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Pharmacokinetic and Pharmacodynamic Issues in the Treatment of Bacterial Infectious Diseases

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Abstract This review outlines some of the many factors a clinician must consider when selecting an antimicrobial dosing regimen for the treatment of infection. Integration of the principles of antimicrobial pharmacology and the pharmacokinetic parameters of an individual patient provides the most comprehensive assessment of the interactions between pathogen, host, and antibiotic. For each class of agent, appreciation of the different approaches to maximize microbial killing will allow for optimal clinical efficacy and reduction in risk of development of resistance while avoiding excessive exposure and minimizing risk of toxicity. Disease states with special considerations for antimicrobial use are reviewed, as are situations in which pathophysiologic changes may alter the pharmacokinetic handling of antimicrobial agents.

Introduction

Since the introduction of penicillin and sulfonamides, clinicians have been challenged with the issue of how to achieve optimal outcomes in patients with bacterial infections. While the discovery of these life-saving agents revolutionized modern medical treatment, balancing their use with the loss of activity resulting from bacterial resistance has become a challenge. For as long as these agents have been used clinically, there has been ongoing investigation into the best way to use antibiotics. As early as the 1940s, the effect of dose and dosing interval on bactericidal activity has been investigated [1], and strategies to optimize antibiotic selection and dosing remain at the forefront of our clinical research today.

The appropriate use of antimicrobial agents requires an understanding of the characteristics of the drug, the host factors, and the pathogen, all of which impact selection of the antibiotic agent and dose. Figure 1 illustrates the complexity of the multiple interactions between the patient, the pathogen, and the antibiotic. Characteristics of the patient that must be considered include those that affect the interaction between the patient and the infection, such as comorbid factors and underlying immune status, as well as patient-specific factors such as organ function and weight, which will impact the pharmacokinetics of the antibiotic. Characteristics of the bacteria include its role as a pathogen in causing infection at the site, the pattern of susceptibility to antibiotics, and possible consequences of resistant bacterial subpopulations. Lastly, considerations for selection of the antibiotic include antibacterial activity, clinical efficacy, safety, and potential for drug interactions. Pharmacologic properties such as tissue penetration, protein binding, and metabolism and elimination characteristics will affect the resulting pharmacokinetic profile and must be evaluated as well. This article reviews selected concepts to be considered when using antibacterial agents. Special emphasis is placed on the importance of pharmacologic principles, the application of which may assist in optimizing efficacy while minimizing the risk of drug-related toxicity.

Pharmacokinetics and Pharmacodynamics

As described above, the selection of an antimicrobial treatment regimen is based on many factors, including the pharmacokinetic and pharmacodynamic properties of the antibacterial drugs. Antibiotic pharmacodynamics integrates the complex relationship between organism susceptibility and patient pharmacokinetics. The most routine method for determining pathogen susceptibility and the one used clinically is minimum inhibitory concentration (MIC) testing. Pharmacokinetics describes the fundamen-

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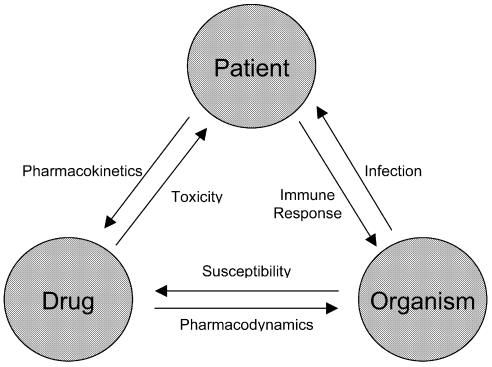

Fig. 1 Schematic representation of the complexity of interactions between patient, pathogen and antibiotic

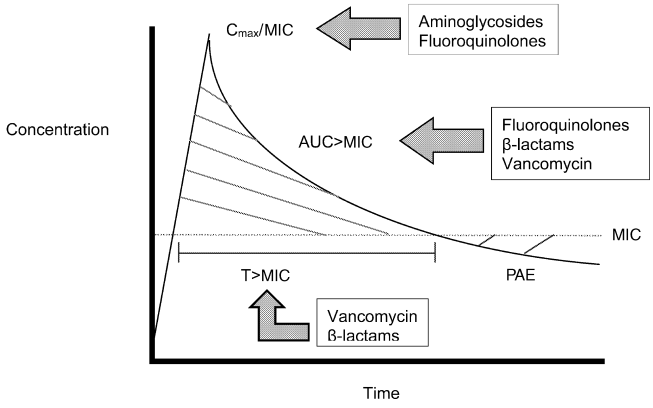

Fig. 2 Concentration-versus-time curve with minimum inhibitory concentration superimposed and pharmacokinetic and pharmacodynamic markers

tal processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo. Pharmacokinetic studies describe parameters such as C_{max} or peak concentration, the serum half-life ($t_{1/2}$), and cumulative exposure to an agent (area-under-the-concentration-time curve [AUC]) for a 24-h period (Fig. 2). Because agents vary in degree of protein binding, it is recommended by some investigators that free drug concentrations be used for dynamic comparisons. To ensure a successful outcome, a specific pharmacodynamic interaction between the antimicrobial agent and its bacterial target must be achieved. These specific relationships provide a surrogate target for predicting outcomes such as bacterial eradication and/or clinical cure. These surrogates relate various pharmacokinetic parameters such as C_{max} or AUC to a measure of the pharmacodynamic interaction (the MIC). Another surrogate relationship is the time that the serum concentration of a given agent exceeds the MIC, or percent time above MIC, (T>MIC). These relationships are illustrated in Fig. 2. When evaluating the concentration-versus-time curve for an antimicrobial agent, the introduction of the MIC onto the graph provides an illustration of the relationship between the concentration and the MIC. An increase in dose will provide a significant increase in C_{max}, while a shorter dosing interval will predominantly increase the time that concentrations remain above the MIC of the infecting pathogen. It should be noted that an increase in dose will increase both C_{max} and AUC, frequently resulting in covariance of these pharmacodynamic targets. Different dosing strategies may be used to optimize dosing for the various classes of antibiotics, as noted in Fig. 2.

Studies using in vitro investigations, animal models, and human clinical trials have established which of these surrogate markers provide the best description of the activity of each antimicrobial class. An overview of key studies for each antibiotic class and the pharmacodynamic target identified is provided in Table 1. In short, the fluoroquinolone and aminoglycoside agents exhibit concentration-dependent killing. Studies have demonstrated that the C_{max}/MIC and AUC/MIC ratios are important predictors of outcome for these antimicrobial agents. For cell-wall-active agents such as the β-lactam antibiotics, T>MIC is generally identified as the most significant pharmacodynamic surrogate. Since glycopeptide antibiotics display relatively slow but concentration-independent killing and are cell-wall-active agents similar to β-lactams, it has been presumed that T>MIC is important for efficacy; however, recent studies have shown that the AUC/MIC ratio is an important predictor of successful outcome with vancomycin. To recommend the most effective dosing of the various antimicrobial classes, it is necessary to understand the target surrogate pharmacodynamic endpoint necessary for the different classes of antibiotics. This review will emphasize the aminoglycosides, the fluoroquinolones, the β-lactam agents, and the glycopeptides.

Data to explain the pharmacodynamics of antimicrobial agents has been derived from numerous sources. Assessment of the in vitro killing demonstrated by antimicrobial agents is the most basic step necessary for understanding the antibacterial activity of an agent. In vitro pharmacodynamic models and animal models of infection have also been used to create a more dynamic environment in which to examine the activity of an antibiotic. These models provide a better understanding of how changes in antibiotic exposure over time may influence activity, yet they remain limited in their ability to accurately reflect the human infection and host environment. Most do not incorporate a means to evaluate the role of the host immune system in bacterial killing. While pharmacodynamic outcome studies in humans are frequently difficult to conduct, their influence on our understanding of antimicrobial activity in vivo is invaluable for evaluating the application of dosing principles. Where data exists, human trials will be emphasized and an approach to application of pharmacodynamics to clinical decision-making will be outlined.

