

Optimizing Clinical Outcomes Through Rational Dosing Strategies: Roles of Pharmacokinetic/Pharmacodynamic Modeling Tools

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Significant progress in previous decades has led to several methodologies developed to facilitate the design of optimal antimicrobial dosing. In this review, we highlight common pharmacokinetic/pharmacodynamic (PKPD) modeling techniques and their roles in guiding rational dosing regimen design. In the early drug development phases, dose fractionation studies identify the PKPD index most closely associated with bacterial killing. Once discerned, this index is linked to clinical efficacy end points, and classification and regression tree analysis can be used to define the PKPD target goal. Monte Carlo simulations integrate PKPD and microbiological data to identify dosing strategies with a high probability of achieving the established PKPD target. Results then determine dosing regimens to investigate and/or validate the findings of randomized controlled trials. Further improvements in PKPD modeling could lead to an era of precision dosing and personalized therapeutics.

Keywords. dose fractionation studies; classification and regression tree analysis; dosing regimen design; Monte Carlo simulations; optimal drug dosing.

The rise of broad-spectrum antimicrobial resistance is a critical situation that clinicians are facing today. With limited options available, there is a growing need to judiciously utilize and optimize our current arsenal of antimicrobials to improve patient outcomes. In previous decades, several advances were made to characterize the concentration–effect relationships of antimicrobials to facilitate optimal drug dosing. In general, pharmacokinetic and pharmacodynamic (PKPD) analyses allow the exploration of the time course of an observed drug effect, which provide a means to relate the effects to drug concentrations in the body [1, 2]. For most nonantimicrobials, their effects can either be measures of clinical response (eg, analgesia) or biomarkers of drug effects (eg, international normalized ratio) [3, 4]. As a result, the dose–response relationship can be elucidated by directly monitoring the physiological and/or biochemical variables of the host [5]. However, these principles

do not apply to antimicrobials as their main target is the pathogen (as opposed to receptor targets in the host).

Dosing of antimicrobials differs greatly from other drugs, as the evaluation of its efficacy relies on 2 factors: (1) drug exposure achieved in the host and (2) pathogen susceptibility to the drug [6]. Due to this distinction, clinical response measures of the host are only indirect aspects of antimicrobial effectiveness. To circumvent the challenge of integrating the above factors, surrogate indices have been proposed to predict clinical success [7]. These measures relate the extent of drug exposure in the host and the susceptibility of the pathogen to the drug (commonly represented by the minimum inhibitory concentration [MIC]). Consequently, these indices represent a complex interplay between factors of the host and pathogen, which help to inform dose selection to achieve favorable outcomes [8, 9]. In an ideal setting, antimicrobial dosing should be individualized based on patient (eg, body weight, renal/hepatic function, plasma albumin) and microbial (eg, MIC, resistance mechanism genotypes) characteristics (ie, precision dosing).

Over the years, many approaches have been developed to facilitate the design of optimal dosing regimens. The objectives of this review are to describe the most common PKPD techniques from an end user's perspective and to facilitate clinician interpretation of studies using these modeling tools. Similar techniques can also be applied to minimizing adverse effects associated with antimicrobial therapy (ie, toxicodynamics). The statistical basis and theory behind these approaches are beyond the scope of this review. For brevity's sake, we will focus

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on the efficacy of antibacterials in this review for the purpose of illustration.

DOSE FRACTIONATION STUDIES AND HOW THEY INFORM PKPD PARAMETER SELECTION

Background

In the early stages of nonantimicrobial drug development, dose-finding studies are essential to inform dose selection for testing in clinical trials [10, 11]. In phase II studies, the effectiveness and safety of an experimental drug are determined, typically through a dose escalation design. Doses in proportion to the maximum tolerated dose, in addition to host clinical responses, are studied to establish the dose–effect relationship of the drug. Study results are used to formulate the most optimal dosing regimen to be investigated in phase III clinical trials [12]. However, this study design is not directly applicable to antimicrobials as efficacy is also affected by pathogen susceptibility to the antimicrobial. More robust surrogate indices (ie, PKPD parameters) have thus been proposed as better predictors of clinical and microbiological success. To identify the PKPD index most closely correlated to bacterial killing (ie, efficacy), dose fractionation studies have commonly been utilized.

