relationship between concentration and the antimicrobial effect. The time course of antimicrobial activity is a reflection of the interrelationship between pharmacokinetics and pharmacodynamics.

Studies over the past 20 years have demonstrated marked differences in the time course of antimicrobial activity among antibacterials [1–3]. Furthermore, the pattern of antimicrobial activity over time is an important determinant of effective dosage regimens [4]. This review will focus on the interrelationship between pharmacokinetics and pharmacodynamics in determining dosing regimens for different classes of antibacterials. The ability of specific pharmacokinetic/pharmacodynamic parameters to predict the efficacy of antibacterial activity in animal models of infection and in human infections will be emphasized.

**Pharmacodynamics: Parameters of Antimicrobial Activity**

MICs and MBCs have been the major parameters used to quantify the activity of an antibacterial drug against the infecting pathogen. Although these parameters are good predictors of the potency of the drug-organism interaction, they do not provide any information on the time course of antimicrobial activity. For example, the MBC does not provide information on the rate of bactericidal activity and whether this rate can be enhanced by

increasing antimicrobial concentrations. Similarly, the MIC does not provide any information on persistent effects of antibacterial agents—inhibitory effects that persist after exposure to an antimicrobial. These persistent effects include the postantibiotic effect (PAE), the postantibiotic sub-MIC effect (PAE-SME), and the postantibiotic leukocyte enhancement (PALE) [5–7]. The effect of increasing concentrations on the bactericidal activity of antimicrobials and the magnitude of persistent effects give a much better description of the time course of antimicrobial activity than is provided by the MIC and MBC.

**Bactericidal Activity**

Shah et al. [8] were the first investigators to propose that antibacterials could be divided into different groups on the basis of their patterns of bactericidal activity. The first pattern is characterized by concentration-dependent killing over a wide range of concentrations. The higher the drug concentration, the greater the rate and extent of bactericidal activity. This pattern is observed with the aminoglycosides and fluoroquinolones and with exposure of anaerobic bacteria to metronidazole [2, 3, 8]. In contrast, the second pattern is characterized by minimal concentration-dependent killing. Saturation of the killing rate occurs at low multiples of the MIC—usually around four to five times the MIC. Concentrations above these values do not kill the organisms any faster or more extensively. Thus, the extent of killing in this pattern of bactericidal activity is largely dependent on the time of exposure. The absence of major concentration-dependent killing is a common characteristic of  $\beta$ -lactam antibiotics, vancomycin, clindamycin, and the macrolides [2, 3, 8, 9].

Figure 2 illustrates the effect of increasing drug concentrations on the in vitro antimicrobial activity of tobramycin, ciprofloxacin, and ticarcillin against a standard strain of *Pseudomonas aeruginosa*. Increasing concentrations of tobramycin and ciprofloxacin were associated with a more rapid and extensive degree of bacterial killing, as exhibited by the steeper slopes of the killing curves. Increased concentrations of ticarcillin, resulted in a change in slope, as the concentration was increased from one to four times the MIC. Higher concentrations were associated with only a slight reduction in bacterial counts over the 8-hour period of measurement. However, higher concentrations were also associated with an earlier initiation of bacterial killing. After 2 or more hours, the rates of

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Received 2 June 1997; revised 23 September 1997.

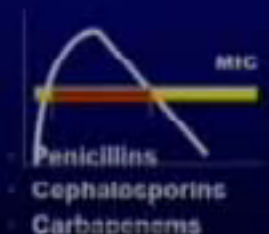
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**Clinical Infectious Diseases** 1998;26:1–22

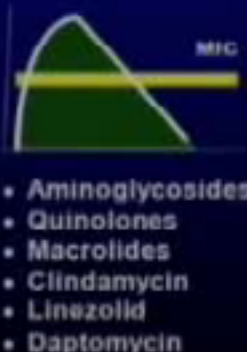
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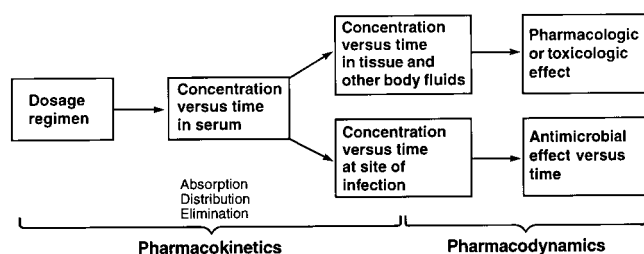
# Pharmacokinetic/Pharmacodynamic Profiles

***Time > MIC***  
(time-dependent killing)



***AUC<sub>24</sub>/MIC***  
(concentration-dependent killing)





**Figure 1.** Overview of pharmacokinetics and pharmacodynamics in antimicrobial chemotherapy.

killing for concentrations of ticarcillin from four to 64 times the MIC were virtually identical.

### Persistent Effects

PAE refers to the persistent suppression of bacterial growth following exposure to an antimicrobial [2, 7, 10]. PAE can be considered the time it takes for an organism to recover from the effects of exposure to an antimicrobial; this phenomenon was first described in the 1940s with regard to the activity of penicillin against staphylococci and streptococci [11–13], but these early observations were not applied to newer drugs and gram-negative organisms until the late 1970s. PAE is demonstrated in vitro by observing bacterial growth kinetics after a drug is removed.