Aminoglycoside Antibiotics

When considering pharmacodynamic effects of antibiotics, aminoglycoside antibiotics are among the most readily understood because serum concentration data is frequently

Table 1 Pharmacodynamic surrogate markers predictive of outcome

Drug class	Author [ref.]	Drug	Organism(s)	Setting	Parameter	Value
Fluoroquinolones						
	Blaser et al. [14]	enoxacin	*P. aeruginosa*, *K. pneumoniae*, *E. coli*, *S. aureus*	in vitro	peak:MIC	8:1
	Hyatt et al. [15]	ciprofloxacin	*S. pneumoniae*, *S. aureus*, *P. aeruginosa*	in vitro	AUC/MIC	350–450
	Lister [20]	gatifloxacin	*S. pneumoniae*	in vitro	AUC/MIC	>30
	Drusano et al. [134]	lomefloxacin	*P. aeruginosa*	neutropenic rat	peak:MIC	>10:1
	Forrest et al. [12]	ciprofloxacin	various gram-negative organisms	human	AUC/MIC	≥250
	Ambrose et al. [19]	levofloxacin, gatifloxacin	*S. pneumoniae*	human	AUC/MIC	30–40
	Preston et al. [18]	levofloxacin	*S. pneumoniae*, *S. aureus*, *P. aeruginosa*, other gram-negative organisms	human	peak:MIC	12:1
Aminoglycosides						
	Blaser et al. [14]	netilmicin	*P. aeruginosa*	in vitro	peak:MIC	8:1
	Moore et al. [4, 5]	gentamicin, tobramycin, amikacin	various gram-negative organisms	human bacteremia	peak:MIC	>8:1
	Kashuba et al. [9, 135]	gentamicin, tobramycin, amikacin	various gram-negative organisms	human pneumonia	peak:MIC	≥10:1
Beta-lactam agents						
	Gustaffson et al. [136]	amoxicillin and cefotaxime	*Streptococcus pyogenes* and *E. coli*	in vitro	T>MIC	50–60% T>MIC
	Craig [137]	broad-spectrum cephalosporins	streptococci and *Enterobacteriaceae*	animal	T>MIC	60–70% T>MIC
			S. aureus			40–50% T>MIC
	Tam et al. [64]	cefepime	various gram-negative organisms	human pneumonia	T>MIC	100% T>4×MIC
	Schentag et al. [17]	cefmenoxime	various organisms	simulation of pneumonia	AUC/MIC	140
Glycopeptides						
	Hyatt et al. [15]	vancomycin	*S. aureus*	human	AUC/MIC	>125
	Moise et al. [41]	vancomycin	*S. aureus*	human pneumonia	AUC/MIC	>340

measured clinically. Aminoglycosides exhibit rapid, concentration-dependent killing, with an enhanced rate of bacterial kill demonstrated with increasing concentrations. Because of the potential dose-limiting nephrotoxicity associated with these agents, pharmacokinetic monitoring is routinely used to maintain aminoglycoside concentrations within a "therapeutic range". However, after decades of monitoring and myriad studies designed to assess concentration-effect relationships for both efficacy and toxicity, the optimal dosing regimen that will ensure efficacy without inducing toxicity continues to be debated. Aminoglycoside dosing was traditionally based on the results of early studies demonstrating that peak gentamicin and tobramycin concentrations of >5 μg/ml for most serious gram-negative infections and ≥8 μg/ml for gram-negative bacterial pneumonia were associated with better outcome [2, 3]. These target peak concentrations were initially created without consideration of MIC values. Subsequently, peak-concentration-to-MIC ratios of >8:1 for aminoglycosides have been associated with treatment success [4, 5].

Unfortunately, pharmacodynamic evaluation of toxicity was initially performed only rarely, and only recently has it become widely accepted that accumulation of aminoglycosides in the renal tubule, a saturable process, is an initiating factor for nephrotoxicity [6]. Since elevated trough or C_{min} concentrations have been linked to an increased risk of toxicity [7], extension of the dosing interval has been proposed to reduce the risk associated with drug accumulation. For convenience, and because it provides undetectable concentrations by the end of the dosing interval in patients with normal renal function, dosing 5–7 mg/kg every 24 h has become the convention for high-dose, extended-interval aminoglycoside dosing. The use of larger doses administered less frequently takes advantage of the concentration-dependent pharmacologic activity and minimizes the toxic characteristics of these agents. Because aminoglycosides are eliminated predominantly renally, dosage regimens require significant individualization to achieve optimal C_{max}:MIC ratios in patients with various degrees of renal function [8]. Kushuba et al. [9] documented that individualizing the aminoglycoside component of an antibiotic regimen with a C_{max}:MIC ratio of 10:1 was associated with improved clinical outcomes in patients with nosocomial pneumonia. This method provides optimal antibacterial activity but reduces the excess exposure that may be incurred when using a high, fixed, mg/kg dose in all patients.

With once-daily dosing, high peak concentrations are achieved, but aminoglycoside concentrations drop below the MIC for a protracted period of time unless renal function is impaired or MIC values are very low (0.25 μg/ml or less). While studies comparing once-daily dosing to divided dosing have rarely shown a difference in clinical outcomes, it is likely due to the fact that most studies have utilized concomitant β-lactam agents. Since these agents both contribute to the activity of the regimen, it is difficult to evaluate the impact of alternative dosing regimens of either agent alone. The postantibiotic effect (PAE), as depicted in Fig. 2, is frequently cited in order to justify the low trough concentrations often seen with once-daily aminoglycoside dosing. Aminoglycoside antibiotics demonstrate a 2- to 10-hour concentration-dependent PAE for many gram-negative organisms in animal models [10]. However, since human correlates have not been determined, the role of PAE in developing clinical dosing schemes is unknown. It is likely that a large dose of aminoglycoside provides a rapid reduction in bacterial inoculum, allowing the β-lactam agent to effectively eradicate the remaining organisms. It is not clear that aminoglycoside monotherapy with once-daily regimens, which allows a prolonged period of time below the MIC, would be similarly equally efficacious to divided dosing.

Fluoroquinolone Antibiotics

Like the aminoglycosides, the fluoroquinolone agents interrupt protein synthesis, resulting in rapid and concentration-dependent killing. Fluoroquinolones, however, do not suffer from similar dose-limiting toxicity as a consequence of accumulation and can be dosed to optimize both peak:MIC and AUC/MIC values, both of which have been linked to efficacy [11, 12, 13]. Blaser et al. [14] noted that peak concentrations of enoxacin greater than three times the MIC were associated with a >99% reduction in the initial inoculum at 4 hours; however, bacterial regrowth occurred at 24 hours unless the peak:MIC ratio exceeded 8:1. Using in vitro methods, it has been demonstrated that the estimated AUC/MIC for maximal killing with ciprofloxacin in vitro is 350 to 450 [15]. Dudley et al. [16] examined the effect of ciprofloxacin against *Escherichia coli* and *Pseudomonas aeruginosa* in an in vitro dynamic model. Complete killing of the *Escherichia coli* strain was noted after the first dose. Although an initial bactericidal effect was observed for the *Pseudomonas aeruginosa* strain, regrowth of resistant organisms occurred. A peak:MIC ratio of 150:1 was noted for the *Escherichia coli* strain, while the peak:MIC ratio for the *Pseudomonas aeruginosa* strain was <5:1. These results are consistent with clinical outcomes achieved in humans with similar exposure.

