Pharmacokinetic and Pharmacodynamic Principles of Anti-Infective Dosing

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Abstract

Purpose—An understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) principles that determine response to antimicrobial therapy can provide the clinician with better-informed dosing regimens. Factors influential on antibiotic disposition and clinical outcome are presented, with a focus on the primary site of infection. Techniques to better understand antibiotic PK and optimize PD are acknowledged.

Methods—PubMed (inception – April 2016) was reviewed for relevant publications assessing antimicrobial exposures within different anatomical locations and clinical outcomes for various infection sites.

Findings—A limited literature base indicates variable penetration of antibiotics to different target sites of infection, with drug solubility and extent of protein binding providing significant PK influences in addition to the major clearing pathway of the agent. PD indices derived from *in vitro* and animal models determine the optimal magnitude and frequency of dosing regimens for patients. PK/PD modeling and simulation has been shown an efficient means of assessing these PD endpoints against a variety of PK determinants, clarifying the unique effects of infection site and patient characteristics to inform the adequacy of a given antibiotic regimen.

Implications—Appreciation of the PK properties of an antibiotic and its PD measure of efficacy can maximize the utility of these life-saving drugs. Unfortunately, clinical data remains limited for a number of infection site-antibiotic exposure relationships. Modeling and simulation can bridge preclinical and patient data for the prescription of optimal antibiotic dosing regimens, consistent with the tenets of personalized medicine.

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Introduction

Antibiotics are a key component of modern medicine, utilized in over half of all US hospitalizations, with over 250 million additional treatment courses provided in the outpatient setting per year.[1,2] Along with other classes of anti-infectives, they represent a uniqueness in pharmacotherapy, where one patient's prescription can have a direct effect on others', as antimicrobial utilization remains the primary driver of organism resistance.[3,4] Despite antibiotic resistance having long been declared a major threat to global public health,[3,5,6] the landscape of antimicrobial development has remained arid, with no agents with novel mechanisms of action against resistant Gram-negative organisms currently in late-stage clinical trials.[7-9] It is abundantly clear that optimization of antibiotic prescribing is necessary to preserve our current armamentarium. While stewardship practices focusing on the restriction of use and shortening of treatment duration are well-cited,[10,11] further research on antibiotic pharmacokinetic (PK) and pharmacodynamic (PD) properties that maximize the probability of successful outcome is needed.

This review serves to provide the clinician with the principal PK/PD considerations for the most common antibiotics encountered in US hospital settings (beta-lactams, vancomycin, fluoroquinolones, and aminoglycosides). The information contained herein can assist in producing dosing regimens that maximize clinical benefit while minimizing the risk of toxicity. While these concepts remain salient to antifungals and antivirals, such agents are beyond the scope of this review. Particular emphasis will be placed on the site of infection when applying these concepts to patient care. This review is by no means exhaustive, and the interested reader is encouraged to access the provided references and available textbooks[12,13] for a more in-depth discussion of antimicrobial PK/PD. Instead, the goal is to discuss the key principles related to rational selection of an antibiotic dosing regimen, which remain applicable to agents not discussed here in addition to new agents as they enter clinical practice.

Methods

PubMed (inception – April 2016) was searched for relevant publications using combinations of the search terms "antibiotic", "penicillin", "cephalosporin", "carbapenem", "vancomycin", "fluoroquinolone", "aminoglycoside", "penetration", "blood", "bloodstream", lung", "epithelial lining fluid", "soft tissue", "interstitial fluid", "bone", "central nervous system", "cerebrospinal fluid", "pharmacodynamic", and "outcome". Reference lists of identified publications were also reviewed for relevant articles.

Antimicrobial Pharmacokinetics

General Considerations

The kinetics of a drug refer to its rate of change as it traverses through a biological system, and is governed by the four essential processes of absorption, distribution, metabolism, and excretion. While antibiotic PK is often considered in terms of the body's effect on the drug, the agent's physicochemical properties must also be considered to predict its disposition. Chief among them is the relative solubility of the antimicrobial, which can have a significant impact on its volume of distribution, and thus may prove key in selecting agents expected to attain adequate penetration to the site of infection.[14,15] Also influential is the extent of protein binding the antibiotic exhibits, as only free, unbound drug is capable of exerting antimicrobial effects.[16-19] As albumin is the primary plasma binding protein for the majority of antibiotics, its concentrations should be considered when implementing and adjusting dosing regimens, with highly protein bound agents being most affected.[14,20-22] Finally, the agent's major route of elimination warrants appreciation, particularly in times of changing clinical condition where development of end-organ dysfunction or critical illness can greatly enhance (renal failure)[23,24] or reduce (augmented renal clearance) antibiotic exposures.[25-27] Table 1 summarizes these properties for the most commonly utilized parenteral antibiotics in the US hospital setting.