All antibacterials produce PAEs in vitro when susceptible gram-positive bacteria, such as staphylococci and streptococci, are exposed to these drugs [10]. Prolonged PAEs for gram-negative bacilli are observed after exposure to antibacterials that are inhibitors of protein synthesis or nucleic acid synthesis. Such drugs include the aminoglycosides, fluoroquinolones, tetracyclines, macrolides, chloramphenicol, and rifampin [10]. In contrast, short PAEs or no PAEs are observed for gram-negative bacilli after exposure to  $\beta$ -lactam antibiotics. The only exception to this class has been the carbapenems, such as imipenem and meropenem, which produce prolonged PAEs, primarily with strains of *P. aeruginosa* [14, 15].

The PAE has also been demonstrated in vivo in a variety of animal infection models [16]. The neutropenic mouse thigh-infection model has been used in most in vivo studies [17]. There are several important differences between the in vivo and in vitro PAE that cause concern about the value of in vitro measurements. First, the length of the in vitro PAE is not predictive of the duration of the in vivo PAE [10, 18]. In most cases, in vivo PAEs are longer than in vitro PAEs. In vivo PAEs of aminoglycosides and fluoroquinolones are further prolonged by the presence of leukocytes and the simulation of human pharmacokinetics [16, 19]. Second, prolonged PAEs are observed in vitro but not in vivo after streptococci are exposed to penicillin and cephalosporins [16, 17, 20]. Third, the results of in vitro studies that suggest that the PAE of aminoglycosides decreases and disappears over a prolonged

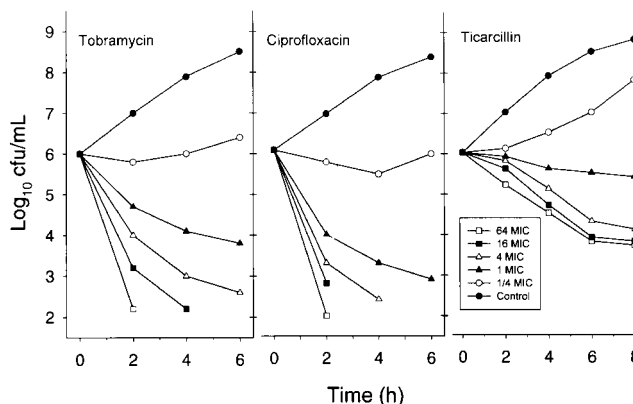
dosing interval or with repeated doses have not been observed in in vivo studies [21, 22].

Sub-MIC concentrations of antibiotics are known to slow growth and produce morphological changes such as filaments [23]. Sub-MIC concentrations can also prolong the duration of the PAE [24]. Measurement of the PAE-SME includes both the PAE and the enhanced duration produced by sub-MIC concentrations. For example, subsequent exposure of organisms in the PAE phase to drug concentrations of macrolides at one-tenth and three-tenths of the MIC increases the duration of the in vitro PAE by ~50% and 100%, respectively [6, 9]. In vivo sub-MIC concentrations likely account for the longer PAEs observed in vivo relative to those observed in vitro. Prolongation of sub-MIC concentrations of amikacin by simulating the drug's half-life in humans (2 hours) extended the duration of in vivo PAEs by 40%–100% over values observed with a dose producing the same area under the concentration-vs.-time curve (AUC) but eliminated with a half-life of 20 minutes in mice [19].

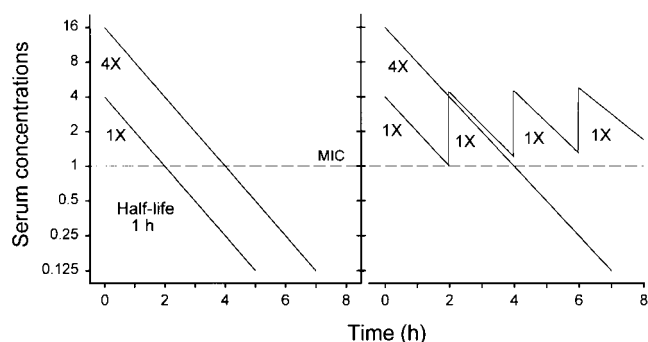
PAE refers to the observations that bacteria in the postantibiotic phase are more susceptible to intracellular killing or to phagocytosis by leukocytes. This phenomenon can also prolong the duration of the PAE, both in vitro and in vivo [7, 10]. Antimicrobials that produce the longest PAEs tend to exhibit maximal effects when exposed to leukocytes. In general, the presence of neutrophils tends to double the duration of the PAE of aminoglycosides and fluoroquinolones for gram-negative bacilli exposed to these drugs [16, 19]. However, leukocytes have no major effect on the minimal in vivo PAEs observed for gram-negative bacilli exposed to  $\beta$ -lactams.

