The Pharmacodynamics of β-Lactams

J. D. Turnidge

From the Department of Infectious Diseases and Microbiology, Monash Medical Centre, Clayton, Victoria, Australia

Considerable information on the pharmacodynamics of β-lactams has accumulated in the past 20 years. In vitro, β-lactams demonstrate time-dependent killing and variable postantibiotic effects. Animal models have shown that the time for which drug levels exceed the minimum inhibitory concentration (MIC) correlates best with bacterial eradication, and this is now being borne out in human studies. In investigations on osteomyelitis and endocarditis, trough serum inhibitory titers have generally correlated better with cure than have peak titers, and studies that have analyzed outcomes in relation to the MIC for the infecting pathogen have shown decreasing clinical efficacy with increasing MICs. One prospective study has shown that time above MIC correlated better with time to pathogen eradication than did area under the curve. In some continuous-infusion studies, significantly better outcomes were achieved with continuous infusion against susceptible bacteria or for patients with persistent, profound neutropenia. With use of time above MIC as the predictor of efficacy, it is possible to reexamine current dosing schedules critically.

The first β-lactam, penicillin G, was introduced into clinical practice more than 50 years ago. Investigators immediately recognized that penicillin was rapidly eliminated from the body and that frequent dosing was required to maintain ''adequate'' blood levels [1]. At this time the principle that guided dosing schedules was the maintenance of blood levels above the MIC for most or all of the dosing interval. Despite the lack of any strong evidence to either support or negate this concept, this principle became the standard technique for the development of dosage schedules for β-lactams for the next 40 years. However, as early as the late 1940s, seminal studies on animal models by Eagle and co-workers raised important questions about optimum dosage schedules for penicillin [2–6]. In some circumstances these investigators were able to demonstrate that bacteria did not appear to resume growth in vivo for short periods after exposure to penicillin.

Little attention was paid to this work until the rediscovery of the postantibiotic effect in the mid-1970s [7]. From this time on there has been an escalating interest in the concepts of antimicrobial pharmacodynamics and how they can be applied to the design of optimum dosage schedules. At present there is a wealth of evidence to support the concept that the principal determinant of efficacy of β-lactams is the time above the MIC—the time for which drug levels at the site of infection exceed the MIC. This review attempts to provide this evidence, focusing specifically on evidence accumulated to date from studies of humans.

Lessons from In Vitro Studies

Pivotal Role of the MIC

The MIC remains the only satisfactory in vitro measurement of the intrinsic activity of antimicrobials. This test has always been open to criticism because it is performed with use of artificial media and fixed concentrations of antimicrobial, in conditions that may often be quite different from those expected at the site of infection. The endpoint of no visible growth is subject to error, and the usual reading time of 24 hours hardly seems relevant to a treatment course lasting days to weeks. Nevertheless, the MIC has withstood the test of time, and although somewhat arbitrary, it can still act as the fundamental yardstick against which the in vivo activity of antimicrobials can be compared. The reasons for this are that it is reproducible and is likely to approximate the activity of the unbound fraction of an antibiotic at the site of infection. In addition, it provides a simple measure of concentration that can be directly compared to the concentrations of an antibiotic that can be measured in blood, body fluids, or tissues.

Time-Dependent Killing

Unlike aminoglycosides and quinolones, β-lactams exhibit little concentration-dependent killing. As killing is principally a function of time, this type of killing is termed *time-dependent*. With use of in vitro killing-curve studies, maximum killing is usually achieved at 3–4 times the MIC [8]. Some authors have suggested that cephalosporins do show significant concentration-dependent killing [9], but this is more related to an earlier onset of bactericidal activity, while the subsequent killing rate remains the same [10].

This article is part of a series of papers presented at a symposium entitled ''Pharmacodynamics of Antimicrobials'' that was held on 21–23 July 1995 in Québec City, Québec, Canada. This symposium was organized by the International Society for Antiinfective Pharmacology.

Reprints or correspondence: Assoc. Prof. John Turnidge, Department of Microbiology and Infectious Diseases, Women's and Children's Hospital, North Adelaide, 5006, Australia.

Clinical Infectious Diseases 1998; 27:10–22

1058–4838/98/2701–0003$03.00

Minimum concentration–dependent killing is a key property of β-lactams that is frequently ignored when doses are chosen. Because of the low toxicity of β-lactams, it has been instinctively appealing, and common practice, to use higher dosages for the treatment of more severe infections. Most β-lactams developed in recent years have been studied only at higher dosages, for more severe infection. Yet because there is little or no direct additional killing at higher dosages, no additional benefit is likely to be achieved by their use. Indeed, in severely ill patients, excretory mechanisms are usually impaired, permitting the use of lower dosages to achieve the same amount of drug exposure, a phenomenon well understood in dosage selection of the potentially toxic aminoglycosides.

Significance of Tolerance

β-Lactam drugs are bactericidal agents, and therefore the MBC, as measured by standard techniques, is usually the same or within one twofold dilution of the MIC. Occasionally, bacterial strains have been detected for which the MBC is manyfold higher than the MIC. Such strains are considered to have phenotypic tolerance [11]. When specifically sought, organisms expressing phenotypic tolerance of β-lactams in vitro have been isolated with variable frequency in the clinical setting but almost always are gram-positive bacteria, as summarized by Handwerger and Tomasz [11]. Although there are a considerable number of anecdotal reports of β-lactam failure attributed to tolerance, few prospective clinical studies have compared outcomes of β-lactam treatment against tolerant vs. nontolerant strains. The two largest studies were of staphylococcal bacteremia and endocarditis, and both concluded that although clinical response in patients with endocarditis was slower when infections with tolerant strains were being treated, overall outcomes and mortality were the same as those for infections with nontolerant strains [12, 13]. There were no differences in clinical response associated with tolerant and nontolerant strains in patients with bacteremia who did not have endocarditis [12].

Significance of Inoculum Effect

Although it has been widely studied, the significance of the inoculum effect for β-lactams remains uncertain. The inoculum effect may be clinically relevant because the number of bacteria at the site of infection may be manyfold higher than that traditionally used for susceptibility testing. Brook has summarized studies performed with β-lactams used against a wide variety of bacteria [14]. In general, significant inoculum effects are seen with bacteria that possess β-lactamases that may have some activity against the agent being studied. In gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas aeruginosa, Haemophilus influenzae,* and *Bacteroides fragilis,* moderate inoculum effects have been seen with ureidopenicillins and third-generation cephalosporins but not with second-generation cephalosporins or imipenem. For agents with high potency, such as the third-generation cephalosporins, the effect is usually insufficient to cause the organisms to be categorized as resistant.

Indirect support for the importance of an inoculum effect has been provided by animal models. Reduced killing by penicillin of streptococci at higher inocula has been noted by Eagle [15], and Gerber and colleagues provided good evidence that the reduced killing of *P. aeruginosa* with increasing time between introduction of infection and initiation of ceftazidime treatment was due to an inoculum effect rather than to slow growth [16]. Furthermore, Soriano et al. showed good correlation between the inoculum effect, as demonstrated in vitro, and dosages required to reduce mortality in a rat model of *Escherichia coli* bacteremia [17].

Importance of Protein Binding

The isoxazoylpenicillins and many cephalosporins are highly protein-bound, principally to albumin [18]. A high degree of protein binding has been shown to increase MICs in vitro when albumin or serum is added [19, 20], although less than predicted for cephalosporins, which interact with an ultrafilterable factor in serum [21]. How this affects activity in vivo has been more controversial, and methods of evaluating this have been elusive until recently.

Using the mouse thigh model of infection, a recent study by Andes et al. showed that the efficacy of the highly protein-bound cefonicid against *Klebsiella pneumoniae* was enhanced twofold to sixfold by administration of excess albumin to the mice [22]. Although the excess albumin decreased the level of unbound drug, it doubled the elimination half life (because cefonicid is excreted only by glomerular filtration) and thus prolonged the time that drug levels exceeded the MIC. Failure to take into account the high protein binding of cefonicid, which has been shown to affect activity in vitro [23], has resulted in significant clinical failures in the treatment of staphylococcal endocarditis [24].

Nevertheless, high protein binding can work favorably for some β-lactams. For instance, it is now common practice to use comparatively low doses of ceftriaxone for the treatment of infections caused by the common Enterobacteriaceae. Ceftriaxone is very highly protein-bound and does not undergo renal tubular excretion. As a result, it has the longest elimination half-life of any β-lactam in clinical use. In addition, it has high potency (low MICs) against many susceptible gram-negative bacteria. When MICs are closer to achievable unbound levels in vivo, high protein binding may negate the effect of prolonged half life and thus may reduce efficacy.