Although many clinical studies have been performed with the fluoroquinolones, very few have assessed the relevance of pharmacokinetic surrogates. Two landmark studies demonstrate the contributions of both the peak:MIC and the AUC/MIC to clinical patient outcomes. The first, by Forrest et al. [12], was designed to assess the relationship between antimicrobial exposure to ciprofloxacin and bacterial susceptibility to ciprofloxacin. The area under the inhibitory curve, or AUIC, is the nomenclature used to describe the integrated AUC above MIC versus time, a value similar to the AUC/MIC. A threshold $AUIC_{24}$ of 125 (SIT^{-1}∗24 h) was determined to be necessary for the onset of effective antibacterial action [17]. A ciprofloxacin $AUIC_{24}$ of 125 to 250 predicted slow bacterial killing, with bacterial eradication requiring about 7 days. When $AUIC_{24}$ values exceeded 250,

bacterial killing was extremely fast, with eradication averaging 1.9 days regardless of the species of bacteria [12]. In another study evaluating levofloxacin for the treatment of respiratory, skin, or urinary tract infections, clinical and microbiological outcomes were found to be optimal when the peak:MIC value was at least 12.2 [18]. This was evaluated for infections due to multiple microorganisms, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*.

The results were similar in an in vitro study evaluating the rate of kill for ciprofloxacin against strains of *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* for which the MIC of ciprofloxacin was 0.5 μg/ml. At in vitro concentrations that achieved $AUIC_{24}$ values of ≥250, optimal and similar kill rates were attained for all three organisms [15]. Thus, as the earlier clinical study had demonstrated, MIC was predictive of antibacterial activity across bacterial species when the same $AUIC_{24}$ value of 250 was achieved.

In more recent evaluations, the optimal pharmacodynamic endpoint for the fluoroquinolones has been found to vary by pathogen. Ambrose et al. [19] identified an AUC/MIC breakpoint of 33.7 against *Streptococcus pneumoniae* using free drug concentrations for levofloxacin and gatifloxacin. This lower AUC/MIC requirement of 30–40 for newer fluoroquinolones against *Streptococcus pneumoniae* is supported by numerous in vitro pharmacokinetic and animal models [20, 21].

Beta-Lactam Antibiotics

In contrast to fluoroquinolone and aminoglycoside antibiotics, β-lactam antibiotics demonstrate primarily time-dependent killing. As early as the 1940s, the effect of dose and dosing interval on bactericidal activity has been investigated. Since that time, multiple studies have supported the initial findings of Eagle et al. [1]. The aggregate time that serum concentrations remain above the MIC of the organism (T>MIC) is the pharmacokinetic surrogate parameter most frequently demonstrated to impact bactericidal activity. Little increase in bactericidal activity is seen when concentrations of β-lactam agents are increased above a point of maximal killing, approximately four times the MIC [22, 23]. This would support that the degree of bacterial killing is determined by the duration of exposure (T>MIC) rather than the magnitude of exposure above the MIC, which would be reflected in a higher C_{max}. However, there is also evidence that the magnitude of concentration obtained above the MIC may also play a role in the bactericidal activity of β-lactam antibiotics, and correlation of AUC/MIC with efficacy has also been found in various circumstances [24, 25, 26].

Numerous in vitro models and animal studies have assessed the effect of various concentration-versus-time profiles on the rate of bacterial killing of β-lactam antibiotics. Using in vitro models with varying concentrations of drug, T>MIC—expressed as percentage of the dosing interval—has been well correlated with bactericidal activity [25, 27, 28, 29]. Nishida et al. [28] evaluated the activity of three cephalosporins against *Escherichia coli* using an in vitro model. By varying drug concentration and exposure time, they demonstrated that longer exposure time at or above the MIC resulted in greater bactericidal effect up to a point of maximal killing. Maximal effect was seen at one to four times the MIC, with no further significant reduction in bacterial counts occurring at concentrations exceeding four times the MIC. Zinner et al. [29] examined simulations of four dosing regimens of cefoperazone against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* using an in vitro capillary model. Doses studied were either 2 g or 4 g and were given at differing intervals that simulated a single dose in 24 hours or two 12 hourly doses. Against *Escherichia coli* and *Klebsiella pneumoniae*, no differences in the rate of killing were demonstrated with any regimen, and all regimens provided estimated AUC/MIC values of ≥1,000. However, against the less sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa*, the concentrations reflecting smaller doses given more frequently provided a greater T>MIC value and were more effective at preventing bacterial regrowth.

Vogelman et al. [24] and White et al. [25], using a neutropenic mouse thigh model, demonstrated that T>MIC was the most important pharmacokinetic parameter related to efficacy as assessed by change in $\log_{10}$ colony-forming units (cfu) per milliliter over 24 hours. Infections caused by gram-negative bacteria required serum cefazolin concentrations continuously above the MIC to attain maximal efficacy. In contrast, when treating staphylococcal infections, while T>MIC was still the most important parameter, maximal efficacy was achieved with concentrations above the MIC for only approximately 55% of the 24-hour dosing period. Gerber et al. [30] evaluated ticarcillin as treatment of *Pseudomonas aeruginosa* infections in a granulocytopenic mouse thigh model. Using the same total daily dose of ticarcillin and thereby holding the AUC constant, they compared the effect of dosing every 3 hours with dosing every 1 hour on bacterial growth within the thigh. The study was performed over a range of concentrations of ticarcillin, and in each instance ticarcillin given every hour resulted in a greater decrease in bacterial counts than the same total dose given at 3-hour intervals. In a recent study, Onyeji et al. [31] investigated the optimal T>MIC required for ceftibuten and cefaclor in a non-neutropenic mouse intra-abdominal infection model. Cefaclor, but not ceftibuten, was shown to exhibit a dose-dependent effect against *Staphylococcus aureus* and *Klebsiella pneumoniae*. Using regimens that produced equal times above the MIC, larger doses elicited greater efficacy. With an inoculum size of $1x10^6$ cfu/ml of *Staphylococcus aureus*, maximal bactericidal activity was seen at concentrations equal to the maximum bactericidal concentration (MBC). When a larger inoculum size (2×10^8 cfu/ml) was tested, even concentrations exceeding 128 times the MIC did not achieve maximal killing. For *Klebsiella pneumoniae*, with the smaller inoculum of 5.5×10^5 cfu/ml, the maximal effect was seen at the MBC;

however, with an increase in inoculum to 5.5×10^7 cfu/ml, maximal killing was seen at 64 times the MIC. The authors concluded that, due to the inoculum effect, maximization of both dose and T>MIC may be necessary for optimal bactericidal effect.

Although few clinical trials exist that relate schedule of β-lactam antibiotic administration to clinical outcome, data derived from human studies provide support for results demonstrated using in vitro and animal models. To optimize the T>MIC, continuous infusion of β-lactam antibiotics has been investigated. Bodey et al. [32] compared carbenicillin plus intermittent cefamandole (3 g given every 6 h) to carbenicillin plus continuous infusion cefamandole (12 g/day) in febrile cancer patients. In 235 documented infections, 65% of patients receiving continuous cefamandole were cured compared to 57% of patients receiving intermittent infusions. In patients remaining profoundly granulocytopenic (i.e., absolute neutrophil count <100 cells/mm^3) the continuous infusion was significantly more effective than intermittent infusion, with a 65% cure rate compared to 21% (P=0.03) [32].

Schentag et al. [26] examined the influence of various pharmacokinetic parameters of the β-lactam cefmenoxime on length of time to bacterial eradication in patients with nosocomial pneumonia. A significant linear correlation was demonstrated between T>MIC and the time to eradication of bacteria from respiratory secretions; AUC/MIC was also found to be well correlated with microbiological response. After deriving the optimal ratio of AUC/MIC, a subset of patients was prospectively dosed to achieve this optimal value. Patients who received prospective individualized dosing to achieve a target AUC produced earlier eradication and allowed for shorter duration of treatment when compared to the group evaluated retrospectively [26].

