Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore

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Since the advent of the modern era of antimicrobial chemotherapy in the 1930s, animal infection models have allowed for the in vivo evaluation of antimicrobial agents for the treatment of experimentally induced infection. Today, animal pharmacokinetic-pharmacodynamic (PK-PD) infection models serve as a cornerstone of the preclinical assessment process for antibacterial agents and dose and dosing interval selection, as decision support for setting in vitro susceptibility breakpoints, and, finally, for the evaluation of the meaning of in vitro resistance. Over the past 15 years, considerable PK-PD data have been derived from infected patients for many classes of antimicrobial agents. These data provide the opportunity to confirm knowledge gained from animal PK-PD infection models.

Pharmacokinetic-pharmacodynamic (PK-PD) concepts were initially identified in the 1940s and 1950s by Dr. Harry Eagle, the founding father of the field. Through experiments conducted in rodents, Eagle identified the time-dependent pattern of penicillin bactericidal activity [1, 2] and noted the concentration-dependent nature of streptomycin and bacitracin and that tetracyclines had a mixed pattern of bactericidal activity [3]. Moreover, Eagle realized the implications of these observations for patients. He noted that, for penicillin, continuous infusion was the best way to achieve the most rapid cure while sparing patients excess drug-related toxicities, and that, for concentration-dependent agents, regimens that resulted in high peak concentrations were likely to be the most rapidly effective [3]. In 1987, in tribute to an outstanding career, President Ronald Reagan awarded Eagle America's highest scientific honor, the National Medal of Science.

The full significance of Eagle's investigations was not appreciated until many years later. From the late 1970s through the early 1990s, PK-PD concepts were rediscovered and expanded upon through elegantly designed rodent experiments conducted by Dr. William Craig, among others [4]. Today, we benefit from rodent-derived PK-PD knowledge about virtually every antibacterial class. This information is used during drug development for proof of concept, for dose and interval selection, for determining susceptibility breakpoints, and in evaluating the clinical meaning of antibiotic resistance [5]. Given the vast quantity, quality, and importance of animal-derived PK-PD data, it seems appropriate to ask the question: do PK-PD data really apply to both mice and men? This review will focus primarily on PK-PD studies conducted in humans as a part of drug development programs and will compare those findings to those described in animals. We will emphasise the ability of PK-PD measures to predict drug efficacy in humans.

FIRST PRINCIPLES

Antimicrobial agents can be categorized on the basis of the PK-PD measure that is most predictive of efficacy. The 3 most common PK-PD measures are the duration of time a drug concentration remains above the MIC (T>MIC), the ratio of the maximal drug concentration to the MIC (C_{max}:MIC), and the ratio of the area under the concentration time-curve at 24 h to the MIC (AUC_{0-24}:MIC). The PK-PD measure that ultimately maps most closely to efficacy is dependent upon the agent's pattern of bactericidal activity and the presence and duration of persistent effects.

Some agents, such as streptomycin, display a concentration-dependent pattern of bactericidal activity over a large range of drug concentrations. That is, as drug concentration increases, so too does the rate and extent of bactericidal activity. Other agents, like penicillin, display a time-dependent pattern of bac-

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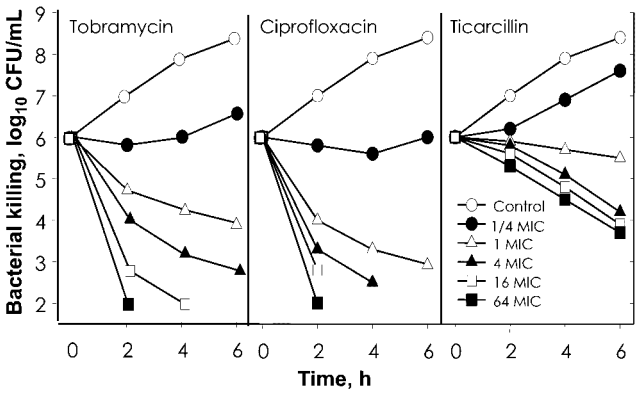

Figure 1. Time-kill curves, ranging from one-fourth to 64 times the MIC, that show the bactericidal pattern of activity of tobramycin, ciprofloxacin, and ticarcillin against *Pseudomonas aeruginosa* American Type Culture Collection (ATCC) 27853. Reprinted with permission from [6]. CFU, colony-forming units.

tericidal activity. For these agents, concentration-dependent bacterial killing occurs over a narrow range of drug concentrations, and the extent of bactericidal activity is a function of the duration of effective exposure.