The Postantibiotic Effect

Delayed regrowth of *Staphylococcus aureus* after brief exposure to penicillin was first described by Bigger in 1944 [25].

The phenomenon was largely ignored until the mid-1970s, after which it became the subject of intensive study and was called the postantibiotic effect (PAE) [26–28]. For β-lactams, all studies to date have consistently demonstrated that penicillins and cephalosporins produce no PAE against gram-negative bacteria at clinically relevant concentrations, while there is a moderate PAE against staphylococci [29]. The PAE of streptococci is more complex. Penicillin shows a moderate PAE against *Streptococcus pneumoniae* in vitro but not in vivo [30]. In contrast to penicillins and cephalosporins, carbapenems produce moderate PAEs against both gram-negative and gram-positive bacteria [31, 32].

The generation of a PAE theoretically permits dosage schedules that allow antibiotic levels to fall below the MIC for a proportion of the dosing interval without compromising efficacy. It has in part been responsible for the successful application of once-daily aminoglycoside dosing [33].

In several instances, bacteria pretreated with β-lactams have been shown to have not only delayed regrowth but also increased susceptibility to the effects of neutrophils, so-called postantibiotic leukocyte enhancement (PALE). Modest PALE has been noted with use of penicillin and amoxycillin against susceptible *S. aureus* and with ampicillin, amoxicillin, and cefoxitin against susceptible *E. coli* [34, 35].

Lessons from Animal Model Studies

Studies of animal models have been instrumental in defining the pharmacodynamics of β-lactams. The earliest investigations were conducted by Eagle and co-workers, who in a series of animal studies showed that penicillin G was most effective in reducing the numbers of *S. pneumoniae, Streptococcus pyogenes,* and *Streptococcus agalactiae* at the site of infection when administered in lower doses more frequently [3, 4, 6]. They concluded that the total time for which levels of penicillin were maintained was the most important determinant of efficacy. Similar findings were noted by Schmidt et al. with regard to penicillin G used against *S. pneumoniae* in rats with peritonitis and lobar pneumonia [36, 37].

The most productive animal model has been the neutropenic mouse thigh model employed by Craig and colleagues, first described in full in 1982 by Gerber and Craig [38]. Initial studies in this model revealed that ticarcillin was more effective in reducing bacterial counts in the thigh when administered hourly than when the same total daily dose was administered on a q3h schedule [39].

Because this model lends itself easily to the administration of a very wide variety of dosing schedules, it has been possible to compare the amount of bacterial killing at the site of infection with different pharmacokinetic parameters, such that they can be examined as virtually independent factors. The three most important parameters are peak level, time above MIC (T>MIC), and area under the curve (AUC). For every β-lactam organism combination examined to date by means of a sigmoid (E_{max}) dose-response model [40], T>MIC has been the parameter that best predicts bacterial killing in vivo [41, 42]. The E_{max} model is the most widely accepted method for analyzing dose-effect responses [43] and takes the form of the following equation.

Equation 1

$$Effect = \frac{E_{\max} \times (Dose\ parameter)^n}{EC_{50}^n \times (Dose\ parameter)^n}$$

where

Effect = bacterial suppression or killing compared to that in controls, or mortality;
E_{max} = maximum effect;
Dose parameter = T>MIC, AUC, or peak concentration;
n = constant related to the slope; and
EC_{50} = dose parameter value at which 50% of E_{max} is achieved.

With use of this model, T>MIC has proven to be the best predictor of efficacy for penicillin against *S. pneumoniae,* cefazolin against *S. aureus* and *E. coli,* and ticarcillin against *P. aeruginosa* [41]. The findings have been the same for ceftazidime against *K. pneumoniae* in mice with pneumonia [40] and against *E. coli* in thigh infection [42]. These studies have also demonstrated that for β-lactam/organism combinations in which there is no PAE in vivo, maximum killing is achieved only when the T>MIC approaches 90%–100% of the dosing interval [41]. For β-lactam/organism combinations that do have in vivo PAE, maximum killing is achieved when the T>MIC is only 50%–60% of the dosing interval [41]. These conclusions have been reinforced by analysis of a wide variety of drug/organism combinations in the thigh and lung models [44].

Other investigators have supported the finding that T>MIC is important for β-lactams in different animal models. Bakker-Woudenberg et al. used a rat pneumonia model to show that more frequent administration or continuous infusion of penicillin resulted in better efficacy against *S. pneumoniae,* especially in the setting of immunodeficiency [45, 46]. This group of investigators reported similar findings in the same model with *K. pneumoniae* and ceftazidime [47, 48]. Frimodt-Møller et al. also demonstrated the importance of T>MIC as the most predictive parameter in mice infected intraperitoneally with *S. pneumoniae* by examining 14 cephalosporins with a wide range of elimination half-lives [49].

Studies of β-lactams in animal models of endocarditis have also produced evidence in support of the concept that T>MIC is important. Using four different regimens of methicillin resulting in equal total daily doses, Gengo et al. showed that q4h or q8h dosing yielded significantly better results than q12h dosing or continuous infusion, despite similar AUCs in serum [50]. Failure of the continuous-infusion regimen in this study may be explained by the results of two studies by Joly and Pangon et al., who have studied the pharmacodynamics of three cephalosporins in experimental *E. coli* endocarditis [51, 52].

These investigators showed that significant killing of bacteria in vegetations by ceftriaxone occurred only when drug concentrations in the vegetations were >200-fold higher than the MBC. This may well be due to the steep concentration gradient for ceftriaxone in cardiac vegetations, as demonstrated by autoradiography [53]. This group was also able to show that cephalosporins that have shorter elimination half-lives—in this case cefotiam and cefmenoxime—kill less in vivo than ceftriaxone, despite their similar in vitro activity and administration at the same total daily dose.

Only one animal model study has suggested that T>MIC is not the most important parameter. In rabbits implanted with fibrin clots infected with *H. influenzae* and treated with four different dosing regimens of ampicillin, cefuroxime, or aztreonam at the same total daily dose, Lavoie and Bergeron showed better correlation of bacterial killing with the ratio of AUC in clots over serum than with T>MIC in the clots [54]. As pointed out by the investigators, these results may reflect the uneven nature of drug penetration into fibrin clots with different modes of drug administration.

Clinical Studies of β-Lactam Pharmacodynamics

With the exception of studies of single doses for uncomplicated urinary tract infection, unfortunately few clinical studies have directly examined the effects of different β-lactam dosage schedules on clinical or bacteriologic outcome. Human studies are complicated by the ethical requirement of avoiding dosages that might be predicted to result in failure. It is therefore not feasible to use the broad-ranging dosage schedules that are possible in animal models. However, a number of studies have provided indirect evidence of the importance of T>MIC as the key parameter predicting efficacy.

Clinical Outcome vs. Serum Inhibitory or Bactericidal Titers

The clinical utility of serum inhibitory titers or serum bactericidal titers (SBTs) has been controversial for many years [55], and critical reviews have generally concluded that they are not good predictors of efficacy [56–58]. However, none of these reviews has examined the data with regard to pharmacodynamic parameters. In an effort to clarify the utility of SBTs, the same group of investigators conducted two large multicenter studies, one of osteomyelitis [59] and another of endocarditis [60]. Sufficient numbers of patients were included to allow critical analysis of peak and trough levels in comparison with clinical outcome. The therapeutic agents used were not stated specifically in either of these studies. However, in the osteomyelitis study, 42 of 48 patients received a β-lactam alone or in combination, and β-lactams are the mainstay against endocarditis with all causative pathogens apart from methicillin-resistant staphylococci. A summary of the findings is presented in figure 1.