### Pharmacokinetic and Pharmacodynamic Parameters and Efficacy

The pharmacodynamic characteristics described above suggest that the time course of antimicrobial activity can vary



**Figure 2.** Time-kill curves for *Pseudomonas aeruginosa* ATCC (American Type Culture Collection) 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one-fourth to 64 times the MIC. Reprinted with permission from *Scandinavian Journal of Infectious Diseases* [3].



**Figure 3.** Effect of increasing the dose or changing the dosing regimen of a hypothetical drug on peak/MIC ratio, AUC (area under the concentration-vs.-time curve)/MIC ratio, and duration of time that serum levels exceed the MIC. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [25].

markedly for different antibacterial agents. For example, the  $\beta$ -lactams exhibit minimal concentration-dependent killing and produce prolonged in vivo PAEs only with staphylococci. High drug levels will not kill organisms more effectively than lower concentrations. Furthermore, regrowth of most organisms will commence very soon after serum drug levels decrease below the MIC. Thus, the goal of a dosing regimen for these drugs would be to optimize the duration of exposure. The duration of time that serum levels exceed the MIC should be the major pharmacokinetic/pharmacodynamic parameter determining the in vivo efficacy of the  $\beta$ -lactam antibiotics.

On the other hand, the aminoglycosides and fluoroquinolones exhibit major concentration-dependent killing. Infrequent dosing of large doses would also be possible because the prolonged PAEs would protect against bacterial regrowth when serum levels fall below the MIC. The goal of a dosing regimen for these drugs would be to maximize their concentrations. The peak/MIC and/or AUC/MIC ratios should be the major pharmacokinetic/pharmacodynamic parameters correlating with efficacy of the aminoglycosides and fluoroquinolones.

These predictions can be difficult to prove for humans because of the design of most clinical trials. Most studies evaluating the efficacy of different dosage regimens compare two or more dose levels of drug administered at the same dosing interval. As shown in the left panel of figure 3, a fourfold-higher dose produces a higher peak/MIC ratio, a higher AUC/MIC ratio, and a longer duration of time above the MIC. If the higher dose produces a better therapeutic effect than the lower dose, it is difficult to determine which pharmacokinetic/pharmacodynamic parameter is of major importance, as all three increase. However, much of the interdependence among pharmacokinetic/pharmacodynamic parameters can be reduced by comparing the results of dosage regimens that are based on different dosing intervals. As shown in the right panel of figure 3, a dose administered every 2 hours, compared with a fourfold-higher dose given every 8 hours, resulted in a lower peak/MIC ratio but a longer

duration of time that the levels exceeded the MIC. The 24-hour AUC/MIC ratio for the two regimens would be the same. Such study designs are rarely used in human clinical trials but are easily performed with animal infection models.

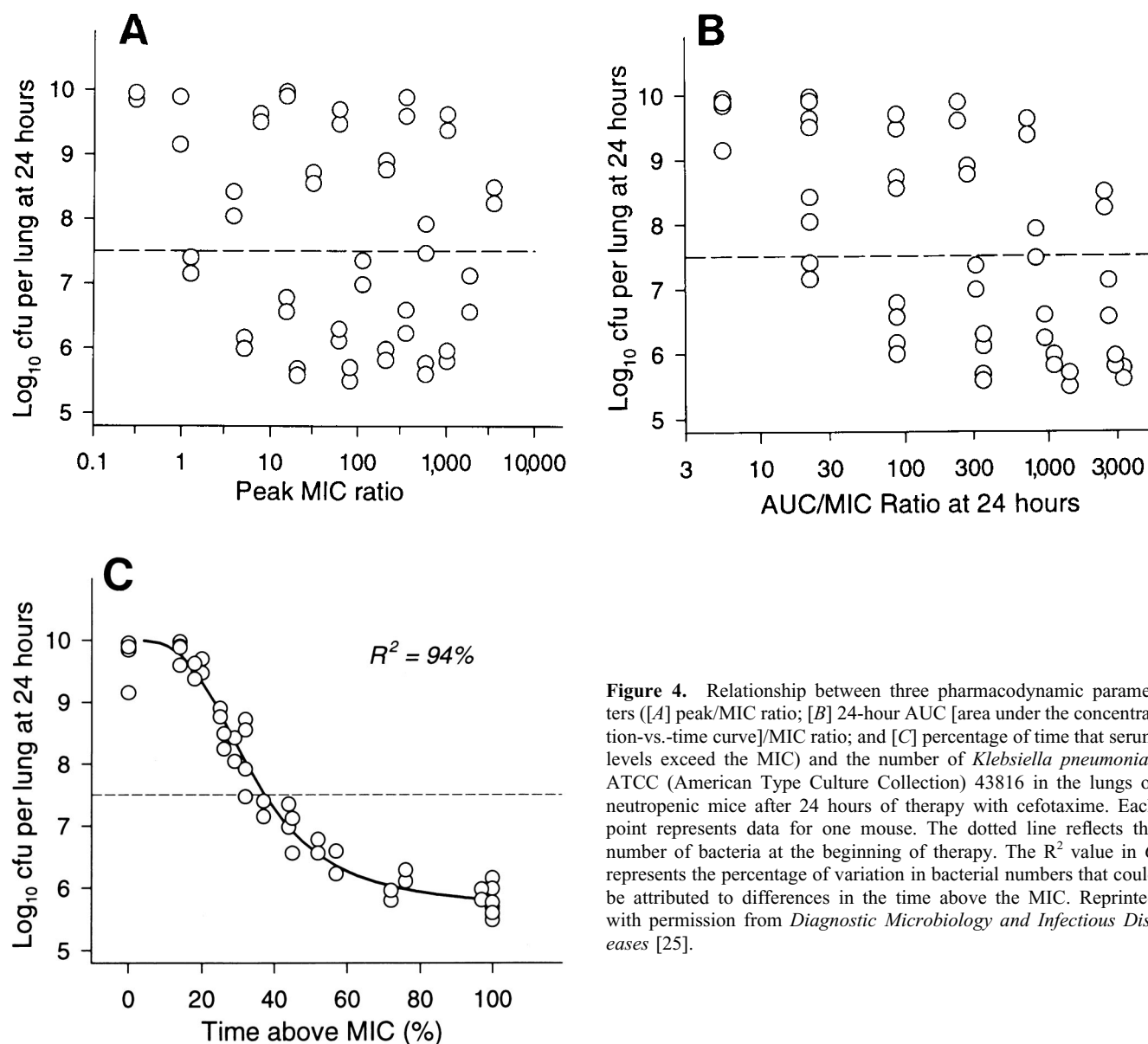
Several investigators have used multiple dosage regimens in animal infection models to correlate specific pharmacokinetic/pharmacodynamic parameters with the efficacy of various antibacterials against both gram-positive and gram-negative bacilli [9, 25–31]. The results of a study of cefotaxime activity against a standard strain of *Klebsiella pneumoniae* in the lungs of neutropenic mice are shown in figure 4. In this study, pairs of mice were treated with multiple dosage regimens that varied both in the dose and the dosing interval. The number of cfus remaining in the lung after 24 hours of therapy, the peak/MIC and 24-hour AUC/MIC ratios, and the percentage of time that serum levels exceeded the MIC were determined and calculated for each dosage regimen. As shown by the scattergrams in figures 4A and 4B, there was a poor relationship between cfus per lung and the peak/MIC and 24-hour AUC/MIC ratios. On the other hand, a highly significant correlation was observed between the number of bacteria in the lungs and the percentage of time that serum levels exceeded the MIC.