Figure 1 shows the bactericidal effect of varying drug concentrations on a strain of *Pseudomonas aeruginosa* [6]. Tobramycin and ciprofloxacin display a concentration-dependent pattern of bactericidal activity, whereas ticarcillin displays a time-dependent pattern. Note that, when tobramycin and ciprofloxacin concentrations increase, so too does the rate (slope steepness) and extent (change in $\log_{10}$ CFU/mL) of bacterial killing across a wide range of exposures. In contrast, increasing ticarcillin concentration results in an increased kill rate over a relatively narrow range of exposures. For ticarcillin, there is an obvious point of diminishing returns—that is, drug concentrations >4 times the MIC result in only a nominal further reduction in bacteria over the time course of the experiment.

An agent's bactericidal pattern of activity is not entirely predictive of the PK-PD measure most closely associated with efficacy. The presence and duration of postantibiotic effect is also important. The postantibiotic effect is the time period beginning after organisms are exposed to a drug until the survivors begin to multiply to a significant degree. This phenomenon was first recognized in the 1940s for penicillin against staphylococci [7]. Moderate-to-long postantibiotic effect is the rule, rather than the exception, for gram-positive bacteria like staphylococci [8]. However, for gram-negative bacteria, a significant postantibiotic effect is primarily observed with agents that inhibit protein or nucleic acid synthesis, such as chloramphenicol, macrolides, quinolones, rifamycins, and tetracyclines [8]. β-Lactams, with the exception of carbapenems (primarily against *P. aeruginosa*), have little postantibiotic effect against gram-negative bacteria [9].

Despite the usefulness of static in vitro experiments, the PK-PD measure most closely associated with efficacy is best adjudicated by in vivo or dynamic in vitro PK-PD systems. One challenge to identifying the PK-PD–linked measure is the colinearity that exists between measures—that is, when the dose increases, so too does T>MIC, C_{max}:MIC, and $AUC_{0–24}$:MIC. One way to break the colinearity and identify the PK-PD measure most closely associated with efficacy is through the use of dose-fractionation studies. In such studies, the same total drug exposure is administered using different dosing intervals. For instance, a dose might be delivered as 1 g once daily or in 4 equally divided doses throughout the day. Regardless of dosing interval, each regimen would have identical $AUC_{0–24}$:MIC values, but different T>MIC and C_{max}:MIC values.

Figure 2 shows the results of a dose-fractionation study that evaluated the PK-PD profile of gatifloxacin against *Salmonella enterica* serotype Typhi in an in vitro PK-PD infection model [10]. Two isolates were used—1 susceptible strain and 1 resistant. There was a strong correlation between bacterial killing