The above studies suggest that bactericidal activity of β-lactam antibiotics is optimal when the duration of time that concentrations are above the MIC is maximized. The magnitude by which concentrations must exceed the MIC for this prolonged period remains controversial. In a recent study, Tam et al. [33] described pharmacodynamic relationships for cefepime in the treatment of patients with gram-negative infections. The results supported previous findings that the bactericidal activity of cefepime was optimal at concentrations approximately four times the MIC against various gram-negative organisms. It appears that there may be situations in which T>MIC is not the only important parameter to contribute to clinical outcome, and that some magnitude of concentration in excess of the MIC may be required to optimize therapy. With further understanding of bacterial populations, it is becoming increasingly evident that both the magnitude of serum concentration achieved and T>MIC are important to the efficacy of β-lactam antibiotics. In instances in which there was testing of very sensitive organisms or in which the investigators were using a low bacterial inoculum, concentration independence has been demonstrated and T>MIC has been identified as the significant pharmacokinetic parameter. However, in studies utilizing more resistant organisms or larger inoculum sizes, there is a demonstrated concentration-dependent effect, which is likely related to the distribution frequency of resistant subpopulations, and subsequent derepression or selection of resistant organisms during therapy.

Glycopeptide Antibiotics

While there is ample literature relating various surrogate pharmacokinetic parameters with efficacy of fluoroquinolones, β-lactam agents, and the aminoglycosides, data is lacking to adequately characterize the importance of serum concentrations and pharmacokinetic surrogates for the glycopeptide antibiotics vancomycin [34, 35, 36] and teicoplanin. In vitro studies have demonstrated that like β-lactam antibiotics, glycopeptide antibiotics demonstrate concentration-independent killing [37, 38, 39]. Peetermans et al. [38] examined concentration-effect relationships in vitro for vancomycin and teicoplanin against *Staphylococcus aureus* using a 3-hour exposure period. For each agent, concentration dependence was seen only when concentrations were at or below the MIC. Above this concentration, no further increase in killing rate was observed. Cantoni et al. [39] evaluated vancomycin for the treatment of experimental *Staphylococcus aureus* endocarditis. Time-kill studies were done using varying concentrations of vancomycin. Little concentration dependence was seen using concentrations ranging from 2 to 40 times the MIC for the organism.

As glycopeptide antibiotics have demonstrated relatively slow, concentration-independent killing and are cell-wall-active agents similar to β-lactam antibiotics, it has been presumed that the T>MIC is an important pharmacokinetic surrogate related to efficacy. Examination of the literature offered little data addressing this concept, even though time-dependent bactericidal activity for both teicoplanin and vancomycin has been suggested [40]. In fact, for vancomycin treatment of *Staphylococcus aureus* infections (MIC_{50}≈0.5 μg/ml), clinically achievable concentrations (generally with C_{min}>5 μg/ml) will most frequently attain a T>MIC of 100%. Therefore, with MIC values so low, discerning optimal dosing based on attainment of this parameter becomes futile. Data describing the relationship between AUC/MIC and outcome has more recently become available. Hyatt et al. [15] conducted a retrospective analysis of 84 patients treated in whom vancomycin was used to treat a variety of infections. Patients were further grouped based upon AUC/MIC (<125, 125–250, >250). A significant relationship was found between the vancomycin AUC/MIC and outcome. Patients with an AUC/MIC of <125 had a higher probability of failure (P=0.004). Only one patient with unsatisfactory outcome had a vancomycin trough concentration below the MIC. The fact that trough values in those patients with unsatisfactory outcomes were generally above the MIC suggests that both concentration and the T>MIC may be important pharmacokinetic surrogates for vancomycin efficacy. Additional work by Moise et al. [41]

Table 2 Pharmacokinetic variation in pathophysiologic states

Pathologic state	Physiologic change	Pharmacokinetic change	Drug classes affected	Considerations for dosing
Critical illness/ sepsis				
	↓ gastrointestinal perfusion, altered gastric emptying	↓ oral absorption	all oral antibiotics	Increased doses or i.v. antibiotics may be necessary if absorption cannot be assured.
				Monitor for efficacy and drug interactions.
	↓ serum albumin	↓ protein binding	beta-lactam agents [81]	For highly protein-bound drugs, increase monitoring for adverse effects and drug-drug interactions.
	↑ fluid volume	↑ volume of distribution	aminoglycosides [58]	Increased doses may be required to maintain optimal pharmacodynamic targets.
			beta-lactam agents [60, 61]	
	↓ renal perfusion	↓ renal clearance	beta-lactam agents [43, 44, 45, 46]	Extended intervals and/or reduced doses may be required. Increase monitoring for clinical response and adverse effects.
			fluoroquinolones [65]	
			aminoglycosides [58]	
	↓ hepatic perfusion	↓ hepatic clearance	clindamycin [48]	Dosage reduction may be advised, particularly in the setting of concurrent renal and hepatic dysfunction.
			beta-lactam agents [50]	
Burns				
	↑ renal perfusion	↑ renal clearance	aminoglycosides [71]	Maximum/increased doses or increased dosing frequency may be appropriate to maintain optimal pharmacodynamic targets.
			vancomycin [72]	
			beta-lactam agents [73]	
			fluoroquinolones [138]	
	↑ fluid volume	↑ volume of distribution	aminoglycosides [71]	Maximum/increased doses may be appropriate to maintain optimal pharmacodynamic targets.
			beta-lactam agents [73]	
Obesity				
	↑ total volume and adipose tissue	↑ volume of distribution	fluoroquinolones [78]	Individualized weight-based dosing may be appropriate to maintain optimal pharmacodynamic parameters.
			beta-lactam agents [85]	
			vancomycin [77]	

further evaluated the association between the ratio of AUC/MIC and the efficacy of vancomycin. In a study evaluating microbiological and clinical response to therapy, the mean AUC/MIC in treatment failures was found to be 306, while treatment cures averaged an AUC/MIC of 491. These authors propose that an AUC/MIC for vancomycin needs to exceed 400 to ensure optimal outcome. As gram-positive resistance continues to emerge, further analyses of optimal endpoints for glycopeptide treatment need to be conducted.

It should be noted that other classes of antimicrobial agents, though less well characterized in human clinical trials, will display killing activity that may be described by these various pharmacodynamic principles. Most data for these agents are derived from in vitro analyses, and clinical data is lacking. It is clear that no one pharmacodynamic endpoint can be applied to all classes of agents. Differing penetration characteristics of antibiotics also call into question the role of evaluating serum concentrations versus tissue concentrations at the site of infection. For agents whose high tissue concentrations contribute to efficacy, e.g., the macrolides and ketolides, relationships with serum concentrations are difficult to describe as a class effect. The reader is referred to specific references for further information regarding pharmacodynamic effects of these other classes of antibiotics.

Pharmacokinetic Variation in Pathophysiologic States

To achieve the desired pharmacodynamic targets in antimicrobial selection, clinicians must consider more than only an organism's susceptibility as reflected in the MIC. To develop individualized therapy, one must also consider patient-specific pharmacokinetic variation. Significant interpatient variability may exist in drug absorption, distribution, metabolism, and elimination that affect the ability to achieve pharmacodynamic targets at conventional doses. Alterations in absorption, protein binding, tissue perfusion, and other factors impact active drug concentrations and, therefore, potential clinical efficacy. Commonly encountered situations in which pharmacokinetics may be vastly altered and dosing individualization may be necessary include renal and hepatic dysfunction, critical illness, sepsis, burns, and obesity; each is discussed briefly below. A summary of important changes in these various disease states is included in Table 2. Numerous other conditions and physiologic states exist that may alter pharmacokinetic and pharmacodynamic response, among which are acute spinal cord injury, pregnancy, and cystic fibrosis. Additional pharmacokinetic variability should be anticipated and specific references consulted to optimize therapy when treating infections in patients with these conditions.

Renal Dysfunction

The most common reason that antibiotic doses must be adjusted is for a reduction in elimination secondary to organ dysfunction. Age-related decline in renal function accounts for an approximately 5–10% reduction in glomerular filtration per decade beyond the age of 30 [42]. Other causes of reduction in renal clearance include acute or chronic renal dysfunction frequently seen in diseases such as diabetes or heart failure. When doses are not adjusted, accumulation results in supratherapeutic concentrations, which increases the likelihood of concentration-dependent adverse effects.