The specific pharmacokinetic/pharmacodynamic parameters correlating with efficacy in animal infection models are listed in table 1. As expected, time above the MIC has consistently been the only pharmacokinetic/pharmacodynamic parameter that correlates with the therapeutic efficacy of  $\beta$ -lactam antibiotics. Time above the MIC is also the parameter that correlates with efficacy of the macrolides and clindamycin.

For aminoglycosides and fluoroquinolones, the AUC/MIC and peak/MIC ratios have been the parameters that correlate with efficacy. Most studies have shown slightly better correlations with the AUC/MIC ratio than with the peak/MIC ratio. Peak/MIC ratios may be more important in infections where there is a significant risk of the emergence of resistant subpopulations [29].

Although vancomycin, the tetracyclines, azithromycin, and quinupristin/dalfopristin do not exhibit concentration-dependent killing, the AUC/MIC ratio has been the major pharmacokinetic/pharmacodynamic parameter correlating with the therapeutic efficacy of these drugs. This result may be due to the much longer in vivo PAEs produced by these drugs than by the  $\beta$ -lactams, clindamycin, and other macrolides [9, 10].

Because most infections occur in tissues and the common bacterial pathogens are extracellular, interstitial fluid concentrations at the site of infection should be the prime determinants of efficacy. Drug concentrations in serum (or plasma) are much better predictors of interstitial fluid levels than are tissue homogenate concentrations. Tissue homogenates mix the interstitial, intracellular, and vascular compartments together. Use of the tissue homogenate concentration tends to result in an underestimation or overestimation of the interstitial fluid concentration, depending on the ability of the drug to accumulate intracellularly.



**Figure 4.** Relationship between three pharmacodynamic parameters ([A] peak/MIC ratio; [B] 24-hour AUC [area under the concentration-vs.-time curve]/MIC ratio; and [C] percentage of time that serum levels exceed the MIC) and the number of *Klebsiella pneumoniae* ATCC (American Type Culture Collection) 43816 in the lungs of neutropenic mice after 24 hours of therapy with cefotaxime. Each point represents data for one mouse. The dotted line reflects the number of bacteria at the beginning of therapy. The  $R^2$  value in C represents the percentage of variation in bacterial numbers that could be attributed to differences in the time above the MIC. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [25].

**Table 1.** Pharmacokinetic and pharmacodynamic parameters correlating with antibacterial efficacy in animal infection models.

Parameter	Drugs
Time above the MIC	Penicillins, cephalosporins, carbapenems, aztreonam, macrolides, and clindamycin
24-hour AUC/MIC	Aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin, and quinupristin/dalfopristin
Peak/MIC	Aminoglycosides and fluoroquinolones

NOTE. AUC = Area under the concentration-vs.-time curve.