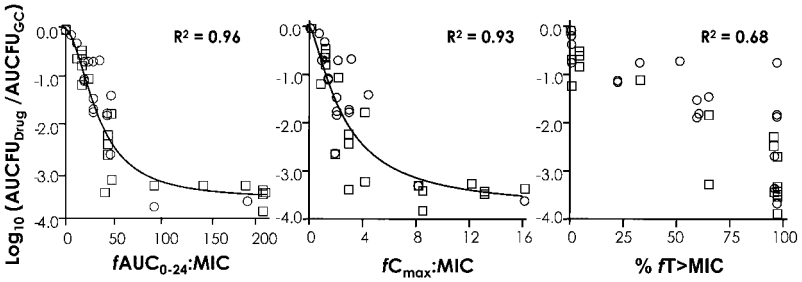

Figure 2. Relationships for gatifloxacin between the ratio of free drug area under the concentration-time curve at 24 h to the MIC ($fAUC_{0–24}$:MIC ratio; left), the ratio of free drug maximal drug concentration to the MIC (fC_{max}:MIC ratio; middle), and the proportion of the dosing interval that the free drug concentration remains above the MIC (% *f*T>MIC; right) for 2 strains of *Salmonella enterica* serotype Typhi with differing MIC values and changes in bacterial density. *Squares,* a susceptible strain with a *GyrA* mutation (Asp87→Asn) and a gatifloxacin MIC of 0.5 mg/mL; *circles,* a resistant strain with *GyrA* (Ser83→Try; Asp87→Gly) and ParC (Thr57→Ser; Ser80→Ile) mutations and a gatifloxacin MIC of 4 mg/mL. Reprinted with permission from [10]. GC, growth control. AUCFU, area under the colony-forming unit time curve.

Table 1. Patten of bactericidal activity in vitro and pharmacokinetic-pharmacodynamic (PK-PD) measures correlating with efficacy.

Antimicrobial agent	Bactericidal pattern of in vitro activity	PK-PD measure(s)
Aminoglycosides	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
β-Lactams		
Penicillins	Time dependent	T>MIC
Cephalosporins	Time dependent	T>MIC
Carbapenems	Time dependent	T>MIC
Monobactams	Time dependent	T>MIC
Clindamycin	Time dependent	AUC_{0-24}:MIC
Glycopeptides/lipopeptides		
Daptomycin	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Oritavancin	Concentration dependent	T>MIC, C_{max}:MIC
Vancomycin	Time dependent	AUC_{0-24}:MIC
Macrolides and clindamycin		
Azithromycin	Time dependent	AUC_{0-24}:MIC
Clarithromycin	Time dependent	AUC_{0-24}:MIC
Teilithromycin	Concentration dependent	AUC_{0-24}:MIC
Metronidazole	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Oxazolidinones		
Linezolid	Time dependent	AUC_{0-24}:MIC
Quinolones	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Tetracyclines		
Doxycycline	Time dependent	AUC_{0-24}:MIC
Tigecycline	Time dependent	AUC_{0-24}:MIC

NOTE. AUC_{0-24}:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{max}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.

and the free drug (*f*) AUC_{0-24}:MIC ($R^2 = 0.96$) and fC_{max}:MIC ($R^2 = 0.93$) values and a comparatively poor correlation for the proportion of the dosing interval that the free drug concentration remains above the MIC (% *f*T>MIC; $R^2 = 0.68$). It is important to note that both the gatifloxacin-susceptible and –resistant strains behaved identically. That is, bacterial killing was associated with similar magnitudes of exposure (e.g, similar $fAUC_{0-24}$:MIC values), regardless of MIC value. Table 1 shows in vitro patterns of bactericidal activity and the PK-PD measure associated with antimicrobial efficacy in animal infection models.

In clinical trials, usually only 1 dose and 1 dosing interval are studied, making discrimination of the PK-PD–linked measure difficult, at best. Therefore, we usually rely on animal and/or in vitro PK-PD infection models to provide this information. Although we also typically identify the magnitude of the PK-PD measure necessary for efficacy in such models, these data should be considered a guide for dose and dosing interval selection for human clinical trials. When available, patient population exposure-response analyses serve as the ultimate arbiter of dose regimen justification. However, there is much to be learned by comparing predictions made by animal models to PK-PD analyses of human data, because the knowledge gained allows us to improve our ability to make the best translations from animal models to man.

HOSPITAL-ACQUIRED PNEUMONIA

Forrest et al. [11] generated some of the first data to correlate PK-PD measures and response in humans. Intravenous ciprofloxacin was evaluated in the treatment of pneumonia that involved predominantly gram-negative bacilli in seriously ill patients. Multivariate logistic regression analyses identified AUC_{0-24}:MIC as being predictive of clinical and microbiological response ($P < .003$). As illustrated in figure 3, a high probability of therapeutic response was observed when ciprofloxacin total-drug AUC_{0-24}:MIC values $\geq$125 against gram-negative bacilli were attained. Because ciprofloxacin is ~40% bound to serum proteins, this value corresponds to an $fAUC_{0-24}$:MIC value of ~75.