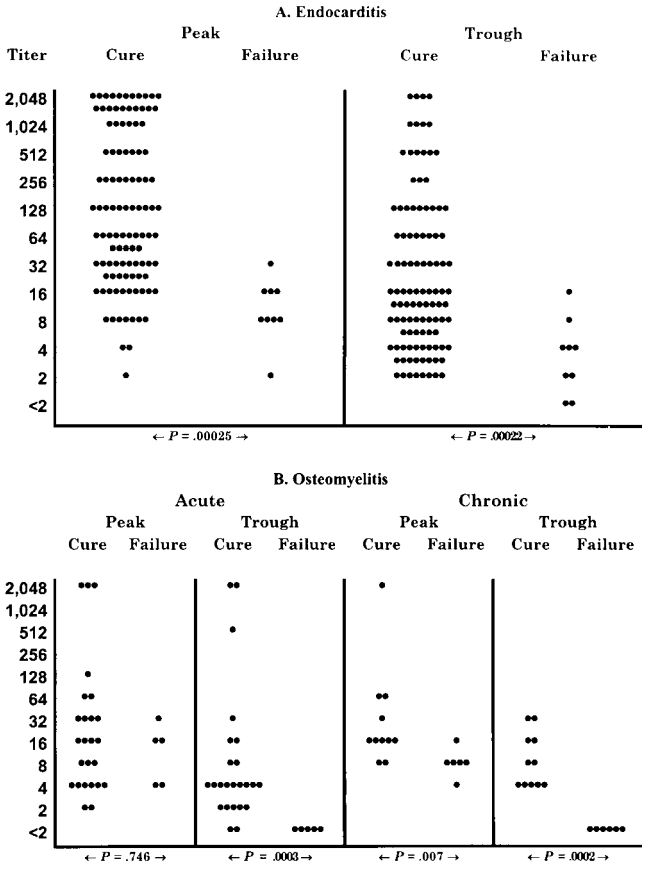

Figure 1. *A,* Peak and trough serum bactericidal titers vs. clinical outcome of infective endocarditis (adapted from [59]). Most patients were treated with β-lactams. Outcomes vs. titers were compared by means of the Mann-Whitney *U* test (not used in original publication). *B,* Peak and trough serum bactericidal titers vs. clinical outcome of acute and chronic osteomyelitis (adapted from [60]). Forty-two of 48 patients were treated with β-lactams. Outcomes vs. titers were compared by means of the Mann-Whitney *U* test (not used in original publication).

A reanalysis of the data from these studies with use of the nonparametric Mann-Whitney *U* test shows a strong correlation between outcome and both peak and trough bactericidal titers. In each case the correlation is stronger for trough concentrations than for peak concentrations. This is indirect support for the concept that T>MIC, rather than peak concentrations or AUC, is the best predictor of efficacy.

It is interesting that when correlations were made concerning the subset of patients with *S. aureus* endocarditis, troughs were slightly less well correlated with outcome than were peak titers ($P = .009$ for peaks and $P = .015$ for troughs by the Mann-Whitney *U* test). A similarly poor correlation of outcome with trough levels was subsequently reported by Rahal et al. following a smaller study of patients with *S. aureus* bacteremia treated with nafcillin (2 g q4h) [13]. However, as β-lactams are known to produce a moderate PAE against *S. aureus,* optimum efficacy

Table 1. Efficacy of cefoperazone in patients with cancer, in relation to the MIC for infecting pathogens.

MIC (mg/L)	No. of clinical responses/total no. of patients (%)	Percentage of dosing interval for which indicated drug level exceeded MIC*			
		3 g q6h		2 g q4h	
		Total drug	Unbound drug	Total drug	Unbound drug
≤0.78	14/16 (81)	100	100	100	100
1.56–3.12	14/18 (77)	100	93–100	100	100
6.25–12.5	10/14 (71)	100	26–59	100	60–100
25	6/7 (86)	100	0	100	0
>25	3/11 (27)	≤70	0	≤76	0

NOTE. Data are from [61].
* Calculated from pharmacokinetic data obtained from healthy volunteers [62].

may well be achieved when T>MIC is only a proportion of the dosing interval.

Clinical Outcome vs. MIC

If T>MIC is an important predictor of efficacy, then it should be possible to compare outcomes with the MICs for the causative pathogens. In an open study of cefoperazone used alone in the treatment of febrile episodes in cancer patients (both nonneutropenic and neutropenic), Bolivar et al. compared the clinical resolution rate with the MICs for the causative pathogens [61]. Patients received cefoperazone in regimens of either 3 g q6h or 2 g q4h, which would give predicted troughs of about 27 mg/L and 36 mg/L, respectively, of total drug or 3 mg/L and 4 mg/L of unbound drug (based on pharmacokinetic data from healthy volunteers [62]). Results, summarized in table 1, showed a significant reduction in clinical efficacy when the MIC for the infecting pathogen was >25 mg/L. At these levels total plasma cefoperazone would have exceeded the MIC for <80% of the dosing interval (see table 1).

Drusano [63] conducted a simulation study of expected trough concentrations of cefoperazone, with use of kinetic values that his group had obtained for healthy volunteers [64] by comparing them with MICs and clinical outcomes obtained in a study of cefoperazone vs. cefamandole/tobramycin against suspected gram-negative bacteremia [65]. On the basis of a predicted trough free-drug concentration of 2 mg/L, he successfully predicted (in a blinded manner) the clinical outcome with use of cefoperazone for nine of 10 bacteremic patients. He predicted 6 successes and 4 failures, when in fact there had been 5 successes and 5 failures. A breakpoint of 16 mg/L (referring to unbound drug) would have predicted nine successes and one failure.

Craig used data summarized from the worldwide experience with the use of cefoperazone to compare the outcome of treatment to the MIC for the infecting pathogen in the 276 instances in which an MIC had been obtained [66]. As figure 2 demonstrates, there is a clear-cut trend toward increased failure with increasing MIC, rising from 4% when the cefoperazone MIC was ≤1 mg/L to 44% when the MIC was ≥64 mg/L. Clinical efficacy fell below 90% when the MIC for the pathogen was >2 mg/L, a finding in concordance with that of Drusano [63].

A similar analysis of cefotaxime efficacy vs. MIC was performed by Doern [67], as shown in figure 2, on the basis of data presented by Murray et al. [68]. The data set was for 1,563 adults treated with 2 g of cefotaxime every 6–8 hours. Clinical efficacy fell below 90% with MICs of >8 mg/L and continued to decrease with higher MIC values. On the basis of data from healthy volunteers, trough concentrations of cefotaxime for these dosages would be in the range of 0.3–1 mg/L.

The emergence of resistance to penicillin due to alterations in penicillin-binding proteins, with a consequent broad range of MICs against *S. pneumoniae,* has provided a serendipitous opportunity to perform a similar comparison of outcome vs. MIC. Recently, Gehanno et al. published the clinical resolution rate of acute otitis media caused by a pneumococcus in children treated with cefuroxime axetil at a dosage of 15 mg/kg twice daily for 8 days [69]. In general, high rates of clinical cure (43 of 46; 93%) were obtained in association with isolates for

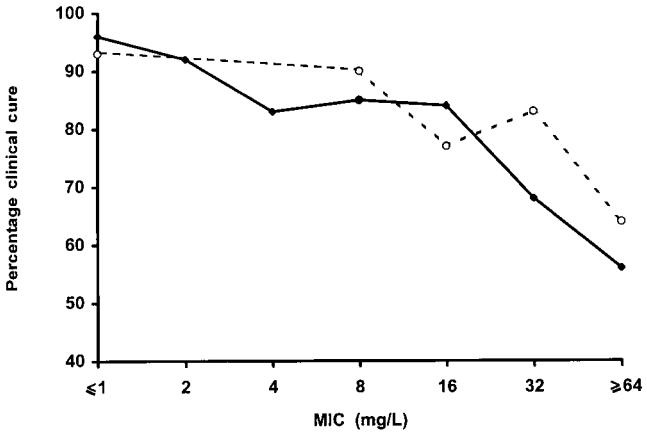

Figure 2. Clinical outcome vs. MIC of cefoperazone (*bold line*) and cefotaxime (*dashed line*). Figure adapted from data in [63, 64].

Table 2. Impact of MIC and dosing interval on frequency of clinical cure with use of cefoxitin in *Bacteroides fragilis* group infections.

Dosing schedule	Proportion of patients with indicated cefoxitin MIC (mg/L)				
	8	16	32	64	Total (%)
q8h	0/1	0/1	0/2	. . .	0/4
q6h	4/4	4/5	1/3	0/1	9/13 (69)
q4h	. . .	1/1	1/1	. . .	2/2 (100)
Total (%)	4/5 (80)	5/7 (71)	2/6 (33)	0/1	. . .
%T>MIC*	52–100	40–79	27–54	15–29	. . .

NOTE. Data are from [71].

* Percentage of the dosing interval for which cefoxitin levels exceeded the nominated MIC (following a 2-g dose), on the basis of kinetic data from healthy volunteers [62].

which the MIC of penicillin or cefuroxime was <1 mg/L, whereas efficacy fell significantly with MICs above this value (29 of 38; 76%). Pharmacokinetic data from healthy children [70] given this dose of cefuroxime axetil suggest that trough plasma concentrations of cefuroxime are about 0.01–0.03 mg/L and that total serum concentrations exceed 1 mg/L for about 40% of the dosing interval.

Snydman and co-workers retrospectively analyzed the clinical outcome for patients with *B. fragilis* group infections treated with cefoxitin [71]. The comparison between outcome and MIC with different cefoxitin dosing schedules is summarized in table 2. Although patient numbers were relatively small, there is an obvious trend toward increasing efficacy with both a shorter dosing interval and a lower MIC. Unfortunately, the authors did not provide the individual dosages administered with the various schedules, so it is not possible to estimate the T>MIC on a per-schedule basis. However, on the basis of data from healthy volunteers and a 2-g dose, T>MIC ranged from about 50% to 100% of the dosing interval for organisms against which the MIC was 8 mg/L, while for organisms against which the MIC was 64 mg/L, the T>MIC was only 15%–30%.