Studies with use of subcutaneously implanted cotton threads have demonstrated that drug concentrations in the interstitial fluid of tissues show little lag in penetration and are very close to drug levels in serum [32, 33]. However, fluid collections such as pleural fluid, peritoneal fluid, synovial fluid, middle ear fluids, seromas, and phlegmons have a lower ratio of surface area to volume than most tissues. Studies of skin-blister fluid have demonstrated that concentrations in these sites will lag behind those in serum, resulting in lower peak levels but higher trough concentrations [32–34]. The AUC of unbound drug in skin-blister fluid is usually similar to that in serum [35]. Thus, use of serum levels, in comparison with fluid collection concentrations, would tend to result in overestimation of the peak/MIC ratio

and underestimation of the duration of time that drug levels exceed the MIC.

### Magnitude of the Pharmacokinetic/Pharmacodynamic Parameter Required for Efficacy

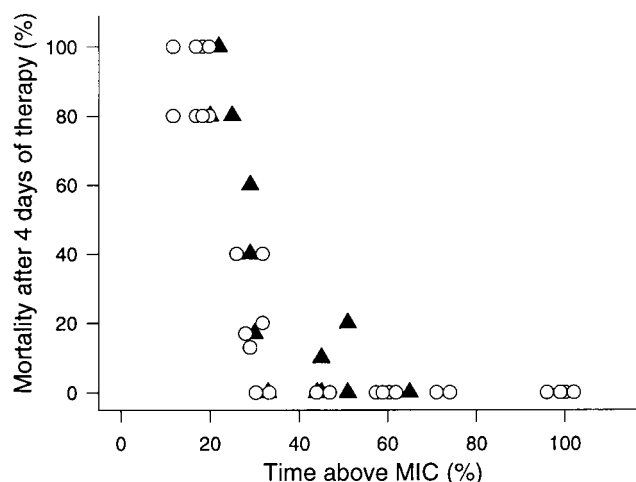
Because pharmacokinetic/pharmacodynamic parameters can correct for differences in pharmacokinetics and intrinsic antibacterial activity, it is likely that the magnitude of these parameters required for efficacy would be similar in different animal species. If this were the case, the results from studies in animal infection models could be used as a guide for establishing human dosage regimens. This would be especially helpful in designing dosage regimens for new antibacterials and in situations where it is difficult to readily obtain sufficient clinical data (e.g., infections due to emerging resistant organisms or rare infections). Current knowledge on the magnitude of pharmacokinetic/pharmacodynamic parameters and efficacy will be presented by antibacterial class.

### $\beta$ -Lactams

Time above the MIC is the pharmacokinetic/pharmacodynamic parameter that correlates with the therapeutic efficacy of the various  $\beta$ -lactam antibiotics. Studies in animal infection models have demonstrated that antibiotic concentrations do not need to exceed the MIC for 100% of the dosing interval to exert a significant antibacterial effect [25–27, 36]. As shown in figure 4 (the efficacy of cefotaxime against *K. pneumoniae* in the lungs of neutropenic mice), an in vivo bacteriostatic effect was observed when serum levels were above the MIC for 30%–40% of the dosing interval, whereas maximum killing was approached when levels were above the MIC for 60%–70% of the time. Very similar times above MIC percentages have been observed in murine thigh- and lung-infection models of several broad-spectrum cephalosporins against gram-negative bacilli and streptococci, providing unbound drug levels were used for assessing the efficacy of highly protein-bound cephalosporins such as ceftriaxone [25].

The percentages for time above the MIC were slightly lower for the penicillins, and lower again for the carbapenems, when these drugs were assessed against the same types of organisms [37]. These differences reflect the variation in rate of killing, which is fastest with the carbapenems and slowest with the cephalosporins. In addition, for staphylococci, the time above the MIC required for efficacy is less than that observed for gram-negative bacilli and streptococci. This difference is due to the prolonged in vivo PAEs observed for staphylococci exposed to  $\beta$ -lactams but not for gram-negative bacilli and streptococci exposed to these drugs.

Figure 5 incorporates all the available data from the published studies in which mortality was used as an end point and in which animals infected with *S. pneumoniae* were treated for several days with penicillins or cephalosporins [38]. Penicillin-

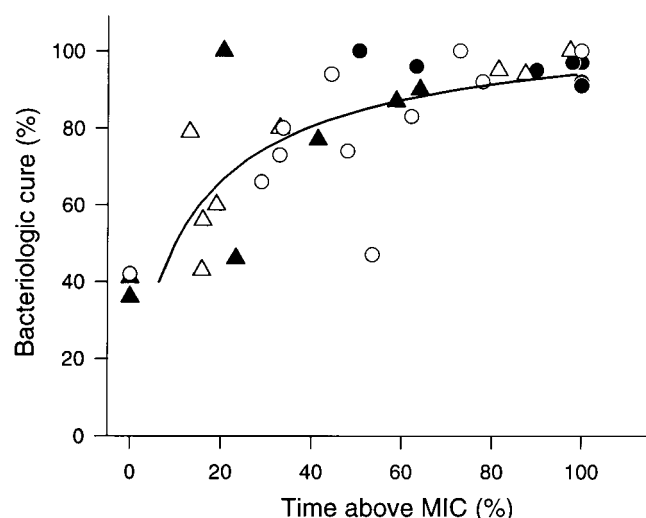


**Figure 5.** Relationship between the duration of time serum levels of  $\beta$ -lactams exceed the MIC and survival in animal models infected with *Streptococcus pneumoniae*. The open circles and solid triangles represent data obtained with penicillins and cephalosporins, respectively. Reprinted with permission from [38].