Site-Specific Considerations

With these PK properties in mind, it becomes clear that the primary infection site is a crucial variable in considering whether sufficient antibiotic exposures are likely to be attained for a given agent and dosing regimen. Indeed, the differing physiology of anatomical sites where bacteria can reside often result in variable degrees of antibiotic penetration and thus concentration at the site where pharmacologic effect occurs.[14] The sections that follow examine the relationship between antibiotic PK and exposures in the blood, lung, soft tissue, bone, and central nervous system (CNS); a summative table outlining hypothetical dose alterations based on antimicrobial PK properties and infection site is provided in Table 2.

Blood—The bloodstream is perhaps the simplest infection site to consider, as it comprises the central compartment from which systemically administered drug distributes to the tissues. When treating a bacteremic patient, the clinician must account for the likelihood of the proposed antibiotic agent – and more importantly its proposed dosing regimen – to maintain sufficient exposures within the blood to rapidly clear the organism, as delays in appropriate therapy are associated with increased mortality.[28-31] Of course, the factors described here must also be reconciled with identification of the primary source of infection, optimizing antimicrobial therapy for that site in parallel with blood to prevent recrudescence and the possibility of antibiotic resistance.

In addition to the underlying pathology of sepsis resulting in significant fluid extravasation and a high probability of augmented renal clearance,[32,33] standard therapy bundles that include volume resuscitation and inotrope support are likely to further alter antibiotic PK, with hydrophilic, renally-cleared agents (beta-lactams, vancomycin, aminoglycosides) being most susceptible.[34-37] Indeed, recent data has suggested that currently prescribed doses of

beta-lactams are prone to underexposure in the critically ill, yielding a lower probability of achieving positive clinical outcomes.[38-41] Similar findings of suboptimal exposure for vancomycin[26,36] and aminoglycosides[42,43] have been observed, correlating with illness severity.[44] In contrast, the lipophilic fluoroquinolones are minimally affected by changes in volume status, owing to their considerable permeability across membranes.[34,45] While it could be inferred that the presence of augmented renal clearance would result in lower exposures of ciprofloxacin and levofloxacin, the evidence supporting this theory is, to date, lacking.

The presence of endocarditis necessitates the additional consideration of antibiotic penetration within the vegetation, as a high bacterial inoculum and production of biofilm can result in suboptimal concentrations and treatment failures.[46,47] Work performed *in vitro* and in animals has demonstrated the general need for higher doses to attain sufficient exposures,[48,49] though clinical evidence remains scarce for the agents under consideration here. Nevertheless, current clinical practice guidelines advocate the use of dosing regimens at the high end of the licensed dosing range (beta-lactams) or measured therapeutic range (vancomycin) to optimize treatment outcomes.[46,50]

Lung—The lung represents an additional infection site associated with high bacterial densities and variable antimicrobial penetration.[14] The epithelial lining fluid (ELF) is considered the target site for the treatment of pneumonia caused by extracellular pathogens, representing an available matrix for the measurement of antibiotic concentrations.[51,52] While sparse, literature does exist describing ELF penetration of various antimicrobials in the clinical setting; the data provided below is focused on infected patients wherever possible.