Experimental Design

Dose fractionation experiments involve studying various dosing regimens with different dosing intervals and fractions of the total daily dose in such a way that the total daily drug exposure is kept constant (Table 1) [8, 13]. This design can be adopted in different preclinical infection models (eg, chemostat, hollow-fiber, neutropenic murine thigh infection/pneumonia models). In the simplest design with a single pathogen, different PKPD indices (eg, C_{max}/MIC , $T > MIC$, area under the curve [AUC]/minimum inhibitory concentration [MIC]) could be compared relying on a specific MIC as the common denominator, as shown in Table 1.

Table 1. Exposure Profiles of a Hypothetical Antimicrobial Exhibiting Linear Kinetics (Volume of Distribution of 40 L, Clearance of 28 L/h, Elimination Half-life of 1 Hour, and Negligible Protein Binding); the Target Pathogen Is Assumed to Have an MIC of 1 mg/L

Dosing Regimen	fC_{max} , mg/L	fC_{min} , mg/L	$fAUC$, mg•h/L	$T > MIC$, %
2000 mg every 24 h	50	Negligible	72	23
1000 mg every 12 h	25	0.01	72	38
500 mg every 6 h	12.5	0.2	72	60

Different antimicrobial pharmacodynamic characterizations may be inferred based on efficacy observed for various dosing regimens. For example, if the regimen given the least frequently (every 24 h) is the most effective, C_{max}/MIC is thought to be the PKPD index most closely linked to an antimicrobial's efficacy. In contrast, $T > MIC$ is most associated with the regimen given most frequently (every 6 h). If there is no difference in efficacy, the AUC/MIC is the index linked to bacterial killing.

Abbreviations: AUC/MIC, area under the curve/minimum inhibitory concentration; CFU, colony-forming units; PKPD, pharmacokinetic/pharmacodynamic.

Alternatively, a scatter plot can be utilized to discriminate antimicrobial effect (typically represented by the bacterial count following 24 hours of treatment) from the PKPD indices (Figure 1). Typically, a regression curve (representing an inhibitory sigmoidal Emax model) that best fits all the data points is generated. The selection of the PKPD index most closely related to bacterial killing is derived from the regression model with the best coefficient of determination (denoted as r^2). Of note, the free, unbounded fraction of a drug is often used in the calculation of PK parameters and is denoted by the prefix f , as this represents the active component of the drug [14, 15]. Results from these studies identify the PKPD index that best predicts antimicrobial efficacy and have historically been derived from 1 of the 3 PKPD indices described above. The methods used to elucidate the PKPD of an antimicrobial can be made even more robust when tested against a range of MICs from a single or multiple pathogens.

Many researchers use this regression approach to discern the PKPD index that is most closely linked to bacterial killing [16–19]. For instance, in a study by Zhou and colleagues, an in vivo neutropenic murine pneumonia model was utilized to characterize the PKPD of minocycline against *Acinetobacter baumannii* [19]. Briefly, the relationship between minocycline exposure and antimicrobial efficacy was described following administration of varying doses of minocycline, and the PK of the drug was elucidated through analysis of serum and epithelial lining fluid concentrations. Through regression modeling, the AUC/MIC ratio was deemed the PKPD index most closely correlated to the antimicrobial activity of minocycline against *A. baumannii*, due to AUC/MIC having the highest coefficient of determination among the 3 PKPD indices studied.

Expert Commentary

Traditional PKPD indices may provide a simplified characterization of antimicrobial efficacy and are used for screening purposes in the early drug development stages. However, they may not fully capture bacterial killing comprehensively [20, 21]. There is an implicit assumption that the characterization of antimicrobial efficacy can be classified into 1 of only 3 distinct PKPD indices (mentioned previously), but there may be other indices that could also accurately describe the bacterial killing of antimicrobials. For instance, the minimum concentration-to-MIC ratio (C_{min}/MIC) may potentially be a better PKPD parameter compared with $T > MIC$, due to a ceiling effect of 100% with the latter [22, 23]. As a result, C_{min}/MIC may offer greater flexibility for antimicrobial exposures to be quantified, especially when the efficacy breakpoint is beyond $T > MIC$ of 100%.