intermediate and penicillin-resistant strains were used in several studies. The mortality was virtually 100% if serum levels were above the MIC for  $\leq 20\%$  of the dosing interval. In contrast, as soon as the duration of time that serum levels exceeded the MIC was  $\geq 40\%$ – $50\%$  of the dosing interval, survival was on the order of 90%–100%.

To assess the relationship between efficacy and the time above MIC in a clinical situation, bacteriologic cure in patients with acute otitis media has been selected as a sensitive indicator of successful clinical response. There have been a reasonable number of clinical trials that have included routine repeated tympanocentesis of middle ear fluid after 2–7 days of therapy to determine whether the infecting organism was eradicated [39–42]. Figure 6 demonstrates the relationship between time above the MIC and the bacteriologic cure rate for many  $\beta$ -lactams against *S. pneumoniae* and *Haemophilus influenzae* in patients with otitis media [38, 43]. In general, a time above the MIC of  $>40\%$  was required to achieve an 85%–100% bacteriologic cure rate.

The impact of penicillin resistance in *S. pneumoniae* on the ability of standard dosage regimens of three oral and four parenteral  $\beta$ -lactams to provide free-drug concentrations above the MIC<sub>50</sub> and MIC<sub>90</sub> for  $\geq 40\%$ – $50\%$  of the dosing interval is shown in table 2. Among the three oral dosage regimens for children, amoxicillin and cefuroxime would provide adequate durations above MIC for penicillin-intermediate strains, while cefaclor would not. For penicillin-resistant strains, only amoxicillin would provide levels above the MIC for  $\geq 40\%$  of the dosing interval. These estimates have recently been shown to predict efficacy for cefaclor, cefuroxime axetil, and amoxicillin/clavulanate in patients infected with drug-resistant *S. pneumoniae* strains who were entered in clinical trials where bacteri-



**Figure 6.** Relationship between the time above the MIC and bacteriologic cure for various  $\beta$ -lactams against *S. pneumoniae* (○) and *H. influenzae* (Δ) in patients with otitis media. The solid and open symbols represent data obtained with penicillins and cephalosporins, respectively. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [38].

ologic cure or clinical cure were used as end points [42, 44, 45]. All four of the parenteral  $\beta$ -lactams provide serum levels that exceed the MIC<sub>90</sub> for resistant strains for >40% of the dosing interval. Thus, it is not surprising that treatment with these drugs in a large number of patients with severe pneumococcal pneumonia did not result in any difference in outcome for patients infected with penicillin-resistant strains than for those infected with susceptible isolates [46].

Slow-growing bacteria in infection sites that require the use of antimicrobial agents with bactericidal activity for efficacy, such as endocarditis and osteomyelitis, may require longer durations of effective serum concentrations of agents than do acute respiratory tract infections. Weinstein and co-workers [47] correlated the results of the serum bactericidal test with

**Table 3.** Relationship of trough serum bactericidal titer to efficacy of therapy with  $\beta$ -lactam antibiotics in patients with acute and chronic osteomyelitis.

Outcome of therapy	No. of patients with SBTs $\geq 1:2$	No. of patients with SBTs $< 1:2$
Cure	26	2
Failure	0	8

NOTE. Data are from [47] and [48]. SBT = serum bactericidal titer.

clinical outcome of therapy for osteomyelitis. As shown in table 3, an analysis of the data for patients who received only  $\beta$ -lactam antibiotics demonstrates that the presence of a detectable trough serum bactericidal titer was an important determinant for cure of the infection [48]. All patients for whom therapy failed had undetectable trough bactericidal titers of  $\beta$ -lactams.

Administration of  $\beta$ -lactams by continuous infusion facilitates maintaining serum levels above the MIC. Despite many potential advantages of continuous infusion, only a few clinical trials have documented the success of this type of dosage regimen [49]. Current clinical trials are designed to determine if continuous infusion will allow for the use of lower daily drug dosages than those required for intermittent administration or will improve efficacy against bacteria with reduced susceptibility. For example, early results with continuous infusion of large doses of ampicillin have demonstrated success against moderately ampicillin-resistant strains (ampicillin MIC = 32–64  $\mu\text{g/mL}$ ) of vancomycin-resistant *Enterococcus faecium* [50].