Antibiotics that require adjustment for reduced renal clearance vary by class. Aminoglycosides and vancomycin are both eliminated primarily by glomerular filtration, and extensive literature is dedicated to dosing recommendations for these agents for various degrees of renal function. For aminoglycosides, nephrotoxicity has been associated with drug accumulation, so it is essential to provide appropriate adjustment to minimize the likelihood of this untoward effect. Many β-lactam antibiotics are eliminated renally, and doses must be adjusted for reduced glomerular filtration; notable exceptions are oxacillin [43], nafcillin [44], cefotetan [45], and ceftriaxone [46]. Simple equations such as those described by Cockroft and Gault [42] or Jelliffe [47] may be used to estimate a patient's creatinine clearance based on the value of the serum creatinine and factors such as age and weight. Dosage adjustments that retain the optimal pharmacodynamics necessary for antibacterial activity should be considered. For example, with aminoglycosides and fluoroquinolones, it is reasonable to administer the usual dose and extend the dosing interval to maintain adequate peak:MIC ratios. For β-lactam agents, a reduction in dose while maintaining an interval that ensures adequate T>MIC may be more desirable. It must be noted that in patients with reduced renal function, significant pharmacokinetic variability may make optimal dosing difficult. References specific to the dosing of antibiotics in patients with renal impairment should be consulted when treating elderly or renally impaired patients. The most extreme extension of this is end-stage renal disease, when essentially no renal elimination of an agent occurs and extensive dose reduction is required to prevent toxicity. Similarly, specific recommendations are available for dosing antimicrobial agents in patients on hemodialysis or peritoneal dialysis.

Hepatic Impairment

While estimations of renal clearance are relatively simple and well characterized using the above equations, estimation of elimination of drugs via the metabolic route is more difficult. In patients with hepatic disease, clearance of many drugs may be impaired; however, the magnitude of the impairment in metabolic function has not been quantified by any single parameter. Adjustment in dosing schedule should be considered for drugs that are

substantially cleared by the hepatobiliary system, such as clindamycin [48] and antituberculous agents [49]. Moreover, when an agent is cleared by both hepatic and renal routes, a reduction in nonrenal clearance may be partially compensated for by an increase in renal elimination. Metabolic clearance may be further reduced in end-stage hepatic cirrhosis. The greatest risk of excessive accumulation exists in patients with both hepatic and renal impairment. When renal clearance is reduced in the presence of concomitant liver dysfunction and ascites, elimination half-life of many antibiotics is prolonged, potentially increasing the risk of adverse effects [50]. In this situation, pharmacokinetic patterns are highly variable, and specific dosing recommendations are difficult to predict.

Critical Illness/Sepsis

Critically ill patients may have pathophysiologic conditions that alter drug absorption, distribution, and clearance. In general, altered distribution and elimination have been observed with a number of antibiotic classes, requiring special consideration of drug selection and dosing in these patients [51, 52].

Gastrointestinal absorption may be impaired, tissue perfusion reduced, volume of distribution elevated, and clearance altered, depending on the degree of renal and hepatic (dys)function [53]. Specifically, in sepsis and septic shock, tissue perfusion is reduced to muscles, skin, and the gastrointestinal tract, and absorption from sites with impaired blood flow is reduced. A decrease in plasma albumin is seen in critical illness, potentially leading to an increase in the free fraction of drug that is ordinarily highly bound to this protein [54]. An increase in the volume of distribution for drugs may occur, resulting from a combination of fluid resuscitation, renal failure, and cardiac compromise and vascular congestion [55]. For antimicrobial agents extensively metabolized by the liver, metabolism will be affected both by changes in liver perfusion and protein binding. Renal failure has been reported with up to a 23% incidence in ICU patients [56]. Many antimicrobial agents depend on renal elimination, and the elimination half-life for these drugs may be prolonged. Because such variability has been demonstrated in critically ill patients, target drug monitoring is often appropriate, when available, to assure the desired pharmacodynamic targets are achieved.

The impact of critical illness on pharmacokinetics has been examined for various classes of antibacterial agents. For the aminoglycosides, the volume of distribution in critically ill patients may be significantly increased (up to 0.43 l/kg), with the elimination rate unchanged, compared with that in non-critically ill patients with comparable renal function [57, 58]. Higher doses than would be calculated from traditional equations may be needed in these patients to provide therapeutic peak concentrations [58]. Furthermore, population-based dosing nomograms that are sometimes used to calculate aminoglycoside doses may be inaccurate in this population [57]. As the patients recover from critical illness, volume of distribution has been shown to normalize; consequently, concentrations may need to be monitored and dosing may need to be adjusted again to account for these changes during the recovery period [59].

The pathophysiologic changes present in critically ill patients results in unpredictable pharmacokinetics of β-lactam antibiotics. Impaired renal perfusion and hepatic metabolism can lead to drug accumulation and higher risk of toxicity. Conversely, fluid resuscitation and retention can increase volume of distribution and result in lower serum concentrations of antibiotics. In an animal model of trauma, aztreonam clearance was initially decreased, followed by a sharp increase of almost 50% of baseline, while volume of distribution was decreased throughout the first week after injury [60]. Volume of distribution of both aztreonam and imipenem-cilastatin were significantly increased in a study of trauma patients with pneumonia; however, clearance was significantly prolonged only for aztreonam [61]. This variation in pharmacokinetics suggests that perhaps adjustments of both dose and interval of β-lactam antibiotics need to be individually considered in critically ill patients.

Intermittent boluses of β-lactam agents in ICU patients can result in variable plasma concentrations, with unpredictable T>MIC [62]. Continuous infusion of ceftazidime has been shown to produce more consistent concentrations in critically ill patients [62] and was found to be more efficacious in killing *Pseudomonas aeruginosa* in an in vitro pharmacokinetic model [63]. However, at many institutions, continuous infusion is not a routine method of antibiotic administration. In the ICU, resistance of infecting organisms may be observed more frequently. Therefore, optimal T>MIC may not be achieved with traditional dosing. For organisms that demonstrate less than full susceptibility, regimens that maximize dosing should be considered, and combination therapy may be needed to achieve optimal pharmacodynamic targets [64].

The fluoroquinolones are commonly used to treat a range of infections in ICU patients. As with most other antibiotic classes, administration of fluids and fluid retention can lead to a large volume of distribution of fluoroquinolones, resulting in lower-than-expected serum concentrations; however, the clinical significance of this is unknown. The clearance of renally eliminated fluoroquinolones may be impaired in patients with reduced renal perfusion and can be altered, to varying extents, with renal replacement therapy [65]. Oral ciprofloxacin, levofloxacin, and gatifloxacin have demonstrated adequate absorption in critically ill patients in the absence of pathophysiologic conditions that may alter gastrointestinal absorption [66, 67]; however, absorption of ciprofloxacin is significantly reduced by enteral feeding (72%) [68] and cationic antacids (50%) [69]. Concomitant administration of agents that impair absorption should be considered before oral fluoroquinolones are recommended; however, administration of oral antibiotics with reliable bioavail-

ability should be encouraged when data are available to support their equivalence to intravenous preparations.

Burns

Patients with thermal injury will undergo physiologic changes that affect the pharmacokinetics of antimicrobial agents during the time following the initial insult. The first 48 hours after thermal injury is marked by an increase in capillary permeability and hypovolemia. Expansion in extravascular volume and fluid resuscitation may lead to an expanded volume of distribution for many agents. This acute phase is then followed by a hyperdynamic phase characterized by the release of vasoactive mediators, increased cardiac output (with resulting increased glomerular filtration rate), plasma protein loss, and fluid shifts. The duration of the hyperdynamic phase may vary with the extent of the injury and can extend through up to 30 days after injury; however, hypermetabolism is most frequently described to persist for 7–10 days [70]. The effect on the pharmacokinetics of antibiotics and the resulting pharmacodynamics can be highly variable.