Only one study has deliberately set out to examine a variety of pharmacodynamic parameters of a β-lactam as predictors of efficacy. Schentag and colleagues examined the efficacy of cefmenoxime in critical care patients with nosocomial pneumonia [72]. Using a surrogate endpoint of efficacy, namely, the time to eradication of the pathogen from tracheal secretions, and an alternative to the MIC that they measured on the Abbott MS-2 system (Abbott Laboratories, Chicago) and called the dynamic response concentration (DRC), these investigators showed a strong relationship between efficacy and both the AUC over the DRC and the time above the DRC. Although they concluded that the relationship was stronger with AUC above DRC, the authors included in their overall analysis data from patients whose doses were prospectively adjusted according to the DRC for the pathogen.

If data from the 14 patients (with 19 different bacterial isolates) who did not have their doses adjusted are analyzed separately, time above DRC shows a stronger relationship with efficacy than does AUC. This analysis is summarized in figure 3, which also includes two different pharmacodynamic parameters that were calculated from the published data, namely, the AUC/DRC ratio and the percentage of T>DRC in the dosing interval. Linear regression of all four pharmacodynamic parameters shows smaller scatter and therefore better correlation with the T>DRC parameters than with the AUC parameters.

Efficacy Studies Related to Dosing Schedule

Continuous infusion vs. intermittent dosing. If T>MIC is important in determining efficacy of β-lactams, then T>MIC can be maximized by administering the drug by continuous infusion [73]. Three clinical studies have compared the clinical efficacy of continuous infusions of β-lactams compared to that of conventional intermittent dosing. Bodey et al. compared intermittent carbenicillin plus continuous tobramycin, intermittent carbenicillin plus continuous cefamandole (12 g/d), and intermittent carbenicillin plus intermittent cefamandole (3 g q6h) in the treatment of cancer patients with fever. Patients given cefamandole received the same total daily dose [74].

Among those patients with documented infections, cure was noted in 48 (65%) of 74 patients receiving treatment with the continuous cefamandole regimen, compared with 52 (57%) of 92 patients treated with the intermittent cefamandole regimen. While this difference did not reach statistical significance ($P = .34$ by Fisher's exact test), analysis of two subgroups did show significant differences. Among patients infected with cefamandole-susceptible bacteria, efficacy was 92% (22 of 24) with continuous cefamandole vs. 63% (19 of 30) for intermittent cefamandole ($P = .02$). Similarly, for patients with persistent neutropenia (<1,000 neutrophils/mm^3, with no increase during the treatment period), efficacy was 65% (13 of 20) with continuous cefamandole vs. 21% (3 of 14) with intermittent cefamandole ($P = .02$).

In contrast, Lagast and colleagues compared continuous (4 g/d) vs. intermittent (2 g q12h) cefoperazone in the treatment of gram-negative septicemia in patients with a variety of underlying diseases [75]. Continuous infusion therapy had an overall efficacy of 70% (14 of 20), while intermittent therapy had 80% efficacy (20 of 25) ($P = .5$). Analysis of subgroups showed no differences between the modes of administration in relation to underlying disease, granulocyte count, site of infection, or pathogen treated.

In a study of 123 adults with proven pneumococcal pneumonia, Brewin et al. compared the efficacy of 360 mg (600,000 U) of procaine penicillin given im daily with 12 g (18 million U) per day of benzylpenicillin given by continuous iv infusion [76]. These investigators were unable to demonstrate a difference in outcome between the two regimens. However, unlike the other studies cited above, it is likely that both regimens resulted in maximum T>MIC (~100%) because of the pharmacokinetic characteristics of im procaine penicillin [77].

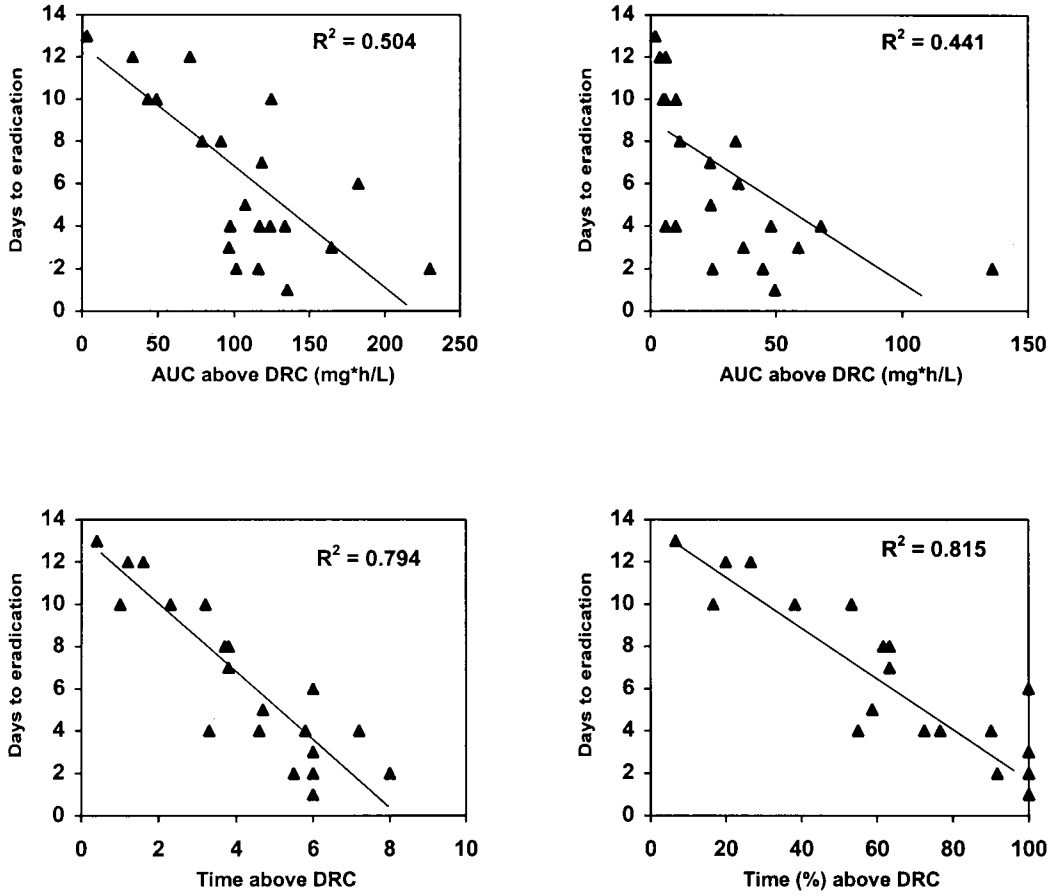

Figure 3. Bacteriologic outcome, measured as days to eradication of the pathogen, as related to several pharmacodynamic parameters for cefmenoxime-treated critical care patients with pneumonia, analyzed retrospectively. Data for area under the time-concentration curve (AUC) above dynamic response concentration (DRC [mg/L]) and time above DRC are taken directly from [72]. Data for AUC/DRC ratio and time (%) above DRC were calculated from data provided in that publication. The fitted line was calculated by linear least-squares regression, with use of Systat (Systat, Evanston, IL). The DRC, a parameter related to MIC, was measured on the Abbott MS II system (Abbott Laboratories, Chicago). (Figure adapted from [72]; mg∗h/L = mg hours per liter).

Three anecdotal reports are also of interest. Daenen and de Vries-Hospers [78] successfully treated two patients who had profound neutropenia and *P. aeruginosa* sepsis with a continuous infusion of ceftazidime (6 g/d after a 2-g loading dose). For both patients, treatment with intermittent ceftazidime (2 g q8h) had failed. Promising results have also been reported in two other studies of cystic fibrosis patients infected with *P. aeruginosa* who were treated with a continuous infusion of ceftazidime (300 mg/[kg · d] [79] and 82–108 mg/[kg · d] [80]).

Infrequent-dosing schedules. Infrequent-dosing schedules are likely to reduce the efficacy of β-lactams with short elimination half-lives if T>MIC is crucial to outcome. Nevertheless, in many situations where they have been examined, β-lactams with a short half-life (<2 hours) have proven to have satisfactory efficacy when administered as infrequently as twice daily. Examples include bacampicillin [81] and cefotaxime [82]. This would appear to argue against the importance of T>MIC. However, a number of factors need to be considered before accepting this as evidence against the role of T>MIC.