In all of the PKPD indices defined above, these measures rely on the MIC to describe antimicrobial PD. Although widely used due to its practicality, key limitations exist with utilizing MIC in PKPD analyses. The MIC represents the drug

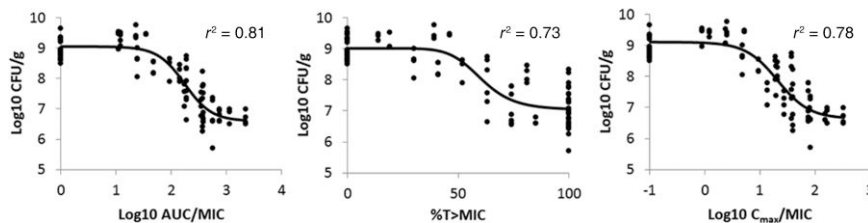


Figure 1. Relationship between PKPD indices of minocycline and *Acinetobacter baumannii* burden in mouse lung tissue at 24 hours [19]. Figure reproduced with permission from the American Society for Microbiology and Zhou et al. [19]. Each data point represented observations of 1 animal. Solid lines represent the best-fit regression curve. In this context, a reduction in log CFU/g (bacterial burden) is associated with bacterial killing. AUC/MIC best depicts *A. baumannii* killing of minocycline; its correlation with bacterial killing has the highest r^2 value. Abbreviations: AUC/MIC, area under the curve/minimum inhibitory concentration; CFU, colony-forming units; PKPD, pharmacokinetic/pharmacodynamic.

concentration that prevents visible growth of bacteria over a fixed time frame [24]. The result can be interpreted as a binary outcome that states that an antimicrobial given at a concentration above the MIC leads to inhibition of bacterial growth, while concentrations below the MIC will fail to prevent bacterial growth. Under these conditions, the MIC does not quantitatively define the rate and extent of bacterial killing, and thus may not reflect the antimicrobial effects comprehensively [25]. Another limitation is that MIC measurements may fail to detect any potential resistant subpopulation(s) present in minute amounts (ie, below the limit of detection within the time frame in which MIC results are evaluated) [26]. Finally, MIC measurements could be subjected to inconsistencies due to laboratory variations [15, 25]. An identical bacterial strain may exhibit different MIC values in 2 different institutions utilizing

2 different types of lab equipment, which may have significant clinical implications if the true MIC lies close to the threshold between susceptible and nonsusceptible interpretations.

Due to the inherent drawbacks of MICs, innovations in non-MIC-based indices might provide further insights into antimicrobial PKPD. Researchers have utilized more objective parameters in PKPD analysis, such as minimum bactericidal concentration (MBC), mutant prevention concentration (MPC), and kill rate-based PKPD integration models [27, 28]. For instance, MPC-based PKPD indices have been used in the study of fluoroquinolones because of their propensity to select drug-resistant mutants that occur gradually through genetic mutations [27]. Although nonconventional PD parameters have been developed to describe antimicrobial effects beyond what the MIC can provide, no single PD parameter may fully characterize bacterial killing. Therefore, a combination of non-traditional and traditional PKPD indices can be used to determine the entire spectrum of antimicrobial mechanisms of action [24, 29, 30]. Further advances in the study of antimicrobial PKPD are needed to distinguish what truly defines their efficacy. Dose-response relationships may be more realistically described as a continuous (nonlinear) function as opposed to discrete categories. Different approaches to ascertain these nonlinear functions are beyond the scope of this review [31, 32].

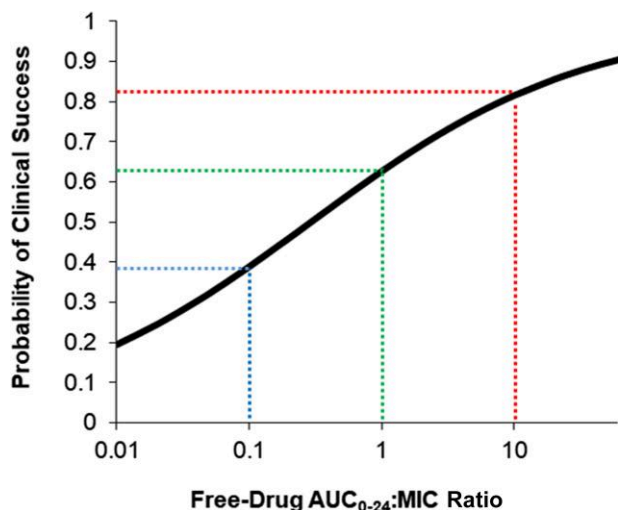


Figure 2. Association of clinical success and tigecycline $fAUC_{0-24}:MIC$ ratio in patients with hospital-acquired pneumonia. Figure reproduced with permission from data reported from Bhavnani et al. [81]. The probability of clinical success associated with an $fAUC/MIC$ of 0.1, 1, and 10 was 39% (blue), 63% (green), and 82% (red), respectively. This approach allows dosing selection to accommodate various clinical circumstances with different benefit-to-risk ratios. Abbreviations: AUC, area under the curve; MIC, minimum inhibitory concentration.