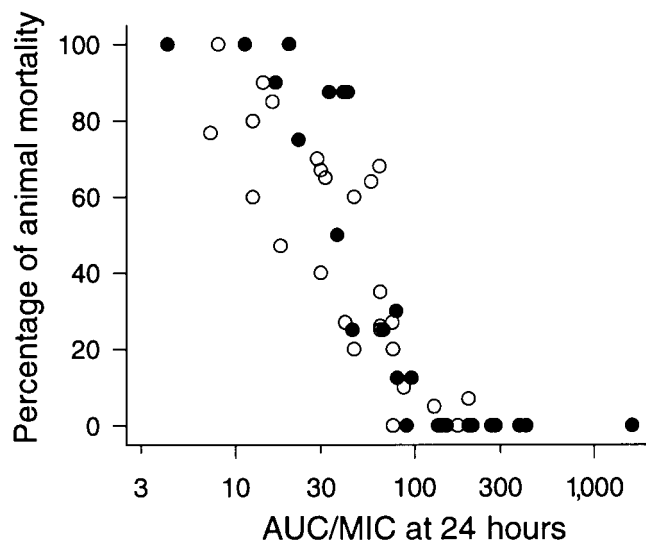
### Fluoroquinolones

The 24-hour AUC/MIC ratio is the parameter that best correlates with the efficacy of the fluoroquinolones [25, 26, 51]. In animal infection models, the magnitude of this pharmacokinetic/pharmacodynamic parameter required to produce a bacte-

**Table 2.** Time above MIC for three oral and four parenteral  $\beta$ -lactam antibiotics tested against penicillin-intermediate and penicillin-resistant strains of *Streptococcus pneumoniae*.

Drug	Regimen	<i>S. pneumoniae</i> (I)		<i>S. pneumoniae</i> (R)	
		MIC <sub>50-90</sub> ( $\mu\text{g/mL}$ )	Time above MIC (%)	MIC <sub>50-90</sub> ( $\mu\text{g/mL}$ )	Time above MIC (%)
Amoxicillin	13.3 mg/kg t.i.d.	0.25–1	80–55	1–2	55–43
Cefaclor	13.3 mg/kg t.i.d.	8–16	20–0	32–64	0
Cefuroxime	15 mg/kg b.i.d.	0.5–2	56–40	4–8	30–0
Ampicillin	1 g q6h	0.5–2	71–100	2–4	71–54
Penicillin G	2 MU q6h	0.5–1	58–66	2–4	50–41
Cefotaxime	1 g q8h	0.25–1	87–63	1–2	63–52
Ceftriaxone	1 g q24h	0.25–1	76–100	1–2	76–48

NOTE. Data are from [38] and [43]. I = intermediate; R = resistant.



**Figure 7.** Relationship between the 24-hour AUC (area under the concentration-vs.-time curve)/MIC ratio and survival among animal models infected with a variety of gram-positive and gram-negative pathogens. The solid and open circles represent data obtained in the high-infection model and other animal models, respectively. The 24-hour AUC/MIC ratio is the sum of the AUCs for all doses administered every 24 hours divided by the MIC. Data are from [27].

riostatic effect is  $\sim 35$  [27]. This value implies that the AUC averages  $\sim 1.5$  times the MIC over a 24-hour period (i.e.,  $1.5 \times 24 = 36$ ). This value is independent of the dosing interval, the fluoroquinolones used, and the site of infection.

The relationship between the 24-hour AUC/MIC values and mortality, as reported in the literature for those studies where animals were treated for  $\geq 2$  days, survival results were reported at the end of therapy, and pharmacokinetic data were provided, is illustrated in figure 7 [27]. Studies of pneumonia and peritonitis and sepsis, performed in mice, rats, and guinea pigs with use of various strains of gram-positive and gram-negative bacteria, were included. In general, 24-hour AUC/MIC ratios of  $< 30$  were associated with  $> 50\%$  mortality, whereas AUC/MIC values of  $\geq 100$  were associated with almost no mortality. Thus, it appears that fluoroquinolone concentrations in serum need to average about four times the MIC for each 24 hours (i.e.,  $4 \times 24 = 96$ ) to produce virtually 100% survival in a variety of experimental animal infections.

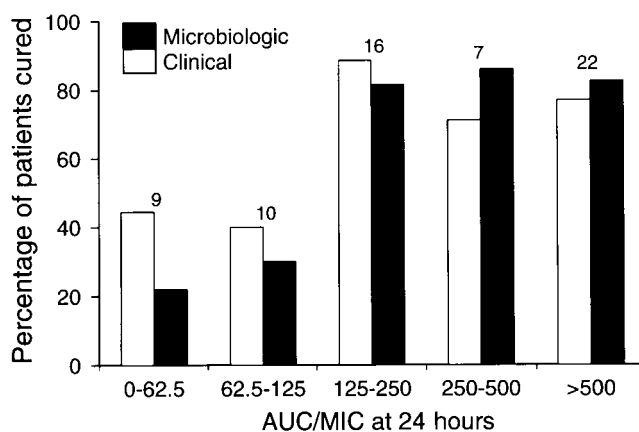
A similar relationship has been observed between the 24-hour AUC/MIC ratio and the therapeutic efficacy of fluoroquinolones in clinical trials. As illustrated in figure 8, Forrest et al. [52] found that a 24-hour AUC/MIC value of  $\geq 125$  was associated with satisfactory outcome for seriously ill patients treated with intravenous ciprofloxacin. Lower values resulted in clinical and bacteriologic cure rates that were  $< 50\%$ . A recent clinical trial with levofloxacin demonstrated that a peak/MIC ratio of  $\geq 12$  or a 24-hour AUC/MIC ratio of  $\sim 100$  were predictive of a successful outcome [53]. A peak/MIC ratio of 8–10 has also been shown both in vitro and in vivo

to prevent the emergence of resistant mutants during therapy with fluoroquinolones [54, 55].