These include knowledge of the infection's rate of resolution in the absence of antibiotic treatment, the importance of the synergy between host defenses and antibiotic therapy in achieving favorable outcomes, and the differences in pharmacokinetics at sequestered sites of infection. Moreover, in elderly or seriously ill patients, there is the possibility of slower elimination due to reduced renal clearance, which will elevate trough levels and increase the T>MIC. This phenomenon has been elegantly demonstrated in two studies in which cefotaxime (q12h) was administered to patients with gram-negative bacteremia [83, 84].

Goodpasture et al. [83] examined trough levels of cefotaxime and desacetylcefotaxime, as well as trough SBTs, in 13 patients with culture-proven gram-negative bacteremia and normal serum creatinine values who were treated with q8h or q12h doses

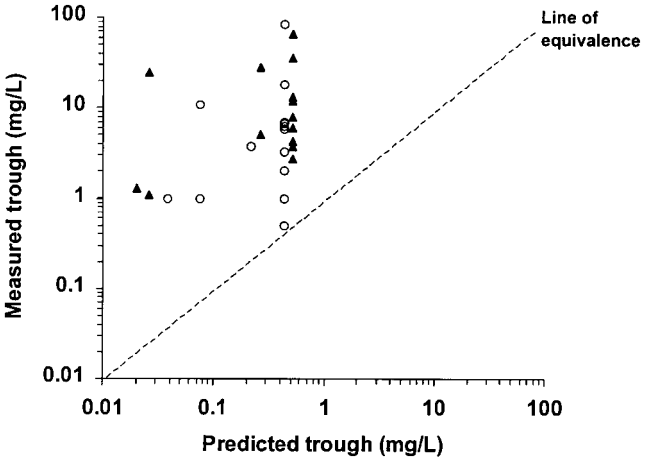

Figure 4. Predicted vs. measured trough levels of cefotaxime (▲) and desacetylcefotaxime (○) in patients receiving the drug q8h or q12h for the treatment of gram-negative septicemia, based on data by Goodpasture et al. [83]. Predicted troughs were calculated from pharmacokinetics in healthy volunteers [62] and have been graphed on a logarithmic scale. Measured troughs are also plotted on a logarithmic scale.

of cefotaxime. Of particular interest are the three patients who received 2 g of cefotaxime q12h and one patient who received 1 g q12h. In these patients troughs ranged from 1.3 to 24.7 mg/L for cefotaxime and from <1 to 10.9 mg/L for desacetylcefotaxime; SBTs ranged from 1/4 to 1/1,024.

Similar results were found in a study by Trenholme et al. [84], who also examined efficacy and drug levels with q8h and q12h doses of cefotaxime. These authors found, in 9 patients given cefotaxime q12h, mean troughs of 3 mg/L for both cefotaxime and desacetylcefotaxime (ranges: from not detected to 8 mg/L and from not detected to 25 mg/L, respectively); the mean SBT was 1/49 (range, 2–256). In both studies all of the target pathogens responded to treatment with these less frequent dosing schedules. As might be expected, elderly patients predominated in these studies, a factor that has been shown to influence cefotaxime kinetics [85]. Both these studies demonstrate much higher trough values than would be predicted by extrapolation from the pharmacokinetics in young, healthy volunteers [86], as emphasized in figure 4.

Potential Application of β-Lactam Pharmacodynamics

Dosing Schedules

Prediction of empirical intermittent-dosing schedules. The weight of evidence supports the concept that T>MIC is the best predictor of efficacy in vivo. By simple extrapolation, this can be achieved with smaller amounts of drug (lower total daily doses) by administering the drug in lower doses at shorter dosing intervals. As the majority of β-lactams have short elimination half-lives, obvious limitations are reached with this dosing strategy.

It is usually impractical to administer drugs iv more frequently than q4h in the hospital setting, and with oral agents in the community setting good compliance is achieved only with once-daily or twice-daily schedules. For these reasons, newer β-lactams are often developed for use at higher doses given less frequently. However, this does not favor β-lactam efficacy, as in general it will lower the T>MIC values.

The reason for this can be deduced from equation 2 below, which shows the relationship between the dose administered, the dosing interval, and the percentage of the dosing interval that levels exceed the MIC. For instance, doubling the dose increases the T>MIC in proportion to the logarithm of the dose, or by one elimination half-life, whereas halving the dosing interval doubles the T>MIC.

Equation 2

$$\%T>MIC = \ln\left(\frac{\text{Dose}}{Vd \times \text{MIC}}\right) \times \frac{T^{1}/_{2}}{\ln(2)} \times \frac{100}{\text{DI}}$$

where

ln = natural logarithm;
Vd = volume of distribution (L);
$T^{1}/_{2}$ = elimination half-life (h); and
DI = dosing interval (h).

The derivation of equation 2 can be found in the appendix.

The simplicity of equation 2 lies in the fact that only the elimination phase need be considered when drugs are administered iv by bolus or brief infusion. As an illustrative example of these principles, consider the dosing of ceftazidime in the treatment of febrile neutropenia. In this setting *P. aeruginosa* is one of the target pathogens, for which the MIC is high and the MIC_{90} for susceptible strains is 4 mg/L. In the absence of neutrophils, the aim would be to exceed the MIC throughout the dosing interval because of the absence of a PAE. A common starting schedule would be 2 g q8h.

Employing pharmacokinetic parameters from healthy volunteers—namely, an elimination half-life of 2 hours and a volume of distribution of about 0.25 L/kg—the formula shows that in a 70-kg individual, ceftazidime levels exceed the MIC throughout the dosing interval (9.7 hours). Given that each 2-g dose yields levels above the MIC for 20% longer than the dosing interval, it might seem possible to reduce the dosing interval to q12h, a strategy recently employed for cefpirome, which has a similar spectrum of activity and pharmacokinetics.

This schedule yields a T>MIC of 81% of the dosing interval, which would be suboptimal in this setting. Indeed, a regimen of 1 g q8h affords a higher value of 96%, and 1 g q6h would result in a 100% value at two-thirds of the original total daily dose (4 g vs. 6 g). Further examples of the application of this formula are demonstrated in table 3, which compares the %T>MIC with different dosing schedules for several antipseudomonal β-lactams against febrile neutropenia.

Table 3. Times above the MIC for *Pseudomonas aeruginosa* and total daily doses of antipseudomonal β-lactams given in various dosage schedules.

β-lactam (target MIC [mg/L])	Dose	Dosing interval	Time (h) for which level is >4 mg/L after each dose*	%Time > MIC*	Total daily dose
Ticarcillin (16)	3 g	q6h	4.5	75	12 g
	3 g	q4h	4.5	100	18 g
	2 g	q4h	3.8	95	12 g
Piperacillin (4)	4 g	q6h	6.2	100	16 g
	3 g	q4h	5.7	100	18 g
	2 g	q4h	5.2	100	12 g
	1 g	q4h	4.2	100	6 g
Ceftazidime (4)	2 g	q8h	9.7	100	6 g
	2 g	q12h	9.7	81	4 g
	1 g	q8h	7.7	96	3 g
	1 g	q6h	7.7	100	4 g
Cefpirome (8)	2 g	q12h	9.1	76	4 g
	2 g	q8h	9.1	100	6 g
	1 g	q6h	6.8	100	4 g
Imipenem (4)	1 g	q8h	3.6	45	3 g
	1 g	q6h	3.6	60†	4 g
	1 g	q4h	3.6	89	6 g

* Calculated with use of equation 2 (see text) and kinetic values from healthy volunteers [62].
† Value may be adequate for carbapenems because of postantibiotic effect.

Equation 2 cannot be applied directly to drugs administered orally or im because the absorption phase of the drug must be considered. However, for drugs that are rapidly absorbed, the small amount of time required to reach the MIC in the absorption phase would have only a small effect on the total T>MIC, and thus the equation provides a reasonable approximation of the true T>MIC. For slowly absorbed drugs, a more complete profile of the concentration-vs.-time curve is needed to accurately measure T>MIC.

Analysis of data from the neutropenic mouse thigh and lung models, as well as other animal models, suggests that the T>MIC needs to be 90%–100% of the dosing interval when there is no PAE and 50%–60% when there is a PAE. While these values may be applicable to the example listed above, most infections occur in the absence of neutropenia. Craig has proposed that in nonneutropenic hosts it may be sufficient to produce a bacteriostatic effect in order to achieve optimum efficacy [66]. Such percentages of T>MIC can be readily calculated from the E_{max} dose-response curves in animal models.