CLASSIFICATION AND REGRESSION TREE ANALYSIS AND PARTITIONING TECHNIQUES TO IDENTIFY GOAL TARGETS

Background

Following the identification of the optimal PKPD index associated with bacterial killing, the next step is to link the index to clinically meaningful efficacy outcomes. Many study end points assessing antimicrobial therapy encode outcomes as a set of discrete states, such as whether a patient survived (mortality) or whether a pathogen continued to be recovered on repeat cultures (persistence). Lower drug exposures in a subject are typically associated with less favorable outcomes, while higher drug exposures are associated with a higher likelihood of

favorable outcomes. When a trend is suspected, one may attempt to correlate different magnitudes of the PKPD index through regression analysis. This technique estimates the quantitative impact of an independent variable (eg, magnitude of drug exposure) on the dependent variable (eg, hospital mortality) [33]. Due to the dichotomy of most outcome variables, logistic regression is traditionally used.

In clinical studies, logistic regression analysis is a powerful tool that yields a probability of achieving the research end points [34]. Furthermore, the analysis output is a prediction equation with coefficients that can be related to the odds ratio. However, the interpretation of these results may be subjective as the goal threshold that describes the most optimal probability of achieving a clinical outcome could be different among practitioners. As opposed to providing probabilities of an outcome based on the exposure variable (eg, AUC/MIC = 10 is associated with 82% clinical success) (Figure 2), clinicians often prefer a target exposure that has the most reliable likelihood of clinical success. For these reasons, recursive partitioning techniques have been used to provide an objective method to determine a single drug exposure value most significantly associated with an outcome of interest.

Analytical Design

Recursive partitioning techniques have been used in epidemiological studies to explore distinct patient subpopulations and identify risk factors associated with a study outcome [35, 36]. The name of this technique refers to the fact that the data set can be split into sections (partitioning) repeatedly (recursive)

Table 2. Reanalysis of Data by Aitken et al. [36] for Illustrating CART Analysis

Cmin/MIC Ratio	Clinical Outcome		P Value
	Success, No.	Failure, No.	
Threshold 1			
≤0.7	0	1	.364
>0.7	21	11	
Threshold 2			
≤1.5	2	1	1
>1.5	19	11	
Threshold 3			
≤2.1	2	6	.015 ^a
>2.1	19	6	
Threshold 4			
≤4	9	8	.282
>4	12	4	

^aBriefly, plasma concentrations of cefepime before the next scheduled dose (Cmin) in 33 patients were normalized to MIC of the pathogen recovered from the same subject. The PKPD exposures were linked to the clinical outcomes observed. The CART program generates a series of 2-by-2 tables correlating every observed Cmin/MIC value and clinical outcome. For illustrative purposes, this table comprises of a subset of 4 tables from the CART analysis. The Fisher exact test was utilized for statistical comparison. In this representative series of 2-by-2 tables, the most statistically significant difference in outcome was found using Cmin/MIC = 2.1 as the threshold.

Abbreviations: CART, classification and regression tree; MIC, minimum inhibitory concentration; PKPD, pharmacokinetic/pharmacodynamic.

until the remaining data points cannot be split further or the program reaches a user-specified stopping criterion [33, 37]. Classification and regression tree (CART) analysis is a type of recursive partitioning technique that produces a clinical decision tree that is easier to interpret compared with logistic regression, making this more practical in clinical settings [38]. Researchers have utilized this methodology to relate the study outcome to antimicrobial PKPD parameters for the identification of breakpoint thresholds associated with clinical success.

Briefly, CART analysis begins with ranking the magnitude of the independent variable in ascending (or descending) order, which can be branched out into 2 subgroups. The group containing the entire sample is designated the parent node, while the subgroups are termed child nodes [33]. In many antimicrobial studies, the splitting criterion is based on the magnitude of drug exposure with the greatest statistical significance with respect to the outcome variable. This would then be designated the breakpoint threshold after further refinement. For example, the relationship between the clinical outcome (eg, mortality) observed for each individual and their drug exposure achieved (eg, serum concentration or PKPD index) can be assessed through a 2-by-2 table. Comparisons are made between patients who did and did not achieve the outcome of interest above a single drug exposure value to outcomes of patients who were below that drug exposure value. Through repeated analysis of each threshold, the magnitude of the PKPD index found to be most significantly associated with the study outcome is deemed the breakpoint (Table 2).