A second analysis involving patients with hospital-acquired pneumonia who were treated with levofloxacin also found AUC_{0-24}:MIC to be predictive of response [12]. This analysis demonstrated that a total-drug AUC_{0-24}:MIC value $\geq$87 correlated with the eradication of gram-negative bacilli ($P = .01$). Because levofloxacin is ~29% bound to serum proteins, this

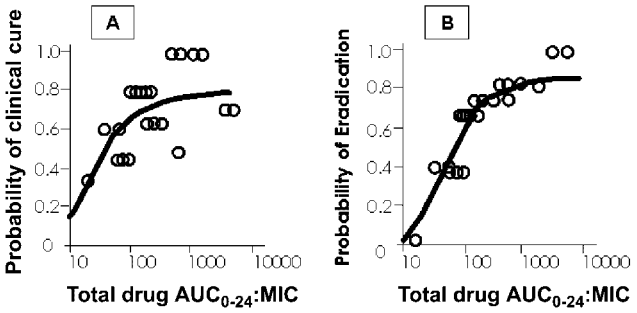

Figure 3. Relationship between the ratio of total drug area under the concentration-time curve at 24 h to the MIC (total drug $AUC_{0–24}$:MIC) for ciprofloxacin and clinical *(A)* and microbiological *(B)* response in critically ill patients with infection associated with primarily gram-negative bacilli. Adapted from [11].

value corresponds to an $fAUC_{0–24}$:MIC value of ~62. $fAUC_{0–24}$:MIC values ⩾62 were associated with 90% of patients having a positive microbiological response to therapy, whereas those patients with $fAUC_{0–24}$:MIC values <62 had a 43% response to therapy.

Similar relationships have been found between $AUC_{0–24}$:MIC and response in rodent infection models. Jumbe et al. [13] demonstrated that, for levofloxacin and *P. aeruginosa*, a total-drug AUC_{24}:MIC value of 88 in immunosuppressed mice was associated with a 99% reduction in bacterial burden; in addition, Craig et al. [14] showed that, for fluoroquinolones and, primarily, gram-negative bacilli in immunosuppressed animals, $AUC_{0–24}$:MIC was predictive of survival (figure 4). Note that, as $AUC_{0–24}$:MIC increased, mortality decreased, and essentially all of the animals with $AUC_{0–24}$:MIC values >100.

COMMUNITY-ACQUIRED RESPIRATORY TRACT INFECTIONS

More studies correlating PK-PD measures and responses in humans have been conducted to analyze community-acquired respiratory tract infection than any other therapeutic area [15–20]. Preston et al. [15] evaluated the relationship between different PK-PD measures and both clinical and microbiological outcomes in patients treated with levofloxacin for urinary tract, pulmonary, and skin/soft-tissue infections. In patients in whom a C_{max}:MIC value >12.2 was attained, all infecting organisms were eradicated (regardless of infection site); in patients in whom C_{max}:MIC ($P < .001$) values ⩽12.2 were achieved, 81% had a favorable microbiological response. Both C_{max}:MIC ($P < .001$) and $AUC_{0–24}$:MIC ($P \leqslant 0.006$) were significantly associated with clinical and microbiological outcome, which is not surprising given the nondose fractionation study design. In a study of the subset of patients with pneumococcal infections, all patients in whom $fAUC_{0–24}$:MIC values >30 were attained had favorable clinical and microbiological outcomes [21].

Ambrose et al. [17] evaluated the relationship between the $fAUC_{0–24}$:MIC values of gatifloxacin and levofloxacin against *Streptococcus pneumoniae* and the clinical and microbiological response of patients enrolled in either of 2 randomized clinical trials. $fAUC_{0–24}$:MIC values >33.7 were associated with 100% of patients having a positive microbiological response, whereas patients with an $fAUC_{0–24}$:MIC value <33.7 had a 64% response ($P < .01$). As shown in figure 5, the high probability of therapeutic response in 121 patients with respiratory tract infections who were treated with fluoroquinolones was higher for patients having an $fAUC_{0–24}$:MIC value ⩾34 (OR, 6.3; $P = .01$) [22].