Craig et al. [20, 44] have reexamined data from the mouse models and generated values for the T>MIC to produce a bacteriostatic effect against a variety of pathogens for which the range of MIC values is broad. For penicillins, T>MIC values for bacteriostasis were 29%–34%; for cephalosporins, 35%–55%; and for carbapenems, 20%–26%. These were virtually independent of the dosing interval [44]. Values for staphylococci were lower, at 24%, than for streptococci (41%) and gram-negative bacilli (36%).

A more-detailed analysis of third- and fourth-generation cephalosporins confirmed the difference between *S. pneumoniae* (38%), gram-negative bacilli (37%), and *S. aureus* (24%), consistent with the importance of an in vivo PAE [20]. The predictive value of these percentages has yet to be tested in the clinical setting, although the findings of Gehanno et al. concerning pneumococcal otitis media concur with these estimates [69].

Dosage adjustment. In theory, if the MIC for the pathogen(s) being targeted by treatment is known, it may be possible to adjust dosing schedules for each patient. However, when considering individualization of dosages, it is important to recognize variation in pharmacokinetics between individuals. The calculation of dosage schedules discussed above uses pharmacokinetic data from young, healthy volunteers. These are average figures that do not take intersubject variation into account. In addition, in elderly and more seriously ill patients, reduced drug clearance is common, resulting in longer elimination half-lives and therefore increased T>MIC values.

This was demonstrated clearly in two studies of less frequent dosing of cefotaxime in patients with gram-negative sepsis [83, 84]. Similarly, wide intersubject variation was noteworthy in a study by Visser and colleagues of continuous infusion of penicillin G and cloxacillin [87]. These investigators found about a 10-fold range in steady-state plasma levels of penicillin (5.2–53.6 mg/L) and cloxacillin (14.5–148.3 mg/L) in adults with serious infections given 7.2 g and 12 g per day, respectively, by continuous infusion. They also noted significant variation in plasma protein binding between patients (penicillin, 13%–70%; cloxacillin, 33%–90%). Thus, in the clinical setting it will be important to adjust dosages on the basis of not only the MIC but also drug levels in each patient.

Such an idea, sometimes called dual individualization, was first introduced by Schentag's group in their study of cefmenoxime in nosocomial pneumonia [72]. Dose adjustments were made on the basis of a measured concentration-vs.-time profile for each patient as well as the directly calculated AUC above their surrogate of the MIC, with the aim of eradicating the pathogen from tracheal secretions in 4 days. Using this method, they showed that eradication of susceptible pathogens could be achieved in a mean of 5 days (range, 4–6 days), compared with 7.1 days (range, 1–13 days) in a previous group of patients for whom dosage adjustments had not been made.

Schentag et al. have subsequently elaborated on the AUC as a predictive pharmacodynamic parameter [88]. The group has successfully shown that in patients with nosocomial pneumonia, there is a strong relationship between the so-called AUIC (area under the inhibitory curve), which is actually the AUC divided by the MIC for the infecting pathogen (AUC/MIC ratio), and fluoroquinolones [89]. It is likely that this ratio is predictive of efficacy for most concentration-dependent drugs, but its applicability to time-dependent drugs such as β-lactams is less clear.

Repeated measuring of drug concentrations to calculate the AUC has obvious practical limitations in clinical practice. AUC values could be estimated also by means of complex calculations or a computer program, from a single level based on population pharmacokinetics or from two widely spaced levels. However, as T>MIC is the critical parameter, it may be sufficient simply to measure a trough level and compare this to the MIC for the infecting pathogen. Alternatively, both these measurements may be combined into a single measure of trough serum inhibitory titers for the infecting pathogen. Given the significant variation in protein binding that may occur in the clinical setting, serum inhibitory titers for highly protein-bound drugs would best be measured with use of the modification proposed by Leggett et al. [90].

Continuous infusion. The demonstrable efficacy of continuous infusion of β-lactams in some clinical settings [74] and the ability to maintain drug levels above the MIC make continuous infusion an attractive alternative for certain infections. With one exception, clinical studies so far have examined only the use of the same (or a higher) total daily dose given by intermittent dosing [74–76]. However, it is possible to maintain levels above the MIC with reduced dosages.

This has been applied in a pilot study of the efficacy of a continuous infusion of oxacillin, with doses individualized to achieve concentrations of free oxacillin of ~1 mg/L (4–5 times the usual MIC), compared with the efficacy of intermittent dosing (2 g q4h) [91]. For 23 patients with staphylococcal infection, these investigators showed that mean daily doses could be reduced from 12.0 g to 8.1 g and achieved T>MIC values of 100% vs. 62% for continuous infusion vs. intermittent dosing.

Nevertheless, questions regarding the level by which the MIC needs to be exceeded and the impact of intersubject variation in kinetics will require prospective clinical study. It is likely that if reduced doses are used, levels will need to be measured in individual patients to ensure their adequacy. Furthermore, continuous infusion requires specialized and sometimes expensive equipment, drug stability over 24 hours at room temperature, and a dedicated intravenous line. Thus, this mode of administration will be applicable only for certain infections in which levels need to be maintained above the MIC throughout the dosing interval or when it actually simplifies drug administration, such as for home iv antibiotic therapy.

Summary

β-Lactam antibiotics have time-dependent killing and, with the exception of carbapenems, produce no PAE except against staphylococci. Taken together, the data from animal-model and human studies strongly favor the concept that T>MIC is the best predictor of bacterial killing in vivo and of clinical efficacy.

Until more clinical evidence is available, extrapolations from the neutropenic animal data suggest that in the setting of profound neutropenia, penicillin and cephalosporin levels need to exceed the MIC for 90%–100% of the dosing interval for efficacy against gram-negative bacilli and streptococci but only for 50%–60% of the dosing interval for efficacy against staphylococci, because of the PAE. Bacteriostatic drug levels may be all that is required in the nonneutropenic host, in which case levels need exceed the MIC for only approximately 20%, 25%–30%, and 25%–40% of the dosing interval for carbapenems, penicillins, and cephalosporins, respectively.

With use of a simple mathematical formula, T>MIC percentages can be readily calculated on the basis of pharmacokinetics in healthy volunteers and can be used for comparison with current dosage schedules and target T>MIC percentages. Adjustment of dosage schedules should be considered if these percentages are not achieved, in an aim to give lower doses more frequently, as this is more effective than simply increasing doses. Alternatively, continuous infusion may be an appropriate method of administration in selected circumstances.

Appendix: Derivation of Equation 2

For calculating the time for which levels exceed the MIC, one can use the one-compartment first-order elimination equation (equation A). The two-compartment model adds no additional information.

Equation A

$$C = C_0 \times e^{-k \times t}$$

where

C = concentration at time t (mg/L);
C_0 = concentration at time 0 (mg/L);
k = elimination rate constant (h^{-1});
e = the base of natural logarithms; and
t = time (h).

The elimination rate half-life ($T^1/_2$) is related to the elimination constant k by the formula

$$k = \frac{\ln(2)}{T^1/_2}$$

and C_0 can be equated to the volume of distribution (Vd) with the formula

$$C_0 = \frac{\text{Dose}}{Vd}$$

where

Dose = quantity in mg of each individual dose and
Vd = (apparent) volume of distribution (L).

Thus, equation A becomes
Equation B

$$C = \frac{\text{Dose}}{Vd} \times e^{-\ln(2)/T1/2 \times t}$$

Resolving for t gives
Equation C

$$t = \ln\left(\frac{\text{Dose}}{Vd \times C}\right) \times \frac{T^1/_2}{\ln(2)}$$

The time above MIC will occur when C = MIC, which when calculated as a percentage of the dosing interval becomes equation 2.

Equation 2

$$\%T{>}MIC = \ln\left(\frac{\text{Dose}}{Vd \times \text{MIC}}\right) \times \frac{T^1/_2}{\ln(2)} \times \frac{100}{\text{DI}}$$

where

%T>MIC = percentage of the dosing interval for which levels exceed the MIC;
DI = dosing interval (h); and
MIC = minimum inhibitory concentration (mg/L).