Beta-lactams display a wide variability in ELF-to-plasma penetration ratio, ranging from 0.21 for ceftazidime[53] to 1.04 for cefepime.[54] Piperacillin represents perhaps the most studied agent, with a reported ELF:plasma ratio of ~0.50 (with corresponding tazobactam values ranging from 0.65 to 1.21).[55-57] A single report on ampicillin lung penetration found an ELF:plasma ratio of 0.53 (corresponding sulbactam value, 0.61).[58] Preliminary data in healthy volunteers suggests an ELF:plasma ratio of 0.23 for ceftaroline,[59] whereas a Phase I trial of ceftolozane produced a value of 0.48 (corresponding tazobactam value, 0.44).[60] In the ceftolozane study of healthy volunteers, it is important to note the considerably lower degree of tazobactam penetration versus that observed in critically ill patients,[55-57] which could be ascribed to an increase in paracellular permeability that accompanies inflammation;[14] indeed, this study reported a demonstrably lower value for piperacillin as well (0.26). Counterintuitively, the opposite is found when considering meropenem, with lower ELF:plasma ratios reported for severely ill patients (~0.25)[61,62] versus healthy volunteers (0.65),[63] further indicating a critical need for antibiotic penetration studies in the target population. A singular study for ertapenem[64] in critically ill patients suggests an ELF:plasma ratio of 0.30, whereas studies of doripenem[65] and imipenem[66] in healthy individuals report values of ~0.34, and 0.44, respectively. These findings indicate a relatively lower extent of ELF penetration for carbapenems versus penicillins in infected patients, whereas penetration ratios for cephalosporins remain highly variable. This, along with an inability to correlate penetration to extent of protein binding, emphasizes the need for careful

consideration of agent and regimen selection when treating patients for pneumonia.[67,68] Unfortunately, data is lacking for other commonly used beta-lactams such as cefazolin, ceftriaxone, and oxacillin/nafcillin.

Despite its high degree of utilization, the permeability of vancomycin into ELF has been severely understudied, with only a few reports to guide therapeutic decision.[69-71] From this limited literature base, best estimates for ELF:plasma penetration range from ~0.18-0.50, with most authors recommending higher doses to achieve sufficient lung exposures. In stark contrast, lung penetration of ciprofloxacin, levofloxacin, and moxifloxacin has been extensively studied, with the high volume of distribution of fluoroquinolones producing ELF:plasma ratios exceeding 1.[72-78] For aminoglycosides, lung disposition appears more complex, with gentamicin and tobramycin ELF:plasma ratios <1 early in the dosing interval, but >1 after 6-8 hours: this apparent PK hysteresis could be explained by the considerable hydrophilicity of these compounds, resulting in slow rates of movement across biological membranes.[79-81] It must be cautioned, however, that in none of these studies were exposures examined over an entire dosing interval, thus the possibility of redistribution from ELF to plasma remains a significant and unresolved issue.

Soft tissue—Much like ELF for the lung, the interstitial fluid (ISF) concentration of an antibiotic provides the most appropriate measurement of target site exposure for extracellular infections of the soft tissue.[82] Utilizing microdialysis techniques, which consist of implanting a perfused semipermeable membrane into the desired tissue and measuring drug concentrations within the dialysate, the most robust quantification of unbound (free) antibiotic in ISF can be achieved.[83,84] The physicochemical properties of the antibiotic and its degree of protein binding largely dictate the extent of soft tissue penetration, as the vascular endothelium remains highly permeable to these small molecules.[85] Importantly, then, the clinician must remain cognizant of the infected patient's relative proportions of adipose and muscle, as lower exposures of some hydrophilic agents in the ISF of adipose relative to muscle tissue have been observed.[35,86-88] Further, the expected increased volume of distribution of lipophilic agents with increased adipose may result in suboptimal concentrations to treat these infections. While the appreciable influence of obesity is beyond the scope of this review, general measures of body composition (fat free mass, percentage of ideal body weight) may be considered additional factors when determining suitable antibiotic dosing regimens for soft tissue infections.[89,90]

Bone—The composition of bone is unique, consisting of a matrix of collagen and hydroxyapatite that often provides a protected site for bacteria, evading the effects of the immune system and many antibiotics.[14] With osteomyelitis being associated with a high relapse rate and protracted antibiotic courses, emphasis should be placed on optimization of dosing regimens and a better understanding of PK properties that can influence exposure at the target site.[91,92] While again the literature is sparse, some overarching patterns can be discerned, albeit the majority of data has been derived from non-infected patients.[92,93]

As may be expected based on discussions of previous infection sites, beta-lactams display variable penetration into bone, with ratios compared to serum ranging from ~0.1 for oxacillin to ~1 for cefepime.[94,95] Most beta-lactams, however, manifest bone:serum ratios

between 0.1 and 0.3, consistent with their hydrophilic nature.[96-102] Similar variability and point estimates have been found for vancomycin in infected patients, with an average bone:serum ratio of ~0.20.[100,103] Higher doses would thus be necessary if mirroring drug exposures in the blood is desired. Fluoroquinolones, maintaining high volumes of distribution secondary to their lipophilicity, achieve higher bone:serum ratios than beta-lactams or vancomycin, ranging from ~0.35 (ciprofloxacin) to ~0.75 for levofloxacin.[104-106] Though studies are lacking for aminoglycosides, their high degree of hydrophilicity would be hypothesized to severely limit the penetration of these agents across the bone matrix.