Craig et al. [23] have conducted numerous studies in mice to identify both the PK-PD measure predictive of efficacy and the magnitude of this measure required for fluoroquinolone efficacy against pneumococci. Figure 6 illustrates the relationships between the $fAUC_{0–24}$:MIC value and both animal survival and change in bacterial density for immunocompetent mice infected with *S. pneumoniae* who were treated with various fluoroquinolones. The $fAUC_{0–24}$:MIC value required to achieve ~90% animal survival or a 99% decrease in bacterial counts for fluoroquinolones against *S. pneumoniae* ranged from 25 to 34.

The PK-PD of telithromycin, a macrolide, was evaluated in patients with community-acquired pneumonia [20]. Multivariate logistic regression analyses identified $AUC_{0–24}$:MIC and weight as being predictive of microbiological response. The response rate was 91% in patients with an $AUC_{0–24}$:MIC value

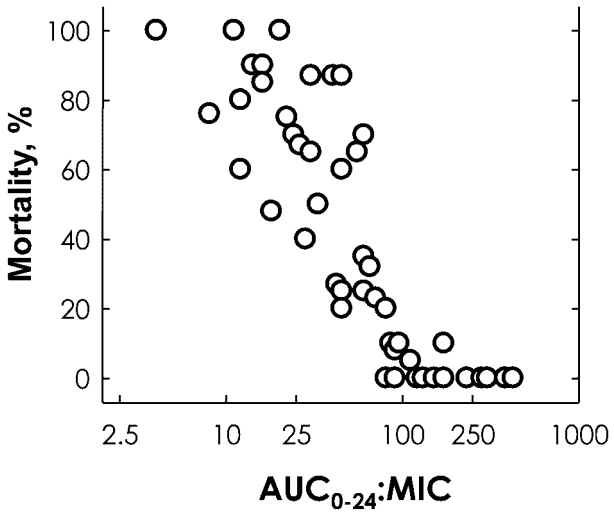

Figure 4. Relationship between the ratio of total drug area under the concentration-time curve at 24 h to the MIC ($AUC_{0–24}$:MIC) for fluoroquinolones and mortality in immunosupressed animals infected with gram-negative bacilli and a few gram-positive cocci. Adapted from [14].

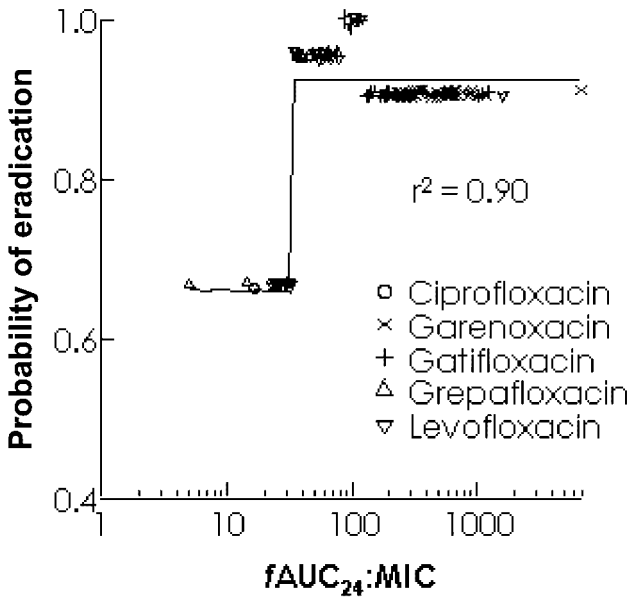

Figure 5. Jitter plot of the relationship between the the ratio of free drug area under the concentration-time curve at 24 h to the MIC (fAUC$_{0-24}$:MIC) for 5 quinolones (ciprofloxacin, garenoxacin, gatifloxacin, grepafloxacin, and levofloxacin) and microbiological response in 121 patients with respiratory tract infection (pneumonia, acute exacerbation of chronic bronchitis, or acute maxillary sinusitis) associated with *Streptococcus pneumoniae*. Microbiological eradication was higher in patients with a fAUC$_{0-24}$:MIC value >34 (92.6%) and lower in patients with values <24 (66.7%). The x-axis is log transformed for graphical clarity [22].