The alteration in pharmacokinetics of aminoglycosides due to burn injury was first described in 1976 [71]. The study reported doses of 7.4 mg/kg/day required to maintain therapeutic concentrations of gentamicin, much higher than the 3–5 mg/kg/day used in non-burn patients. This increased dose has been attributed to both an increase in the volume of distribution (due to fluid resuscitation and fluid shifts) and an increase in glomerular filtration and clearance of the aminoglycoside. Similar kinetic studies have been repeated, each demonstrating the need for higher aminoglycoside doses, but overall there was great variability in both the range of dose needed and factors predicting the increase. Over time, with resolution of the hypermetabolic state and with normalization in fluid status, pharmacokinetics similar to those of non-burn patients may be approximated [70].

Similarly, burn patients may require higher-than-usual vancomycin doses. In one study, doses required ranged from 28.9 to 42.7 mg/kg/day, compared to 30 mg/kg/day for non-burn patients [72]. Vancomycin clearance was elevated in burn patients compared to non-burn controls, and was correlated with elevated creatinine clearance (r^2=0.77). Because of this enhanced clearance, burn patients require higher or more frequent doses to achieve concentrations similar to those produced with normal dosing in non-burn patients.

Studies of β-lactam agents and fluoroquinolones in burn patients have also demonstrated variable pharmacokinetic profiles. Most frequently described are larger volumes of distribution and faster elimination rates, suggesting that these patients would benefit from larger doses than those normally required. In a study of 11 burn patients, pharmacokinetic parameters of imipenem-cilastatin were found to be no different than those in healthy volunteers, nor was any correlation found between burn size and imipenem-cilastatin clearance; however, wide interpatient variability was observed [73]. Individualized dosing of many antimicrobial agents should be recommended in burn patients to ensure that the pharmacokinetics and pharmacodynamics are being taken into consideration.

Obesity

Pathophysiologic changes due to obesity are demonstrated most by the increased volume of adipose tissue and hence volume of distribution of drugs. Changes may appear in renal elimination as well as in hepatic metabolism, particularly if fatty liver deposits are present. Creatinine clearance of obese patients may need to be calculated using an adjusted body weight (ABW) that accounts for a percentage of excess body weight [ABW=IBW (ideal body weight) + correction factor × (TBW (total body weight)−IBW)] [74]. Likewise, an adjusted body weight (with a correction factor of 0.4) is recommended to determine aminoglycoside dose in order to adjust for an increase in volume of distribution [75]. Elimination rates have not been reported to change, so dosing intervals should not require adjustment [75, 76]. In the same way, the vancomycin volume of distribution increases by up to 49% in obese patients compared to non-obese patients; in addition, clearance may increase by 2.5 times [77]. Most studies of vancomycin pharmacokinetics recommend that doses be based on 15–20 mg/kg total body weight for obese individuals. Data is conflicting with regard to whether the dosing interval should be shortened. A single trough concentration may be of use in these patients to assure adequate serum concentrations. There are limited studies of the pharmacokinetics of other antimicrobial agents in obesity. Distribution of each class of antibiotic into adipose tissue varies. While fluoroquinolones demonstrate penetration into most body tissues, they have been shown to distribute only partially into adipose tissue [78, 79]. Beta-lactam antibiotics are hydrophilic and distribute readily into total body water, while their distribution into adipose tissue is limited [78]. Individualized dosing based on a percentage of excess body weight reflective of adipose distribution may be more appropriate for fluoroquinolones and β-lactam agents in morbidly obese patients.

Special Considerations in Optimizing Selection of Antimicrobial Agents

Tissue Penetration

For antimicrobial agents to be effective, they must reach the site of infection, which may be within an isolated tissue or organ system. Tissue penetration of antibiotics is governed by passive diffusion, transport mechanisms, lipid solubility, and protein binding. In experimental settings, antibiotic concentrations have been measured in a wide range of fluids and tissues, but in clinical practice our

ability to measure these are limited to blood/serum, urine, and possibly CSF. Serum concentrations do not always correlate with concentrations at the site of infection, and methodological problems with analysis limit the applicability of experimentally derived "tissue concentrations" [80]. However, serum concentrations probably provide a better estimation of the tissue concentration of antibiotics with low protein binding (quinolones, aminoglycosides) than of those with higher protein and tissue binding (some β-lactam agents) [81]. Consideration of tissue concentration is particularly important for infections localized in body sites affected by barriers to drug transport or avascular regions. Some examples described below include meningitis and osteomyelitis. Intracellular infections represent a special problem because the organism is contained within host cells, which are not accessible to many available antimicrobial agents.

Meningitis

The major determinant of CSF penetration is lipid solubility. Nonionized, lipophilic compounds (such as metronidazole and rifampin) penetrate the blood-brain barrier most readily. Beta-lactam agents are weak acids, ionized at physiologic pH, and therefore have limited penetration. Aminoglycosides and first- and second-generation cephalosporins (such as cefazolin and cefuroxime) have unreliable CSF penetration, limiting their applicability in treating meningitis. Inflammation of the meninges increases antibiotic penetration to the extent that vancomycin, the penicillins, and third-generation cephalosporins can be useful for meningitis treatment [82]. Studies of β-lactam agents in experimental pneumococcal meningitis have demonstrated that maximal killing is observed when the CSF concentration is above the minimum bactericidal concentration (MBC), another measure of antibacterial killing activity, for 75–100% of the dosing interval [83, 84]. Third-generation cephalosporins have been evaluated in meningitis caused by gram-negative bacteria. Ceftazidime CSF concentrations after administration of 2 g and 3 g doses varied, with mean concentrations above the MICs for most *Pseudomonas aeruginosa* strains [85]. Concentrations achieved in CSF in patients without meningeal inflammation were lower [86], suggesting that higher daily doses of up to 12 g/day may be required to maintain adequate ceftazidime CSF concentrations in patients with gram-negative infections of the central nervous system (CNS) without meningitis [87]. Similarly, CSF concentrations have been measured in patients with external ventriculostomies who were treated with cefepime for nosocomial pneumonia. CNS penetration was reported to be variable (4–34% of the serum concentration), and was comparable to the penetration of other third-generation cephalosporins [88].

High-dose fluoroquinolones are another potential treatment option for gram-negative meningitis. After intravenous doses of ciprofloxacin 400 mg every 8 hours, CSF levels reached only 0.9 mg/l, while peak serum levels were 10.3 mg/l [89]. In an animal model of gatifloxacin in the treatment of meningitis, the AUC/MBC ratio correlated to a greater extent with efficacy (coefficient of determination, 0.74), while peak/MBC and T>MBC showed correlation as well (0.69 and 0.68, respectively) [90]. Because of the serious nature of the infection and the difficulty in achieving adequate CSF concentrations of antibiotics, combination therapy is almost always recommended for the treatment of gram-negative meningitis.

Osteomyelitis

Antibiotics used to treat osteomyelitis must be used at maximum doses (as appropriate for renal function) in attempts to assure that adequate concentrations are reached within the infected bone. Experimental measurement of bone concentrations is complicated by methodological difficulties and interpatient variability; however, pharmacokinetic data is available for several antimicrobial classes. Clindamycin bone concentrations have been reported to reach 40–50% of serum levels, well above the MIC of methicillin-susceptible staphylococci [91, 92]. In 14 patients with osteomyelitis or hip arthroplasty, vancomycin concentrations varied but were greater than the MIC for methicillin-resistant staphylococci in the majority of bone samples [93]. Quinolone antibiotics have been used in the treatment of gram-negative osteomyelitis. Ciprofloxacin bone concentrations were reported to reach 1 mg/kg of tissue after a single 750 mg dose in 10 patients with osteomyelitis, again, well above the MIC for many gram-positive and gram-negative organisms [94]. The pharmacodynamic relationship of bone concentration to MIC and patient outcomes has not been determined.