CNS—The combination of tight junctions and active transport systems that form the blood-brain barrier (BBB) create a substantial impendent to the penetration of most antibiotics into the cerebrospinal fluid (CSF).[107-109] As such, here perhaps more than any other infection site are the agents' PK properties determinant of attaining sufficient pharmacologic exposures. Also of critical impact is the presence of inflammation within the meninges, as this significantly alters the permeability of the BBB, profoundly increasing CSF exposures for the majority of antibiotics.[107,108,110]

Degree of lipophilicity appears the most influential characteristic associated with an antibiotic's CSF penetration, as this property affords passive diffusion across the otherwise impervious cerebral membranes.[111-113] Indeed, fluoroquinolones achieve far higher CSF:plasma ratios than other antimicrobial classes, with values averaging ~0.50,[114-116] versus ~0.10 for beta-lactams (range, 0.007 – 0.25),[117-123] ~0.15 for vancomycin,[124] and ~0.20 for aminoglycosides[108] in intact meninges. With inflammation, however, the tight junctions that connect cerebral endothelial cells become more porous, allowing up to an order of magnitude higher CSF penetration for hydrophilic compounds.[108,124-128] This knowledge must be reconciled clinically with the frequent use of corticosteroids to decrease meningeal inflammation, which in addition to blunting the immune system's response to infection can decrease the CSF exposure of first-line agents, thus larger doses are likely necessary to ensure antimicrobial success, consistent with guideline recommendations.[128,129] As would be expected, the effect of inflammation on CSF penetration is attenuated with fluoroquinolones, though enhancements have been reported in a limited number of patients.[130,131]

Collectively, these findings make it clear that target site penetration is an important factor for reconciling PK differences between and within antibiotic classes, and interpreting published literature on antimicrobial effect. It is also apparent that the study of antibiotic exposures at the site of infection is deficient, with much of the evidence base from trials conducted decades ago, hindered by suboptimal experimental designs, limited numbers of observations, and outdated methodologies. Importantly, while published studies often observe infection site concentrations above the minimum inhibitory concentrations (MICs) of common pathogens despite various barriers to entry, as will be presented in the following section, these PK snapshots are ill-suited for drawing definitive conclusions on the adequacy of a given antibiotic regimen.

Antimicrobial Pharmacodynamics

Guiding Principles

The MIC represents the most elemental PD measure for antibiotics; however, this value simply reflects the potency of the given agent, providing no information regarding the time course of antimicrobial effect nor whether the rate of bacterial killing may be altered by changing drug exposure.[132] Far more informative is the incorporation of PK information to assess the ability of a given antibiotic and its chosen dosing regimen to kill the infecting pathogen and predict clinical outcome. Three major PD indices – the percent of time that free drug remains above the MIC over a 24-hour period ($fT_{>MIC}$), the ratio of free drug area under the concentration-time curve to MIC over a 24-hour period (fAUC:MIC), and the ratio of maximum concentration to MIC (C_{max}:MIC) – sufficiently link the kinetics of antimicrobial disposition to efficacy.[132-134] An additional factor is the agent's post-antibiotic effect (PAE), which quantifies the persistence of bacterial suppression after short exposure to the drug, thus adding to the overall duration of antimicrobial effect.[135] Consideration of these metrics is essential in appropriately selecting and adjusting antibiotic regimens in clinical practice, and should be done in concordance with individual patient status and suspected site of infection. Representative PD and dosing characteristics for the antimicrobial classes discussed previously are provided in Table 3; while the field of antimicrobial PD was borne from *in vitro* and animal study, for which a rich literature exists,[132,134,136,137] the focus here will be on recent clinical applications and appraisals. Thus, alternative PD measures associated with the minimization of antimicrobial resistance such as the mutant prevention concentration (MPC) will not be discussed, as they at current have not been assessed in the clinic, though remain an important focus for future research.[138,139] Further, owing to less overall evidence supporting their use, alternative PD indices including measures related to percent of time free drug remains above a low multiple of the MIC (e.g. $fT_{>4 \times MIC}$),[140] and minimum free drug concentration to MIC ratio (fC_{min}:MIC)[141] are beyond the scope of this review.