⩾3.375 and 76% in patients with lesser exposures (OR, 5.9; $P = .0002$).

Although the PK-PD measure identified in humans is the same as that in animals, the magnitude of the AUC$_{0-24}$:MIC value necessary for efficacy is lower in man. Craig et al. [24] evaluated telithromycin in a neutropenic mouse thigh infection model. Total- and free-drug AUC$_{0-24}$:MIC values of 1000 and 100, respectively, were needed to achieve net bacterial stasis. One partial explanation for this discordance involves immune system status. The telithromycin-treated patient population was immunocompetent and was treated on an outpatient basis, whereas the mice were neutropenic. One would expect the AUC$_{0-24}$:MIC value necessary for effect would decrease markedly, by >3–4-fold, in immunocompetent mice. Although immune system status explains a large measure of the discordance, the remaining difference may be accounted for by interspecies differences in epithelial lining fluid concentrations and/or the inclusion of *Haemophilus influenzae* and *Moraxella catarrhalis* with *S. pneumoniae* in the clinical exposure-response dataset. Given that exposures for macrolides in epithelial lining are much greater when compared with serum, the use of nonimmunosuppressed rodent pneumonia infection models may improve the translation between mice and man for drugs such as telithromycin.

BACTEREMIA

Bhavnani et al. [25] evaluated the exposure-response relationship of oritavancin, an investigational intravenous glycopeptide, in patients with *Staphylococcus aureus* bacteremia. fT>MIC was identified as the PK-PD measure most closely associated with efficacy. In patients in whom an fT>MIC value ⩾22% of the dosing interval was attained, 93% of patients responded favorably, whereas 76% responded favorably when lesser exposures were achieved (OR, 8.8; $P = .05$). These findings are concordant with those of Boylan et al. [26], who examined oritavancin against *S. aureus* in a neutropenic mouse thigh infection model. In both the clinical and animal analyses, all 3 PK-PD measures were reasonably predictive of response. In neutropenic mice, fC$_{max}$:MIC and fT>MIC were most closely associated with efficacy. In mice, an fT>MIC of 20% of the dosing interval was associated with net bacterial stasis to a 0.5–

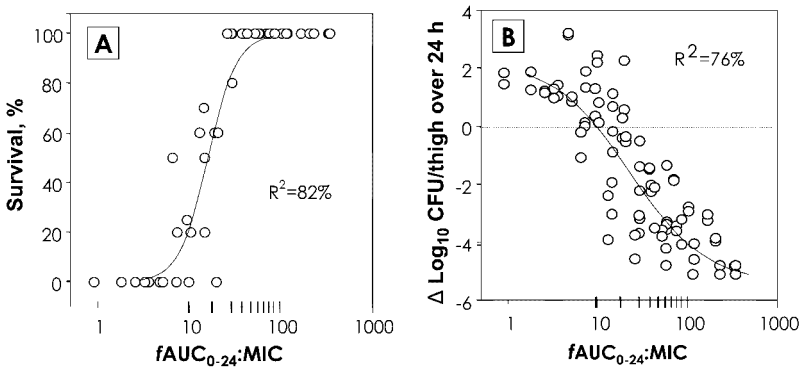

Figure 6. Relationship between ratio of free drug area under the concentration-time curve at 24 h to the MIC (fAUC$_{0-24}$:MIC) for 6 quinolones (ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and sitafloxacin) and survival *(A)* and bacterial density *(B)* in immunocompetent mice infected with *Streptococcus pneumoniae*. When the fAUC$_{24}$:MIC value was greater than ~30, survival was >90% *(A)* and there was a 99% reduction in bacterial burden *(B)*. *Dashed line,* the initial bacterial inoculum [23].