Intracellular Penetration

Antimicrobial susceptibilities are determined under extracellular conditions and may not completely account for intracellular processes. Some organisms are able to invade leukocytes and survive inside phagosomes, lysosomes, or the cytosol. These intracellular organisms are important in a variety of infections, including respiratory (*Legionella* spp., *Chlamydia* spp., *Mycobacterium* spp.), gastrointestinal (*Salmonella*, *Shigella*), and other infections (*Listeria* spp., *Neisseria gonorrheae*). Intracellular penetration of antimicrobial agents is determined primarily by pH, since acidic drugs are excluded intracellularly and basic drugs penetrate effectively. For example, the β-lactam agents and aminoglycosides exhibit little to no intracellular penetration, whereas the fluoroquinolones and, to a greater extent, the macrolides penetrate leukocytes well [95]. Because polymorphonuclear leukocytes (PMNs) are attracted to sites of infection, the phenomenon of intracellular accumulation may help to facilitate drug delivery to target sites. Extrusion from carrier cells at the target site again depends on pH and efflux mechanisms. Azithromycin exhibits prolonged retention within cells

with slow antibiotic efflux, including neutrophils. These conditions are very favorable for delivery of azithromycin to sites of infection [96].

Combination Therapy

Combination therapy is commonly employed for empiric therapy when the infectious agent is not known, but it may also be utilized after the pathogen is identified. More than one antibiotic may be necessary when optimal pharmacodynamic targets are not achieved by one drug or when difficult-to-treat pathogens are involved. Using two agents with mechanisms directed at different bacterial sites of action, it is frequently possible to achieve greater bactericidal activity with the two agents together than with either agent alone. This phenomenon is known as synergy. Antibiotics are said to have additive effects if the combination of the two agents does not result in any enhancement or impairment of the effect expected from the sum of each agent alone [97]. Not every antibiotic combination results in positive effects. When an antibiotic combination results in a worsening of the effect predicted from the sum of each agent alone, the combination is referred to as antagonistic. It should be noted that, according to this strict definition, antagonism may be present, but the activity of the combination may still be greater than the activity of either agent alone, as long as it is less than the predicted effect of the combination. One example of antimicrobial antagonism may be illustrated by the use of a bacteriostatic agent in combination with a bactericidal agent. Bactericidal agents such as β-lactam agents rely on actively growing organisms to result in cell death. When a bacteriostatic agent, such as tetracycline, is used in combination with a β-lactam agent, the result could potentially impair the action of β-lactam agent. It is also possible for the presence of one antibiotic to induce resistance to another; e.g., some β-lactam agents promote the production of β-lactamases active against another agent.

Sulfamethoxazole plus trimethoprim is an example of two agents combined into one drug product that produces a synergistic effect by acting at separate reactions of the folate metabolic pathway [98]. Quinupristin-dalfopristin is another agent used in the treatment of resistant gram-positive infections that takes advantage of synergy. It is believed that quinupristin binds to a unique site on the 50 s ribosome that facilitates the binding of dalfopristin to a separate ribosomal target site. These drugs then act together to interrupt protein synthesis [99]. Combinations of antibiotics such as these are marketed as multi-ingredient drug products. Other combination agents include those formed by the addition of a β-lactamase inhibitor to a β-lactam agent to improve the activity against β-lactamase-producing organisms. Examples of this type of combination available commercially as multi-ingredient products include amoxicillin-clavulanic acid, ticarcillin-clavulanic acid, ampicillin-sulbactam, and piperacillin-tazobactam [100].

There are many examples of infections that are optimally treated with a combination of antibiotics. Single-agent therapy has proved to be inferior for the treatment of enterococcal endocarditis. This infection is characteristically difficult to treat because of the high inoculum of slow-growing organisms in the vegetation. Usually, a cell-wall-active agent (ampicillin, penicillin) is used in combination with an aminoglycoside or other protein synthesis inhibitor [101]. Each agent alone would be expected to have a bacteriostatic effect against enterococci. However, the cell-wall-active agent enhances the uptake of the aminoglycoside into the cell, causing a bactericidal effect against the enterococci [102]. More recently, there has been investigation into the use of two cell-wall-active agents for the treatment of enterococcal endocarditis. Ampicillin and ceftriaxone target different penicillin-binding proteins. The addition of ceftriaxone reduced the MIC of ampicillin for enterococci two- to eightfold [103]. The practice of using dual β-lactam therapy for endocarditis is not routine.

Serious pseudomonal infection is another example of infection for which combination therapy is frequently recommended. Combination therapy (with an antipseudomonal penicillin plus an aminoglycoside) has been shown to be beneficial in the treatment of *Pseudomonas aeruginosa* bacteremia [104]. In a prospective observation of 200 patients with *Pseudomonas aeruginosa* infection, those receiving monotherapy had a 47% mortality rate, whereas those receiving combination therapy with a β-lactam agent and an aminoglycoside had a 27% mortality rate (P=0.02). In a smaller randomized trial of granulocytopenic patients with gram-negative bacteremia (predominantly *Pseudomonas aeruginosa*), ceftazidime plus 9 days of amikacin was compared to a short course (3 days) of amikacin. The longer duration of combination therapy resulted in a higher response rate (81% vs. 48%, P=0.002) [105].

Combination therapy with a β-lactam agent and a protein synthesis inhibitor has not produced a mortality benefit in all studies. In a retrospective review of 57 patients with *Pseudomonas aeruginosa* bacteremia, combination therapy failed to result in lower mortality than appropriate (predominantly β-lactam agent) monotherapy (13% vs. 14%) [106]. Similarly, in a review of 245 cases of *Pseudomonas aeruginosa* bacteremia in patients with cancer, no mortality benefit was demonstrated [107]. Combination therapy may be beneficial if for no other reason than to prevent the development of resistance during therapy of gram-negative bacteremia, including that due to *Pseudomonas aeruginosa*. A review of 173 studies evaluated the incidence of treatment-emergent resistance, reporting that resistance was more likely to develop during monotherapy with an aminoglycoside or a penicillin and was less likely to develop during combination therapy [108]. It should also be noted that for many of the studies in which combinations were compared to monotherapy, the achievement of pharmacodynamic targets were not addressed. It is possible that monotherapy for susceptible organisms may result in clinical efficacy if the appropriate

pharmacodynamic target is reached. In cases in which monotherapy cannot achieve the pharmacodynamic endpoint, e.g., in therapy of infections caused by more resistant strains, combination therapy may be required. The decision to use monotherapy versus combination therapy should be based on available clinical data combined with the ability to attain optimal pharmacodynamic targets with each strategy.

Safety Considerations in Antimicrobial Therapy

Lastly, when selecting an antimicrobial regimen, one must consider the potential untoward effects that may result from the use of a given regimen. Adverse effects of medications range from transient laboratory abnormalities to life-threatening hypersensitivity. These side effects can limit the choice of antimicrobial agents used and/or the doses that may be tolerated. The relative risk of adverse effects and the risk-to-benefit ratio of such effects must be considered in individual patients. For example, elderly patients are often at higher risk of adverse effects of medications and of drug-drug interactions [109]. As discussed in previous sections, due to age-related decline in renal function, elderly patients often require lower daily doses of many renally eliminated antimicrobial agents [110].

Mechanisms of Adverse Effects of Antimicrobial Agents

Optimal selection of antimicrobial therapy requires an understanding of not only the mechanism of action, but also the mechanism of toxicity.

Allergy/Hypersensitivity

Allergic reactions are reported to occur in 1–10% of patients receiving penicillin. Cutaneous reactions are most common; however, anaphylaxis is estimated to occur in 1–5 patients per 10,000 treated. The potential for cross-allergenicity among β-lactam agents precludes the use of cephalosporins or carbapenems in patients with a history of anaphylaxis to penicillins; however, monobactams such as aztreonam can be used safely in penicillin-allergic patients [111]. Penicillin-induced hemolytic anemia is a rare immunologic reaction resulting from drug binding to erythrocytes. Positive Coombs tests develop in approximately 3% of patients receiving large doses of penicillin; however, only a small percentage of these patients develop hemolytic anemia [112]. Allergy to sulfonamide antibiotics is also common, responsible for rashes in an estimated 3.7% of patients receiving therapy. The cutaneous reactions associated with sulfa allergy can range from a mild rash to the less common, life-threatening Stevens-Johnson syndrome [113]. Multiple desensitization protocols are available for both sulfonamides and β-lactam agents when use of these agents is deemed a medical necessity and no other acceptable alternative agent exists.