References

1. Rammelkamp CH, Keefer CS. The absorption, excretion, and distribution of penicillin. J Clin Invest **1943**;22:425–37.
2. Eagle H, Musselman AD. The slow recovery of bacteria from the toxic effects of penicillin. J Bacteriol **1949**;58:475–90.
3. Eagle H, Fleischman R, Musselman AD. The bactericidal action of penicillin in vivo: the participation of the host, and the slow recovery of the surviving organisms. Ann Intern Med **1950**;33:544–71.
4. Eagle H, Fleischman R, Musselman AD. Effect of schedule of administration on the therapeutic efficacy of penicillin. Am J Med **1950**;9:280–99.
5. Eagle H, Fleischman R, Levy M. On the duration of penicillin action in relation to its concentration in serum. J Lab Clin Med **1953**;41:122–32.
6. Eagle H, Fleischman R, Levy M. ''Continuous'' vs. ''discontinuous'' therapy with penicillin. The effect of the interval between injections on the therapeutic efficacy. N Engl J Med **1953**;248:481–8.
7. McDonald PJ, Craig WA, Kunin CM. Brief antibiotic exposure and effect on bacterial growth. Chemotherapy **1976**;2:95–102.
8. Craig WA, Ebert S. Kinetics and regrowth of bacteria in vitro: a review. Scand J Infect Dis Suppl **1991**;74:15–22.
9. Shah PM, Junghanns W, Stille W. Dosis-Wirkungs-Beziehung der Bakterizidie bei *E. coli, K. pneumoniae and Staphylococcus aureus.* Dtsch Med Wochenschr **1976**;101:325–8.
10. Nishino T, Nakazawa S. Bacteriological study on the effects of the β-lactam group of antibiotics in high concentrations. Antimicrob Agents Chemother **1976**;9:1033–42.
11. Handwerger S, Tomasz A. Antibiotic tolerance among clinical isolates of bacteria. Rev Infect Dis **1985**;7:368–86.
12. Rajashekaraiah KR, Rice T, Rao VS, Marsh D, Ramakrishna B, Kallick CA. Clinical significance of tolerant strains of *Staphylococcus aureus* in patients with endocarditis. Ann Intern Med **1980**;93:796–800.
13. Rahal JJ, Chan Y-K, Johnson G. Relationship of staphylococcal tolerance, teichoic acid antibody, and serum bactericidal activity to therapeutic outcome in *Staphylococcus aureus* bacteremia. Am J Med **1986**;81:43–52.
14. Brook I. Inoculum effect. Rev Infect Dis **1989**;11:361–8.
15. Eagle H. The effect of the size of the inoculum and the age of infection, and the curative dose of penicillin in experimental infections with streptococci, pneumococci, and *Treponema pallidum.* J Exp Med **1949**;90:595–607.
16. Gerber AU, Greter U, Segessenmann C, Kovak S. The impact of pretreatment interval on antimicrobial efficacy in a biological model. J Antimicrob Chemother **1993**;31(suppl D):29–39.
17. Soriano F, Ponte C, Santamaria M, Jimenez-Arriero M. Relevance of the inoculum effect of antibiotics in the outcome of experimental infections caused by *Escherichia coli.* J Antimicrob Chemother **1990**;25:621–7.
18. Craig WA, Suh B. Protein binding and the antimicrobial effects: methods for the determination of protein binding. In: Lorian V, ed. Antibiotics in laboratory medicine. 3rd ed. Baltimore: Williams & Wilkins, **1991**:367–402.
19. Wise R. Protein binding of β-lactams: the effects on activity and pharmacology, particularly tissue penetration. I. J Antimicrob Chemother **1983**;12:1–18.
20. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis **1995**;22:89–96.
21. Leggett JE, Craig WA. Enhancing effect of serum ultrafiltrate on the activity of cephalosporins against gram-negative bacilli. Antimicrob Agents Chemother **1989**;33:35–40.
22. Andes D, Walker R, Ebert S, Craig WA. Increasing protein binding of cefonicid enhances its in-vivo activity in an animal infection model [abstract no A81]. In: Program and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy (Orlando, Florida). Washington, DC: American Society for Microbiology, **1994**:146.
23. Dudley MN, Nightingale CH, Quintiliani R, Tilton RC. In vitro activity of cefonicid, ceforanide, and cefazolin against *Staphylococcus aureus* and *Staphylococcus epidermidis* and the effect of human serum. J Infect Dis **1983**;148:178.
24. Chambers HF, Mills J, Drake TA, Sande MA. Failure of a once-daily regimen of cefonicid for treatment of endocarditis due to *Staphylococcus aureus.* Rev Infect Dis **1984**;6(suppl 4):S870–4.
25. Bigger JW. Bactericidal action of penicillin on *Staphylococcus pyogenes.* Ir J Med Sci **1944**;227:553–85.
26. McDonald PJ, Craig WA, Kunin CM. Brief antibiotic exposure and effect on bacterial growth. Chemotherapy **1976**;2:95–102.
27. McDonald PJ, Craig WA, Kunin CM. Persistent effects of antibiotics on *Staphylococcus aureus* after exposure for limited periods of time. J Infect Dis **1977**;135:217–23.

28. Bundtzen RW, Gerber AU, Cohn DL, Craig WA. Postantibiotic suppression of bacterial growth. Rev Infect Dis **1981**;3:28–37.
29. Craig WA, Gudmundsson S. Postantibiotic effect. In: Lorian V, ed. Antibiotics in laboratory medicine. 3rd ed. Baltimore: Williams & Wilkins, **1991**:403–31.
30. Vogelman B, Gudmundsson S, Turnidge J, Leggett J, Craig WA. In vivo postantibiotic effect in a thigh infection in neutropenic mice. J Infect Dis **1988**;157:287–98.
31. Bustamante CI, Drusano GL, Tatem BA, Standiford HC. Post-antibiotic effect of imipenem on *Pseudomonas aeruginosa.* Antimicrob Agents Chemother **1984**;26:678–82.
32. Nadler HL, Pitkin DH, Sheikh W. The postantibiotic effect of meropenem and imipenem on selected bacteria. J Antimicrob Chemother **1989**; 24(suppl A):225–31.
33. Craig WA. Once-daily aminoglycoside dosing. Can J Infect Dis **1994**; 5(suppl C):28C–32C.
34. McDonald PJ, Wetherall BL, Pruul H. Postantibiotic leukocyte enhancement: increased susceptibility of human bacteria pretreated with antibiotics to activity of leukocytes. Rev Infect Dis **1981**;3:38–44.
35. Pruul H, Wetherall BL, McDonald PJ. The effect of exposure of *Staphylococcus aureus* to penicillin on susceptibility to the bactericidal activity of human neutrophils. Pathology **1982**;14:263–7.
36. Schmidt LH, Walley A, Larson RD. The influence of the dosing regimen on the therapeutic efficacy of penicillin. J Pharmacol Exp Ther **1949**; 96:258–68.
37. Schmidt LH, Walley A. The influence of the dosage regimen on the therapeutic effectiveness of penicillin G in experimental lobar pneumonia. J Pharmacol Exp Ther **1951**;103:479–88.
38. Gerber AU, Craig WA. Aminoglycoside-selected subpopulations of *Pseudomonas aeruginosa:* characterization and virulence in normal and leukopenic mice. J Lab Clin Med **1982**;100:671–81.
39. Gerber AU, Craig WA, Brugger H-P, Feller C, Vastola AP, Brandel J. Impact of dosing intervals in the activity of gentamicin and ticarcillin against *Pseudomonas aeruginosa.* J Infect Dis **1983**;147:910–7.
40. Leggett JE, Fantin B, Ebert S, et al. Comparative antibiotic dose-effect relationships at several dosing intervals in murine peritonitis and thigh-infection models. J Infect Dis **1989**;159:281–92.
41. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis **1988**;158:831–47.
42. Fantin B, Leggett J, Ebert S, Craig WA. Correlation between in vitro and in vivo activity of antimicrobial agents against gram-negative bacilli in a murine infection model. Antimicrob Agents Chemother **1991**;35: 1413–22.
43. Holford NGH, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet **1981**;6:429–53.
44. Craig W, Ebert S, Watanabe Y. Differences in time above MIC (T>MIC) required for efficacy of beta-lactams in animal model infections [abstract no 1485]. In: Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). Washington, DC: American Society for Microbiology, **1993**:391.
45. Bakker-Woudenberg IAJM, van Gerwan ALEM, Michel MF. Efficacy of antimicrobial therapy in experimental rat pneumonia: antibiotic treatment schedules in rats with impaired phagocytosis. Infect Immun **1979**; 25:376–87.
46. Bakker-Woudenberg IAJM, van den Bergh JC, Fontijne P, Michel MF. Efficacy of continuous versus intermittent administration of penicillin G in *Streptococcus pneumoniae* pneumonia in normal and immunodeficient rats. Eur J Clin Microbiol **1984**;3:131–5.
47. Roosendaal R, Bakker-Woudenberg IAJM, van den Bergh JC, Michel MF. Therapeutic efficacy of continuous versus intermittent administration of ceftazidime in an experimental *Klebsiella pneumoniae* pneumonia in rats. J Infect Dis **1985**;152:373–8.
48. Roosendaal R, Bakker-Woudenberg IAJM, van den Bergh JC, van Raffe M, Michel MF. Continuous versus intermittent administration of ceftazidime in experimental *Klebsiella pneumoniae* pneumonia in normal and leukopenia rats. Antimicrob Agents Chemother **1986**;30:403–8.
49. Frimodt-Møller N, Benton MW, Thomsen WF. Experimental infection with *Streptococcus pneumoniae* in mice: correlation of in vitro activity and pharmacokinetic parameters with in vivo effect for 14 cephalosporins. J Infect Dis **1986**;154:511–7.
50. Gengo FM, Mannion TW, Nightingale CH, Schentag JJ. Integration of pharmacokinetics and pharmacodynamics of methicillin in curative treatment of experimental endocarditis. J Antimicrob Chemother **1984**; 14:619–31.
51. Joly V, Pangon B, Vallois, et al. Value of antibiotic levels in serum and cardiac vegetations for predicting antibacterial activity of ceftriaxone in experimental *Escherichia coli* endocarditis. Antimicrob Agents Chemother **1987**;31:1632–9.
52. Pangon B, Joly V, Vallois J-M, et al. Comparative efficacy of cefotiam, cefmenoxime, and ceftriaxone in experimental endocarditis and correlation with pharmacokinetics and in vitro efficacy. Antimicrob Agents Chemother **1987**;31:518–22.
53. Crémieux AC, Maziere B, Vallois J-M, et al. Ceftriaxone diffusion into cardiac fibrin vegetations: qualitative and quantitative evaluation by autoradiography. Fundam Clin Pharmacol **1991**;5:53–60.
54. Lavoie GY, Bergeron MG. Influence of four modes of administration on penetration of aztreonam, cefuroxime and ampicillin into interstitial fluid and fibrin clots and on in vivo efficacy against *Haemophilus influenzae.* Antimicrob Agents Chemother **1985**;28:404–12.
55. Stratton CW. Serum bactericidal test. Clin Microbiol Rev **1988**;1:19–26.
56. Coleman DL, Horwitz RI, Andriole VT. Association between serum inhibitory and bactericidal concentrations and therapeutic outcome in bacterial endocarditis. Am J Med **1982**;73:260–7.
57. Jordan GW, Kawachi MM. Analysis of serum bactericidal activity in endocarditis, osteomyelitis, and other bacterial infections. Medicine (Baltimore) **1981**;60:49–61.
58. Wolfson JS, Schwartz MN. Serum bactericidal activity as a monitor of antibiotic therapy. N Engl J Med **1985**;312:968–75.
59. Weinstein MP, Stratton CW, Ackley A, et al. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am J Med **1985**;78:262–9.
60. Weinstein MP, Stratton CW, Hawley HB, Ackley A, Reller LB. Multicenter collaborative evaluation of a standardized serum bactericidal test as a predictor of therapeutic efficacy in acute and chronic osteomyelitis. Am J Med **1987**;83:218–22.
61. Bolivar R, Fainstein V, Elting L, Bodey GP. Cefoperazone for the treatment of infections in patients with cancer. Rev Infect Dis **1983**;5(suppl): S181–7.
62. Vozeh S, Taescher W, Wenk M. Pharmacokinetic drug data. In: Clinical pharmacokinetics drug data handbook. 2nd ed. Auckland: Adis Press, **1990**:1–29.
63. Drusano GL. Role of pharmacokinetics in the outcome of infections [minireview]. Antimicrob Agents Chemother **1988**;32:289–97.
64. Standiford HC, Drusano GL, McNamee WB, Tatem B, Ryan PA, Schimpff SC. Comparative pharmacokinetics of moxalactam, cefoperazone and cefotaxime in normal volunteers. Rev Infect Dis **1982**;4:585–94.
65. Warren JW, Miller EH, Fitzpatrick B, et al. A randomised, controlled trial of cefoperazone vs. cefamandole-tobramycin in the treatment of putative, severe infections with gram-negative bacilli. Rev Infect Dis **1983**;5(suppl):S173–80.
66. Craig WA. Qualitative susceptibility tests versus quantitative MIC tests. Diagn Microbiol Infect Dis **1993**;16:231–6.
67. Doern GV. The in vitro activity of cefotaxime versus bacteria involved in selected infections of hospitalised patients outside the intensive care unit. Diagn Microbiol Infect Dis **1995**;22:13–7.
68. Murray PR, Jones R, Novick W. Analysis of the clinical predictive value of quantitative and qualitative susceptibility tests with cefotaxime. Ab-