$fT_{>MIC}$

Beta-lactams serve as the archetypal class of time-dependent antibiotics, whereby substantially increasing drug concentrations have minimal effects on the overall rate and extent of bacterial killing. Instead, maintaining a free drug concentration above the MIC of the organism for a portion of the dosing interval has been shown to best predict microbiologic efficacy.[142-145] The magnitude of this PD index varies by beta-lactam subclass, with typical $fT_{>MIC}$ values of 60-70% for cephalosporins, 50% for penicillins, and 40% for carbapenems providing maximal bactericidal effect.[132,133]

Clinically, these PD targets have been evaluated in a surprisingly limited number of studies, with the majority focusing on antipseudomonals.[41,146-152] For these agents, a broad range of $fT_{>MIC}$ values from >45-100% have been reported as necessary for achievement of favorable clinical or microbiological outcomes, a likely consequence of heterogeneous patient populations, infecting organisms, and study designs. However, the most robust evidence remains in line with *in vitro* and animal estimates, with cefepime $fT_{>MIC}$ values of >53-74% being associated with up to a 10-fold higher likelihood of favorable outcome.[149,151,152]

Indeed, in a large study assessing the adequacy of contemporary beta-lactam dosing regimens in critically ill patients, the inability to attain a $f\mathrm{T}_{>\mathrm{MIC}}$ >50% was associated with a 32% decreased likelihood of a positive clinical outcome.[41] Extended infusion regimens of certain beta-lactams have become a widespread means of maximizing $f\mathrm{T}_{>\mathrm{MIC}}$ in specific clinical scenarios.[153,154] While likely not warranted in all patients, studies have shown average reductions in mortality of 33-50% when piperacillin/tazobactam and cefepime are dosed over 3-4 hours versus standard intermittent infusions (0.5-1 hour), with the largest benefits seen in critically ill patients and those with multidrug-resistant organisms.[155,156] Extending this concept further, continuous infusions of beta-lactams have also been studied,[155-157] though employment is likely to be reserved only for extreme cases secondary to logistical issues in maintaining dedicated intravascular access for administration. Despite the recent advances in our ability to derive optimized dosing regimens for beta-lactam agents, studies linking PD target attainment and clinical outcomes are limited, an issue that must be reconciled to ensure patients receive the best antimicrobial therapy based on infecting organism, infection site, and clinical status.

*f*AUC:MIC

Measures of free drug exposure over a 24-hour period (*f*AUC) in relation to the organism MIC are correlative with the antimicrobial efficacy for most antibiotic classes, with vancomycin and the fluoroquinolones having accrued the most data.[132-134] Importantly, this metric affords a fair amount of flexibility in dosing regimen, as simultaneously adjusting both the magnitude of the dose and the frequency with which it is administered will result in identical *f*AUC values. Consequently, this PD index incorporates components of both time (vancomycin) and concentration (fluoroquinolones) dependence in determining the rate and extent of bacterial killing.[133,134] Despite initial preclinical data showing maximal bacterial killing over a wide range of total drug AUC:MIC values for vancomycin, the threshold of 400 is ubiquitously used.[158] Early animal and *in vitro* work indicate total drug AUC:MIC values of 30-100 are necessary to achieve maximum kill for fluoroquinolones, based on the infecting organism.[132,159] Correcting for protein binding of these respective agents produces equivalent *f*AUC:MIC values of 200 for vancomycin and 21-70 for fluoroquinolones.

Secondary to the dramatic rise of methicillin-resistant *Staphylococcus aureus* (MRSA) over the past two decades, optimization of vancomycin therapy has received much attention in recent years. Though current practice guidelines recommend the measurement of trough concentrations as a surrogate of total drug AUC:MIC, this may yield overexposure in some patients and thus an increased risk of adverse effects.[50,160,161] Evaluation of total drug AUC:MIC thresholds predictive of favorable outcomes have been conducted in various clinical settings, with results ranging from 211 in patients with complicated MRSA bacteremia and endocarditis to 578 in patients with septic shock due to MRSA; assuming 50% protein binding for vancomycin, equivalent *f*AUC:MIC values are ~106-289.[162-167] In studies that assessed mortality, 2 to 4-fold reductions were observed with attainment of these AUC:MIC thresholds,[163,164,166] emphasizing the need for careful selection of dosing regimens. Notably, recent data suggests that higher total drug AUC:MIC values within the first 48 hours of therapy may be most associated with clinical outcome, with thresholds upwards of 600 (*f*AUC:MIC ~300) being necessary.[168,169] Unfortunately, achievement of

such high vancomycin exposures is likely limited to the most sensitive of isolates, as large dosing requirements produce high likelihoods of toxicity.[170,171]