Drug Interactions

Like adverse effects, drug interactions associated with medications range in incidence and severity, and their ability to limit therapeutic choices needs to be considered in individual patients. There are several mechanisms of drug-drug interactions that are important for antimicrobial drugs.

1. Alteration in Hepatic Metabolism

Erythromycin is a strong inhibitor of cytochrome P_{450} 3A isoenzymes. It has been reported to increase levels of medications metabolized by these enzymes, including theophylline, carbamazepine, cyclosporine, tacrolimus, warfarin, digoxin, lovastatin, triazolam, and disopyramide, among others. Excessive and potentially toxic concentrations of the affected agent may result.

Rifampin is a strong inducer of the cytochrome P_{450} 3A subfamily of isoenzymes and can decrease concentrations of warfarin, cyclosporine, glucocorticoids, fluconazole, ketoconazole or itraconazole, theophylline, quinidine sulfate, digitoxin or digoxin, verapamil hydrochloride, HIV protease inhibitors, zidovudine, delavirdine mesylate, nifedipine, and midazolam. Subtherapeutic concentrations of the affected agent may result.

2. Alteration of Intestinal Flora

Rifampin, tetracycline, and penicillins are all reported to reduce the effectiveness of oral contraceptives in women, leading to potential contraceptive failure. Because antibiotics may alter intestinal flora, this, in turn, alters the enterohepatic circulation of contraceptives [114]. It is likely that all antibiotics may have some effect on this process. Alternative contraception should be recommended to all women of childbearing ages receiving oral contraceptives during a course of antibiotics.

3. Impaired Absorption

The bioavailability of orally administered fluoroquinolones is reduced by up to 90% when administered concomitantly with divalent cations, including antacids containing calcium or magnesium, iron preparations, sucralfate, and dairy products [115]. Erythromycin has a prokinetic effect on gastric motility and may reduce oral absorption of some medications.

Direct Toxicity

Direct toxic effects of antibiotics on a number of organ systems are reported in the literature to varying degrees and differ immensely between individual agents. Consideration of underlying conditions and comorbidities is essential when considering the impact of any potential toxicity.

Cardiac Effects

Prolongation of the QT_c interval has been reported with several antibiotic classes, most notably the fluoroquinolones and macrolides. QT_c prolongation can increase the risk of torsades-de-pointes, a potentially fatal polymorphic ventricular arrhythmia that can lead to ventricular fibrillation. Pharmacokinetic (via receptor interactions) and pharmacodynamic interactions (frequently through inhibition of the cytochrome P_{450} isoenzyme) can be responsible for the prolongation of the QT_c interval [116]. In a recent review of a cohort of 1.1 million patients across the USA, prescriptions for medications implicated in QT_c prolongation were evaluated. The top three potentially QT_c-prolonging drugs prescribed in the USA were antibiotics, with clarithromycin, erythromycin, and levofloxacin accounting for over half of all patients filing claims for QT_c-prolonging drugs (26.3, 20.7, and 13.8%, respectively) [117]. Use of these agents in patients with preexisting cardiac conduction abnormalities or in patients taking anti-arrhythmic agents or other agents with known QT-prolonging effects should be avoided when possible. A careful risk/benefit assessment is needed if these agents are to be used in an at-risk population.

Renal Effects

Nephrotoxicity of the aminoglycosides is well described in the literature. With repeated doses, aminoglycosides accumulate in the proximal tubules, leading to a nonoliguric renal failure of varying severity after several days of treatment [118]. Vancomycin monotherapy infrequently results in adverse renal effects; however, the addition of an aminoglycoside has been shown to lead to a synergistic nephrotoxicity [119]. Trimethoprim-sulfamethoxazole has been associated with hyperkalemia, as trimethoprim reduces renal potassium excretion in much the same mechanism as a potassium-sparing diuretic [120]. Careful monitoring of renal function and electrolytes should be performed while patients are taking any potentially nephrotoxic agents.

Other Effects

A wide range of other toxicities of antimicrobial agents has been described. Myelosuppression has been reported with the use of many antimicrobial agents, including ganciclovir [121], chloramphenicol [122], trimethoprim-sulfamethoxazole, and linezolid [123]. Aminoglycoside ototoxicity has been attributed to free radical formation and damage to the 8th cranial nerve and organ of Corti [124]. Hepatotoxicity has been reported after administration of antimycobacterial agents [125] and, rarely, oxacillin [126]. Phototoxic and photoallergic reactions have been reported with many classes of antimicrobial agents, most commonly sulfonamides, tetracyclines, and quinolones [127]. A working knowledge of the relative incidence of adverse effects of common antimicrobial agents is fundamental for the appropriate use of these agents.

Superinfection

The use of antimicrobial agents changes the composition of the body's normal flora. Treatment with any of a number of antimicrobial agents has been shown to significantly lead to overgrowth of *Candida* in the gastrointestinal tract [128]. Further, antibiotic use has repeatedly been identified as a risk factor for superficial infection such as vaginal candidiasis as well as the development more severe bloodstream infections with *Candida* spp. in hospitalized patients [129]. Antibiotic-associated diarrhea occurs in 5–25% of patients receiving antibiotics, depending on the agent used. Antimicrobial agents most commonly associated with diarrhea are clindamycin and the cephalosporins [130]. Many cases of antibiotic-associated diarrhea can be attributed to the overgrowth of *Clostridium difficile* in the gastrointestinal tract. Clinicians and patients should be aware of the changes that may be expected as a result of alterations in microorganism flora secondary to antibiotic use and avoid prolonged courses of antibiotics when unnecessary.

Other Considerations

The goal of antimicrobial therapy is to cure the infection while minimizing toxicity to the patient and avoiding adverse or antagonistic interactions with concomitant medications. Antibiotic selection and dosing must take into account numerous factors of the host, the infecting pathogen, and the antibiotic to provide the most potent and effective regimen that is relatively nontoxic to the patient. This should be done with the smallest effective dose of drug and for the shortest duration necessary to provide a positive outcome. While a review of appropriate duration of therapy for infection is beyond the scope of this article, the shortest course of therapy that is effective should be used. There are numerous investigations reporting the benefits of short courses of therapy on the subsequent development of resistance and superinfection [131, 132].

In the era of drug resistance, it should be noted that unnecessary exposure to excessively long courses of antimicrobial agents leads to an increased risk of drug resistance. The avoidance of unnecessary therapy also results in a reduction in the cost of therapy, another topic

beyond the scope of this review. Notably, however, the use of pharmacologic principles can potentially help avoid the development of resistance in certain infections. An AUC/MIC >100 for fluoroquinolone antibiotics has been associated with a decrease in the emergence of resistance of gram-negative bacilli. Similarly, combination therapy with a β-lactam agent plus a protein synthesis inhibitor prevented the emergence of resistance to gram-negative bacilli, including *Pseudomonas aeruginosa* [133]. While the development of future resistance is not the primary focus of antimicrobial therapy in an individual patient, these concepts need to be considered, since the use of these agents may ultimately have future public health implications.

Conclusions

This review outlines some of the many factors a clinician must consider when selecting an antimicrobial dosing regimen for the treatment of infection. Integration of the principles of antimicrobial pharmacology and the pharmacokinetic parameters in an individual patient provides the most comprehensive assessment of the interactions between pathogen, host, and antibiotic. For each class of agent, appreciation of the different mechanisms to maximize bacterial killing will allow for optimal clinical efficacy and reduction in risk of development of resistance while avoiding excessive exposure and minimizing risk of toxicity.

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