### Aminoglycosides

In animal infection models, the 24-hour AUC/MIC ratio exhibits a higher correlation with therapeutic efficacy than the peak/MIC ratio. However, the opposite was observed in the major clinical trials correlating pharmacokinetic/pharmacodynamic parameters with the therapeutic efficacy of aminoglycosides [56]. To obtain a clinical response of  $\geq 90\%$ , the peak level needed to exceed the MIC by eightfold to 10-fold. The once-daily dosage regimen for aminoglycosides was designed to enhance peak serum concentrations. As with fluoroquinolones, peak concentrations that are eight to 10 times higher than the MIC can reduce the rate of emergence of aminoglycoside-resistant mutants during therapy [55]. Initial exposure of bacteria to the aminoglycosides down-regulates subsequent uptake of drug. During the period of down-regulation, decreased killing of bacteria and higher MICs are exhibited [57]. Since this phenomenon lasts for several hours, once-daily dosing of the aminoglycosides may allow this effect to dissipate between doses. Once-daily dosing also has the potential to decrease the incidence of nephrotoxicity and ototoxicity associated with the use of aminoglycosides. Uptake of these drugs into renal tubular cells and the endolymph of the ear is more efficient with low sustained concentrations than with high intermittent levels [58, 59].

Although numerous clinical trials have evaluated the efficacy and toxicity of once-daily vs. multiple-daily dosage regimens, inconclusive results on the advantages or disadvantages of the once-daily regimen have been obtained because of the sizes and designs of most of these studies. This has led to multiple



**Figure 8.** Relationship between the 24-hour AUC (area under the concentration-vs.-time curve)/MIC ratio and the microbiological and clinical efficacy of ciprofloxacin in 64 patients with serious bacterial infections. The 24-hour AUC/MIC is the sum of the AUCs for all doses administered every 24 hours divided by the MIC. Data are from [52].



meta-analyses, including a recent review of the previous meta-analyses [60]. The results of these studies suggest a small, nonsignificant trend towards better efficacy and lower nephrotoxicity with the once-daily dosage regimen. Other studies have demonstrated that the onset of nephrotoxicity is delayed for several days when the drug is administered once-daily rather than in multiple-daily dosage regimens [61, 62]. Still, once-daily dosing may not be desirable in all situations. Experimental studies of enterococcal endocarditis have shown a greater reduction in bacterial numbers in vegetations when an aminoglycoside is administered in multiple-dosing regimens than in once-daily regimens [63, 64].

### Other Antibacterials

Much additional work, both with animal infection models and human clinical trials, is needed to establish the magnitude of the pharmacokinetic/pharmacodynamic parameters that correlate with the efficacy of the macrolides, azalides, clindamycin, tetracyclines, glycopeptides, and other antibacterials. Some initial data are available on the macrolides, for which time above the MIC is the important pharmacokinetic/pharmacodynamic parameter correlating with efficacy. Standard doses of erythromycin and clarithromycin in children produce serum levels that exceed the MIC<sub>90</sub> for susceptible strains of *S. pneumoniae* for 88%–100% of the dosing interval [43]. Such doses also result in bacteriologic cure in 93%–100% of children with acute otitis media due to this organism [40, 41].

In contrast, the bactericidal efficacy of these drugs in patients infected with *H. influenzae* was only 15%–20% [41]. These poor results are not surprising, given that serum concentrations never exceed the high MIC values of these drugs for *H. influenzae*. Although it is often argued that it is the tissue levels of the macrolides, rather than the serum concentrations, that must be compared with efficacy, it must be remembered that most of the drug is localized intracellularly in the tissues, while the organism is primarily found in extracellular sites.

### Summary

Investigations over the past 20 years have demonstrated that antibacterials can vary markedly in the time course of antimicrobial activity. These differences in pharmacodynamic activity have implications for optimal dosage regimens. The results of more recent studies suggest that the magnitude of the pharmacokinetic/pharmacodynamic parameters required for efficacy are relatively similar in animal infection models and in human infections. However, there is still much to learn. Additional studies are needed to further correlate pharmacokinetic/pharmacodynamic parameters for many antibacterials with therapeutic efficacy in a variety of animal infection models and in human infections. The potential value of using pharmacokinetic/pharmacodynamic parameters as guides for establishing optimal dosing regimens for new and old drugs and for new

emerging pathogens and resistant organisms, for setting susceptibility breakpoints, and for reducing the cost of drug development should make the continuing search for the therapeutic rationale of antibacterial dosing of mice and men worthwhile.

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