In some of the first studies to assess PD indices and clinical outcomes, fluoroquinolone AUC:MIC values of 125 for ciprofloxacin and 34 for levofloxacin were significantly associated with clinical and microbiologic cure.[172,173] Assuming ~30% protein binding for each, this corresponds to fAUC:MIC values of 88 and 24, respectively, in line with preclinical estimates. Interestingly, later investigations[174,175] reported the necessity of higher values to attain similar outcomes, which may be a consequence of infecting pathogen and severity of infection. In these studies, AUC:MIC values of 250 for ciprofloxacin and 87 for levofloxacin were predictive of favorable outcome, corresponding to fAUC:MIC values of 175 and 61, respectively. Overall, the evidence shows a 2-28-fold higher probability of favorable outcome when these respective PD index values were reached.[174,175]

C_{max}:MIC

Aminoglycosides serve as the exemplar antimicrobial class for which bacterial kill is maximized by attaining higher maximal concentrations.[132] Here, maintaining concentrations above the organism MIC for an extended period of the dosing interval is unnecessary, and in fact discouraged due to an increased risk of adverse effects.[176-178] While preclinical studies originally established AUC:MIC as the most predictive PD index for aminoglycosides,[136] it must be recognized that employment of once-daily doses will yield a high degree of collinearity between measures of C_{max} and 24-hour AUC.[178] As such, the focus here will be on C_{max}:MIC, which remains the clinically targeted metric, and for which clinical outcomes data exist. Additionally, there have been trials with fluoroquinolones that discern the influence of peak concentrations in their overall killing capacity.

Studies of gentamicin and tobramycin in patients being treated for sepsis and nosocomial pneumonia have established a C_{max}:MIC 8-10 as the PD target associated with clinical response.[179-181] For endocarditis caused by *Enterococcus* species, current guidelines indicate aminoglycosides are to be given as lower, multiple daily doses instead of the typical once-daily regimen, albeit the evidence to support such dosing is scant.[46] Nevertheless, it may be anticipated that a measure of total drug exposure (i.e. AUC:MIC) rather than C_{max}:MIC would be a distinct correlate to efficacy for these patients, though such studies have yet to be conducted. While their PD index is often represented by fAUC:MIC, the concentration-dependent nature of bacterial killing by fluoroquinolones also results in C_{max}:MIC as a predictive parameter for response.[182,183] Values 8 for ciprofloxacin and 12.2 for levofloxacin were associated with significantly improved clinical and microbiologic outcomes, though as noted in the respective studies and supported by *in vitro* data, this index is likely most important when faced with an organism capable of rapidly developing resistance, such as *Pseudomonas aeruginosa*.[184,185]

PAE

When considering antimicrobial dosing regimens, the selected agent's PAE, in determining the overall duration of action, can have a significant influence. In general, all antibiotics exhibit some degree of PAE against susceptible Gram-positive organisms, with values

ranging from <2 hours for beta-lactams to nearly 5 hours for vancomycin against *S. aureus,* though point estimates vary considerably.[135,186] Agents that alter protein or nucleic acid synthesis, such as aminoglycosides and fluoroquinolones, tend to display a prolonged PAE against any susceptible organism, as it takes considerably longer for bacteria to regenerate these elements than components of the cell wall.[132,134] PAE values derived from animal models for these agents are on average between 2 and 6 hours (range, 1.2-12.8 hours for aminoglycosides; 1.9-7.5 hours for fluoroquinolones), thus longer intervals between doses are possible without compromising treatment efficacy.[135,187,188] On the contrary, beta-lactams maintain virtually no PAE against Gram-negative pathogens (<1 hour), often requiring multiple daily doses to ensure adequate coverage.[135] An exception here is the carbapenem subclass, whose agents have shown prolonged PAEs of ~2-4 hours against Enterobacteriaceae and *P. aeruginosa*, consistent with their lower fT>MIC requirement versus other beta-lactams.[189-191]