stracts of the Annual Meeting of the American Society for Microbiology **1983**;545:182.

69. Gehanno P, Lenoir G, Berche P. In vivo correlates for *Streptococcus pneumoniae* penicillin resistance in acute otitis media. Antimicrob Agents Chemother **1995**;39:271–2.
70. Ginsburg CM, McCracken GH Jr, Petruska M, Olson K. Pharmacokinetics and bactericidal activity of cefuroxime-axetil. Antimicrob Agents Chemother **1985**;28:504–7.
71. Snydman DR, Cuchural GJ, McDermott L, Gill M. Correlation of various in vitro testing methods with clinical outcomes in patients with *Bacteroides fragilis* group infections treated with cefoxitin: a retrospective analysis. Antimicrob Agents Chemother **1992**;36:540–4.
72. Schentag JJ, Smith IL, Swanson DJ, et al. Role of dual individualization with cefmenoxime. Am J Med **1984**;77(suppl 6A):43–50.
73. Craig WA, Ebert S. Continuous infusion of β-lactam antibiotics. Antimicrob Agents Chemother **1992**;36:2577–83.
74. Bodey GP, Ketchel SJ, Rodriguez V. A randomised trial of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am J Med **1979**;67:608–16.
75. Lagast H, Meunier-Carpentier F, Klastersky J. Treatment of gram-negative bacillary septicaemia with cefoperazone. Eur J Clin Microbiol **1983**;2:554–8.
76. Brewin A, Arango L, Hadley WK, Murray JF. High-dose penicillin therapy and pneumococcal pneumonia. J Am Med Assoc **1974**;230:409–13.
77. Amsden GW, Schentag JJ. Tables of antimicrobial agent pharmacology. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious disease. 4th ed. New York: Churchill Livingstone, **1995**:492–528.
78. Daenen S, de Vries-Hospers H. Cure of *Pseudomonas aeruginosa* infection in neutropenic patients by continuous infusion of ceftazidime [letter]. Lancet **1988**;1:937.
79. David TJ, Devlin J. Continuous infusion of ceftazidime in cystic fibrosis [letter]. Lancet **1989**;1:1454.
80. Kuzemko J, Crawford C. Continuous infusion of ceftazidime in cystic fibrosis [letter]. Lancet **1989**;2:385.
81. Kirby WMM, Craig WA. Theory and application of pulse dosing: a summary of the symposium. Rev Infect Dis **1981**;3:1–3.
82. Turnidge JD. Pharmacodynamic (kinetic) considerations in the treatment of moderately severe infections with cefotaxime. Diagn Microbiol Infect Dis **1995**;22:57–69.
83. Goodpasture HC, Gerlach EH, Jones RN, Peterie JD. Optimum dosing for gram-negative bacteremia: effect on trough serum bactericidal titer and drug concentrations 8 and 12 hr after 1- or 2-g infusions. Diagn Microbiol Infect Dis **1989**;12:101–5.
84. Trenholme GM, Schmitt BA, Nelson JA, Gvazdinskas LC, Harrison BB, Parkhurst GW. Comparative study of different dosing regimens of cefotaxime for treatment of gram-negative bacteremia. Diagn Microbiol Infect Dis **1989**;12:107–11.
85. Ludwig E, Székely É, Csiba A, Graber H. Pharmacokinetics of cefotaxime and desacetylcefotaxime in elderly patients. Drugs **1988**;35(suppl 2):51–6.
86. Turnidge JD. Pharmacodynamic (kinetic) considerations in the treatment of moderately severe infections with cefotaxime. Diagn Microbiol Infect Dis **1995**;22:57–69.
87. Visser LG, Arnouts P, van Furth R, Mattie H, van den Broek PJ. Clinical pharmacokinetics of continuous administration of penicillins. Clin Infect Dis **1993**;17:491–5.
88. Schentag JJ, Nix DE, Adelman MH. Mathematical examination of dual individualisation principles (I): relationships between AIC above MIC and area under the inhibitory curve for cefmenoxime, ciprofloxacin and tobramycin. Ann Pharmacother **1991**;25:1050–7.
89. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother **1993**;37:1073–81.
90. Leggett JE, Wolz SA, Craig WA. Use of serum ultrafiltrate in the serum dilution test. J Infect Dis **1989**;160:616–23.
91. Raber S, Leggett J, Kohlhepp S, Dworkin R, Gilbert D. Continuous versus intermittent infusion of oxacillin in patients with staphylococcal infections [abstract no A104]. In: Program and abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). Washington, DC: American Society for Microbiology, **1996**:20.