Table 2. Pharmacokinetic-pharmacodynamic (PK-PD) targets derived from animal infection models and clinical data.

Disease state, drug	Clinically-derived PK-PD target [reference(s)]	Animal infection model; organism studied	Animal-derived PK-PD target [reference(s)]
Hospital-acquired pneumonia			
Quinolones	*f*AUC_{0-24}:MIC ratio, 62–75 [11, 12]	Neutropenic mouse thigh; gram-negative bacilli	*f*AUC_{0-24}:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]
Community-acquired respiratory tract infections			
Quinolones	*f*AUC_{0-24}:MIC ratio, 34 [22]	Immunocompetent mouse thigh; *Streptococcus pneumoniae*	*f*AUC_{0-24}:MIC ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]
β-Lactams	T>MIC, 40% of the dosing interval [14]	Immunocompetent mouse thigh; *S. pneumoniae*	T>MIC, 30–40% of the dosing interval for 90% animal survival [14]
Telithromycin	AUC_{0-24}:MIC ratio, 3.375 [20]	Neutropenic mouse thigh; *S. pneumoniae*	AUC_{0-24}:MIC ratio, 1000 for stasis [24]
Bacteremia			
Oritavancin	*f*T>MIC, 22% of the dosing interval for *Staphylococcus aureus* [25]	Neutropenic mouse thigh; *S. aureus*	*f*T>MIC, 20% of the dosing interval for a 0.5 log-unit kill [26]
Linezolid	AUC_{0-24}:MIC ratio, 85 for *S. aureus* or *Enterococcus faecium* [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]
Complicated skin and skin structure infections			
Tigecycline	AUC_{0-24}:MIC ratio, 17.9 [28]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 15–20 for stasis [29]
Linezolid	AUC_{0-24}:MIC ratio, 110 [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]

NOTE. AUC_{0-24}:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{max}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.

log-unit reduction in bacterial burden, which is very similar to the *f*T>MIC breakpoint identified in infected patients (*f* T>MIC, 22% of the dosing interval).

Linezolid has also been evaluated in patients who have bacteremia that is associated with methicillin-resistant *S. aureus* or vancomycin-resistant *Enterococcus faecium* [27]. T>MIC and AUC_{0-24}:MIC, which are highly correlated with one another (Spearman $r^2 = 0.87$), were associated with response to therapy ($P \leq .02$). Over 98% of patients in whom total-drug AUC_{0-24}:MIC values were >85 had favorable clinical outcomes, whereas, in those with lesser exposures, 79% responded favorably.

COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

Two clinical studies have evaluated exposure-response relationships in patients with complicated skin and skin structure infections. One study involved patients who were enrolled in a compassionate-use protocol and who had received linezolid [27], and another study involved patients enrolled in 3 clinical trials who had received tigecycline [28]. In the latter study, tigecycline was evaluated in the treatment of hospitalized patients with infections involving *S. aureus* and/or group A streptococci. Multivariate logistic regression analyses identified AUC_{0-24}:MIC as being predictive of microbiological response to therapy. AUC_{0-24}:MIC values greater than ~17.9 were associated with 100% of patients having a positive response, whereas patients with AUC_{0-24}:MIC values <17.9 had only a 50% response (OR, 24; $P = .0008$). A similar exposure-response relationship was also observed for clinical response to therapy.

These findings are concordant with a tigecycline–*S. aureus* neutropenic mouse thigh infection model [29]. AUC_{0-24}:MIC was most closely associated with efficacy, with values of 15–20 associated with stasis to a 90% reduction in bacterial burden.