Modeling and Simulation

The relative paucity of clinical evidence confirming *in vitro* and animal model PK/PD observations speaks to the difficulty in conducting such trials, necessitating an integrative, efficient, and scientifically valid approach. *In silico* modeling of PK data and simulation of treatment course provides a powerful means of assessing the adequacy of current antimicrobial dosing regimens, and deriving those that optimize PD indices.[192] These techniques are being increasingly employed both as a means of bringing new agents to market and for the evaluation of existing antimicrobials, minimizing industry risk on the one hand while maximizing clinical utility on the other.[68,193,194] Through the leveraging of PK/PD data from preclinical models of infection and application of advanced pharmacostatistical modeling, measures of exposure and response can be obtained for various pathogen-antibiotic-infection site combinations. Imputing patient-level data into these models and performing Monte Carlo simulations, which account for interindividual differences in PK parameters and antimicrobial susceptibility, predictions of PD target attainment are possible. This has been shown for numerous agents, with optimal dosing regimens often inferred as those that eclipse the specified PD target (for example, a $fT_{>MIC}$ 50% or a fAUC/MIC 100) with a 90% or higher probability.[195-204] Indeed, much of the aforementioned literature on antimicrobial penetration and efficacy has applied population PK modeling and Monte Carlo simulation to predict exposure-response relationships in patients and infer optimal dosing regimens for the clinical population under study. Extrapolation of the simulation results beyond this should be done with caution, as differing pathogens, infection types, and illness severities are likely to yield differing rates of target attainment for a given drug and dosing regimen; ideally, studies for each combination of antimicrobial agent, infecting pathogen, and clinical scenario should be performed. Additionally, such platforms can be utilized to study the effects of antibiotic resistance[205,206] and rare infections,[207,208] situations where accruing an adequate number of patients in clinical trials is not feasible. Modeling and simulation can thus enhance the translation of preclinical *in vitro* and animal studies to clinical practice, informing trial design to optimize the results of future clinical studies in addition to being directly applicable to contemporary patient care.

Summary and Conclusions

Rising rates of antimicrobial resistance and a limited drug development pipeline underscore the need for preserving the utility of currently available agents. An appreciation of the PK/PD determinants of a given antibiotic can foster more rational and individualized dosing regimens, improving patient outcomes while simultaneously limiting the spread of resistance (Figure 1). Anticipating the extent of distribution to the site of infection is of primary importance for ensuring adequate drug exposures; however, significant knowledge gaps remain. To truly understand the pharmacology of antimicrobials, we must go beyond MICs, employing metrics that account for the rate of bacterial killing, and the effects different dosing regimens have on it. Use of PK/PD modeling and simulation can maximize the amount of clinically useful information derived from limited numbers of patients, guiding optimal therapy and fully aligning with the goals of personalized medicine.