In several instances, CART analysis has been used in the literature to help clinicians identify goal targets for antimicrobials to maximize patient outcomes [23, 39–42]. For example, Kullar and colleagues determined that patients receiving vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia with an AUC/MIC <421 have significantly higher rates of clinical failure [43]. This study, along with other evidence, provided the basis for the recommendation to target AUC/MIC ≥400 when utilizing vancomycin for MRSA infections [44–46].

Expert Commentary

CART analysis has several advantages over logistic regression. It is an objective method for predicting an outcome through classification, which leads to a clinical decision tree that is easily interpreted by clinicians [33, 37, 38]. Moreover, the breakpoint threshold is determined based on the statistical analysis of all PKPD index values observed in a given sample population [47]. CART analysis is a nonparametric technique, so no assumptions need to be made regarding the distribution of the values of the predictor variables [33].

Despite these advantages, there are several limitations of CART analysis. The breakpoints defined from CART analysis are focused on reproducibility, as opposed to being the absolute breakpoint clinicians should target to predict clinical success.

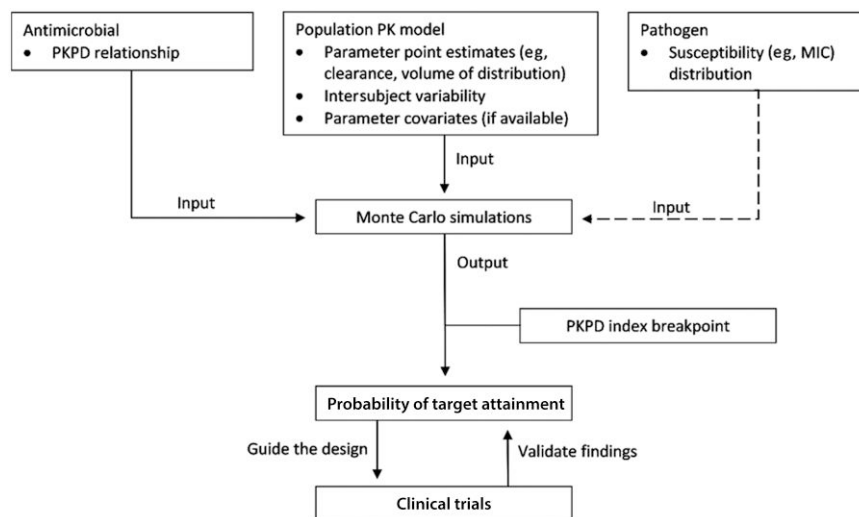


Figure 3. Simple schematic depicting the process of antimicrobial dose design involving Monte Carlo simulations. The necessary a priori input models for Monte Carlo simulations include the antimicrobial PKPD relationship, a robust population PK model with well-defined parameter point estimates, intersubject variability of the parameters, and any available parameter covariates (which informs parameter variation based on subject characteristics) and microbiological data, if needed. As represented by the dashed line, the susceptibility distribution for the pathogens of interest (based on local surveillance data) may be incorporated to evaluate dosing regimens against a range of MICs. The output of simulations is then tested against the PKPD index breakpoint to generate the probability of attaining the PKPD index target specified by the user. Results allow clinicians to deduce dosing strategies that help guide the design or validate the findings of clinical trials. Abbreviations: MIC, minimum inhibitory concentration; PKPD, pharmacokinetic/pharmacodynamic.

If there is an absolute breakpoint, this creates perfectly separable classes that easily predict clinical success and failure. However, there may be instances where patients may still do well clinically below the identified efficacy threshold. In this scenario where a data set is nonseparable, evaluating the steepness of the logistic curve in regression analysis may be helpful in order to assess the benefits vs risks of targeting above the threshold (Figure 2). Second, the data set can only be split in between observed magnitudes of the PKPD index. Thus, the resolution of the threshold is inherently dependent on the distribution of the observed drug exposures. Lastly, CART analysis usually evaluates 1 single end point, but not all patients have end points that align with clinical success. For example, a patient who survived but had microbiological persistence in subsequent cultures might be classified differently depending on the end point used in a CART analysis. This instance illustrates a fundamental disadvantage of CART analysis as it cannot account for multiple clinical end points. Recent clinical studies have gravitated toward the desirability of outcome ranking (DOOR) analytic approach, which assesses the overall clinical outcome of a patient by evaluating the benefits/risks of antimicrobial therapy through ordinal categorization of outcomes [48–50].