COMPLICATED INTRA-ABDOMINAL INFECTIONS

The relationship between tigecycline exposure and response has also been evaluated in patients with complicated intra-abdominal infections [30]. In this analysis, the pathogen isolated from each patient with the highest MIC value was an Enterobacteriaceae (69%)—predominantly *Escherichia coli*—or an anaerobe (21%). Multivariate logistic regression analyses identified weight, intra-abdominal diagnosis, AUC_{0-24}:MIC, APACHE II

score, and presence of *P. aeruginosa* as being predictive of clinical response to therapy. For tigecycline $AUC_{0–24}$:MIC values ⩾3.1, a positive clinical response was observed in 89% of patients; only 50% of patients with lower $AUC_{0–24}$:MIC values experienced a successful clinical response (OR, 33.0; $P = .003$).

PK-PD AND ANTIMICROBIAL RESISTANCE

Antimicrobial resistance poses an ever-increasing threat to public health. Nonclinical PK-PD infection models can be used to identify the conditions where resistance emergence is minimized. For instance, in a mouse thigh infection model involving levofloxacin against *P. aeruginosa,* Jumbe et al. [13] found that an $fAUC_{0–24}$:MIC value ⩾110 was associated with the prevention of amplification of preexisting mutant subpopulations of bacteria. This threshold was nearly twice that necessary to effect a 99% reduction in bacterial burden. The impact of bacterial load on the $fAUC_{0–24}$:MIC value required to suppress the emergence of resistant subpopulations of pneumococci has also been evaluated [31]. For a strain with dual resistance mechanisms (a *parC* and efflux pump mutant), a 2.5-fold higher $fAUC_{0–24}$:MIC value (500 vs. 200) was required to suppress the emergence of resistant subpopulations when a bacterial load of 10^6 and 10^8 CFU/mL, respectively, was studied.

Together, these data demonstrate that we can identify exposures that prevent the amplification of resistant subpopulations of bacteria; these thresholds are larger than those associated with clinical efficacy, and bacterial load at the primary effect site is important. However, more data are urgently needed, not only from nonclinical infection models, but also from the clinic.

FUTURE CHALLENGES

Very few antimicrobials are under development at a time when multidrug resistance threatens public heath in both the outpatient and inpatient sense. Large pharmaceutical companies have not been investing heavily in antibacterial drug development because this area of medicine is less profitable than other therapeutic areas. Moreover, for many indications, such community-acquired respiratory tract infections, there has been considerable regulatory uncertainty while the US Food and Drug Administration grapples with what to do about imprecise clinical trial end points, which make it difficult to ascertain true drug effect.

PK-PD can decrease the risk and cost of antibacterial drug development. Preclinical PK-PD infection models, in conjunction with pharmacokinetic modeling and simulation, can finally put an end to the risk-rich era of dose guessing [32], which is often done at the expense of individual patients and society at large. In clinical trials, the use of PK-PD end points, such as time to bacterial eradication or sign and symptom resolution, offers the possibility of demonstrating the benefits of a challenge regimen relative to a standard therapy, but with relatively few study patients [18]. In this paradigm, more resources could be leveraged to study drug safety. Such studies could be designed far differently than traditional clinical trials and powered to address specific safety concerns. The time has come for a dialogue with regulators, academia, and industry, so that an environment can be created where drugs can be optimally developed prior to a public health disaster.

SUMMARY

Over the past 15 years, numerous PK-PD data have been derived from infected patients. Overall, there has been good concordance between PK-PD animal studies and data from infected patients (table 2). In multiple clinical indications, the magnitudes of exposure necessary for clinical effectiveness were similar to those identified from animal data, even across drug classes. For instance, the magnitude of exposure identified for stasis in immunocompromised animals was similar to the exposure threshold associated with good clinical outcomes for patients treated with oritavancin or linezolid for bacteremia. This means that, in many circumstances, we understand the PK-PD profile needed in animals to attain clinical effectiveness in humans. Consequently, as new antimicrobial agents are developed, we have the ability to preclinically identify treatment regimens that will optimize the probability of clinical outcome. However, there remains much to learn, especially with regard to clinical trial end points. Additional studies are needed to evaluate the time course of drug effect, so that better clinical trial end points can be identified and validated. Once these end points are validated, there will be potential for clinical PK-PD studies to dramatically improve the way drugs are studied and used clinically.

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Potential conflicts of interest. All authors: no conflicts.

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