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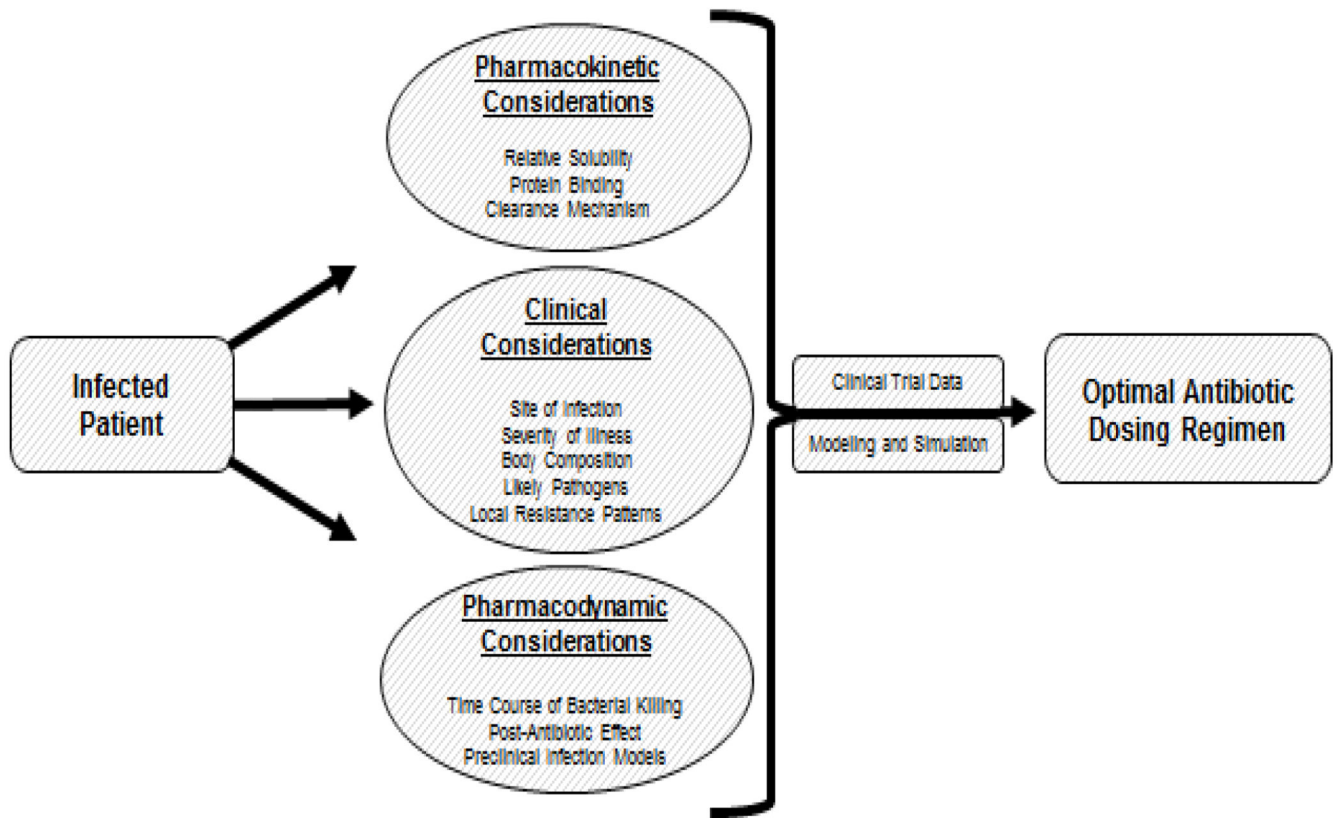
Figure 1.
Approach to the Infected Patient for the Provision of Optimal Antibiotic Therapy.

Table 1

Representative PK Properties of Commonly Administered Antibiotics

Antibiotic	Solubility	Plasma Protein Binding	Clearance
Beta-lactams[a]	Hydrophilic	Low-moderate	Renal
Vancomycin	Hydrophilic	Moderate	Renal
Fluoroquinolones[b]	Lipophilic	Low-moderate	Renal
Aminoglycosides	Hydrophilic	Low	Renal

[a] Exceptions: cefazolin (highly protein bound), ceftriaxone (highly protein bound), ertapenem (highly protein bound), nafcillin/oxacillin (highly protein bound, hepatically cleared)

[b] Exception: moxifloxacin (hepatically cleared)

Table 2

Infection Site, PK Considerations, and Adaptation of Dosing Regimen

Infection Site	PK Alteration	Potential Change to Dosing Regimen
Blood	Expanded V_d, Enhanced CL	Provision of LD, Increase frequency
Lung	Impaired permeability[a]	Increase dose[a]
Soft Tissue	Contingent on body composition	Increase dose in obesity
Bone	Impaired permeability	Increase dose, duration of therapy
CNS	Impaired permeability	Maximal dose

CL = clearance; LD = loading dose; V_d = volume of distribution

[a] Of hydrophilic agents (beta-lactams, vancomycin, aminoglycosides)

Table 3

PD and Dosing Characteristics of Commonly Administered Antibiotics

Antibiotic	PD Index	PAE[a]	Dosing Paradigm
Beta-lactams	$fT_{>MIC}$	Minimal[b]	Higher frequency; prolonged infusions
Vancomycin	fAUC:MIC	--	Flexible
Fluoroquinolones	fAUC:MIC, C_{max}:MIC	Prolonged	Flexible; high dose
Aminoglycosides	C_{max}:MIC, fAUC:MIC	Prolonged	High dose, low frequency[c]

PAE = post-antibiotic effect; $fT_{>MIC}$ = percent of time free drug remains above the minimum inhibitory concentration; fAUC:MIC = ratio of free drug area under the concentration-time curve to minimum inhibitory concentration; C_{max}:MIC = ratio of maximum concentration to minimum inhibitory concentration

[a] For Gram-negative pathogens only

[b] Exception: carbapenems (Prolonged)

[c] Exception: enterococcal endocarditis (lower dose, higher frequency)