MONTE CARLO SIMULATIONS TO EVALUATE DOSING STRATEGIES

Background

With a PKPD target established, the next step is to identify the dosing strategies most likely to attain that goal. During drug

development, PKPD models have been utilized to facilitate the design of clinical trials and propose dosing regimens to maximize efficacy outcomes [51]. Quantitative models to describe biological (pharmacological) processes can be deterministic or stochastic [52]. Models widely used in systems pharmacology are generally deterministic, where the output is determined from a given set of conditions and attempts to predict the average population effect of the system [51]. On the other hand, stochastic processes assume that the inputs in a system are subject to randomness and that the same set of conditions may lead to variable outcomes weighted by their probability. In the study of antimicrobials, Monte Carlo simulations (a form of stochastic forecasting) utilize random sampling to generate a virtual population to predict the probability of an outcome based on prior input data [6, 53, 54]. The premise of Monte Carlo simulations is that if an experiment is repeated multiple times, we can reliably infer that the results of the simulation will be close to the expected outcome [55]. Integrating PK variability and microbiological data, such an analysis can then be utilized to evaluate the likelihood that a particular dosing regimen will achieve an established PKPD target [56, 57]. Furthermore, results can then identify dosing strategies that could be used to guide the design or validate findings of randomized controlled trials [54].

Monte Carlo simulations have been used extensively in antimicrobial development phases for several reasons. It is costly and time-consuming to test different dosing regimens comprehensively in human subjects, and thus it may be more practical

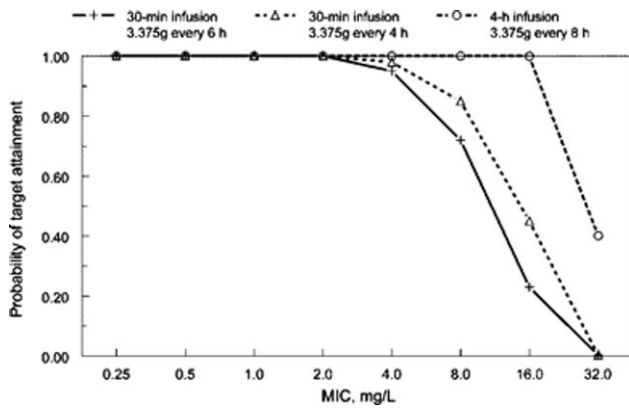


Figure 4. Probability of target attainment analysis for piperacillin/tazobactam therapy. Figure reproduced with permission from the Oxford University Press and Lodise et al. [72]. Both intermittent and extended infusions of piperacillin/tazobactam have high probabilities of target attainment when the MIC is low (≤ 4 mg/L). Within the MIC range of 8–16 mg/L, the probability of target attainment for prolonged-infusion piperacillin/tazobactam is considerably higher compared with standard-infusion administrations. Beyond a certain MIC (16 mg/L in this scenario), clinically relevant dosing strategies are unlikely to achieve optimal exposures needed for bacterial killing. Abbreviation: MIC, minimum inhibitory concentration.

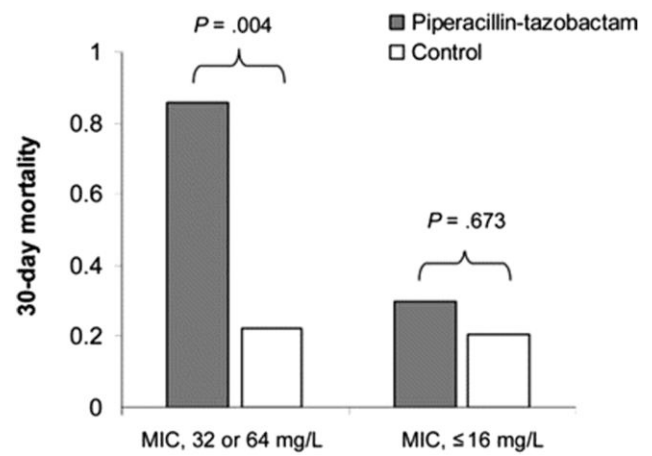


Figure 5. Thirty-day mortality rates for patients with bacteremia due to *P. aeruginosa*. Figure reproduced with permission from the Oxford University Press and Tam et al. [74]. In bacteremic patients due to *P. aeruginosa* with reduced susceptibility to piperacillin/tazobactam (MIC = 32 or 64 mg/L), patients who received piperacillin/tazobactam experienced higher mortality compared with those who received alternative agents. The difference observed was less dramatic if the MIC was ≤ 16 mg/L. Abbreviation: MIC, minimum inhibitory concentration.

to simulate a virtual clinical trial of thousands of subjects. For example, given a simple study design, to assess 3 total daily doses (eg, 2000, 1000, and 500 mg), given in 3 dosing frequencies (eg, every 24, 12, and 6 hours), and infused over 4 infusion times/modalities (eg, over 1, 2, 4, and 24 hours of continuous infusion), 36 different regimens would need to be tested in appropriately sized human trials. Additionally, most dosing adjustments of nonantimicrobials for end-organ dysfunctions are based on normalizing the overall drug exposure (AUC), which may not always apply to antimicrobials (since bacterial killing could depend on a PKPD index other than AUC/MIC). More appropriate antimicrobial dosing adjustments can be obtained through Monte Carlo simulations using the most relevant PKPD index [58, 59]. Similar simulations can also help to inform optimal dosing regimens in special populations, including patients with augmented renal clearance, critically ill patients, and obese patients [32, 60–63]. The literature has shown that these patients have PK variations that would alter the efficacy of antimicrobials at doses known to be effective in the general population. Lastly, studies have integrated Monte Carlo simulations into other analyses such as pharmaco-economic evaluations used for formulary decision-making [64–66]. In this instance, simulations are able to identify the dosing regimens that are the most cost-effective by balancing drug acquisition cost and the likelihood of PKPD target attainment.

Analytical Design

Generally, the prerequisites to perform a Monte Carlo simulation include a robust (population) PK model with well-defined

PK parameters (eg, clearance, volume of distribution) in the target patient population, ideally with a covariate(s) model that informs any PK variations based on patient demographics and characteristics (eg, clearance expressed as a function of glomerular filtration rate) and a PKPD model that defines the relationship between drug exposure and outcome [6, 67]. Once these inputs are introduced, the program creates a simulated population from the PK model where each subject will be randomly assigned PK variables based on the parameter distribution of the model. A concentration–time profile for each subject is constructed and evaluated against specific MICs of a pathogen. The ultimate result would be the likelihood of achieving the predefined PKPD target, more commonly referred to as the probability of target attainment (PTA), for the entire sample population (Figure 3). Some experts believe that a PTA of 90% or higher is an appropriate threshold to support the use of a particular dosing regimen at a given MIC [53]. A weighted distribution of drug susceptibility could also be incorporated based on recent local/regional surveillance data to guide the use of empiric therapy [67]. When actual PK (eg, drug exposure, penetration) and drug susceptibility patterns (eg, MIC, resistance genotypes) are known, these factors may pave the way toward precision dosing of antimicrobial therapy [68, 69].

Multiple studies have utilized Monte Carlo simulations to facilitate the design of optimal dosing strategies for various antimicrobials [70–73]. For instance, extended infusions of piperacillin/tazobactam have shown higher PTAs to a variety of Enterobacterales and *Pseudomonas aeruginosa*, especially at an MIC range of 8–16 mg/L, despite having a lower total daily dose compared with standard regimens, as shown in Figure 4

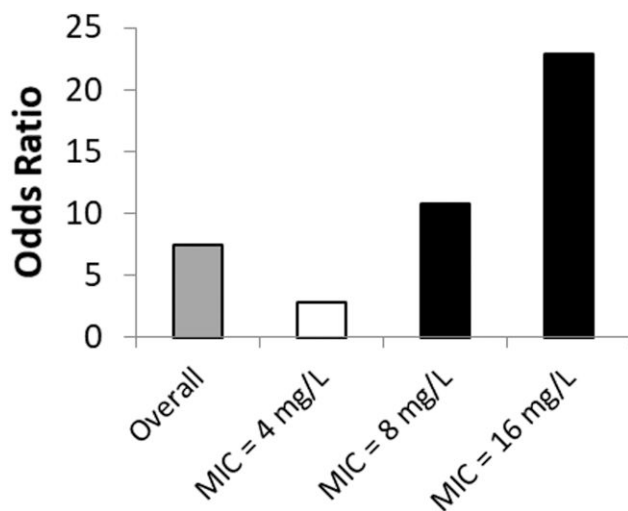


Figure 6. Clinical cure of patients with ventilator-associated pneumonia due to gram-negative bacteria. Figure reproduced with permission from Lorente et al. [75]. Continuous infusion of piperacillin/tazobactam was associated with higher clinical cure rates, compared with standard-infusion administration. The benefit was most prominent when the pathogen MIC was between 8 and 16 mg/L while controlling for patient comorbidities such as age, chronic obstructive pulmonary disease, and APACHE II scores. Abbreviation: MIC, minimum inhibitory concentration.

[72, 73]. When the pathogen MIC is >16 mg/L, the PTAs for piperacillin/tazobactam decrease dramatically, regardless of the dosing strategy used. Two studies presented clinical evidence that validated the findings of the Monte Carlo simulations. Tam et al. found a higher 30-day mortality rate in patients with *P. aeruginosa* bacteremia receiving piperacillin/tazobactam when the MIC was >16 mg/L (Figure 5) [74]. Similarly, when compared with intermittent infusion regimens, continuous-infusion piperacillin/tazobactam was associated with increased clinical cure of ventilator-associated pneumonia when the pathogen MIC ranged from 8 to 16 mg/L (Figure 6) [75]. Thus, optimized PK/PD-based dosing provides the most clinical impact when used against pathogens expressing low to intermediate-level resistance.

These studies have (at least in part) led the Clinical and Laboratory Standards Institute (CLSI) to revise the susceptibility breakpoint in 2012; the CLSI more recently recommended extended-infusion piperacillin/tazobactam dosing in patients with Enterobacterales infections with MICs of 16 mg/L [76].

Expert Commentary

Despite the widespread use of Monte Carlo simulations in antimicrobial development, limitations exist for this methodology. Clinical outcome data from high-quality randomized controlled trials are still required to support the findings of Monte Carlo simulations [54]. For example, Fish and colleagues found that PKPD modeling did not accurately predict

clinical or microbiological success in patients with *P. aeruginosa* pneumonia [77]. Therefore, factors other than PKPD targets may have to be considered when applying simulation results in clinical practice. Debates regarding the modeling tools and exposure targets that best translate preclinical data to clinical practice are ongoing. Several population modeling tools aiming to characterize specific patient populations of different physiologies (eg, neutropenia, nosocomial pneumonia) have been developed; however, assumptions on PK parameter distribution may still not apply to a specific patient [78].

A fundamental limitation of simulations is that results are only as valid as the model assumptions used for the input data [67, 79]. As mentioned previously, Monte Carlo simulations require a robust PK model used to generate PK profiles for a simulated population. For instance, antimicrobial serum concentrations used to formulate a population PK model may not appropriately predict PKPD target attainment in meningitis; using cerebrospinal fluid data as inputs would be more appropriate in this scenario. Also, there is currently no consensus on what sample size is required for a predictive model. Power analysis is typically used to determine the sample size needed in clinical studies to compare an outcome in 2 groups with appropriate statistical power. However, this approach is not directly applicable as the PK model aims to describe the behavior of the drug in the target population (eg, intersubject distribution of PK parameters, etc.). Thus, simulations based on population PK models involving a small sample size may not capture the realistic PK variability of the target population [67].

To improve the validity of results obtained from Monte Carlo simulations, new PK (or outcome) data involving additional subjects may be incorporated sequentially into the original data set [80]. This longitudinal process of merging more observed data to further refine output functions is referred to as stochastic feedback. In general, this is an iterative process that involves continually adding new data as they become available to the previous PK model and validating the simulation findings in order to produce a more informative Monte Carlo analysis. Such processes would potentially overcome the limited robustness of the initial simulation, and more optimal dosing strategies could be identified. Further advances in mathematical modeling are needed to integrate PKPD principles into the clinical setting, with an emphasis on validating simulations with experimental findings.

CONCLUSIONS

Several methodologies used to facilitate the design of optimal antimicrobial dosing in drug development were reviewed. Future advances in the application of more comprehensive modeling tools for dosing regimen design can lead to an era of precision dosing and personalized therapeutics.

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Author contributions. Both authors drafted, revised, and approved the manuscript for submission.

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