

EMPLOYING PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES TO OPTIMIZE ANTIMICROBIAL TREATMENT IN THE FACE OF EMERGING RESISTANCE

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ABSTRACT

Antimicrobial efficacy *in vivo* is not exclusively defined by the activity of an antibiotic as determined in the *in vitro* susceptibility test. Knowledge of the pharmacokinetics and pharmacodynamics of antimicrobials and all phenomena occurring between antimicrobial agents and microorganisms is imperative. The pharmacodynamic (PD) parameters most often used in studies of antibiotic effect include the following relationships: the maximum free concentration (fC_{max}) to minimum inhibitory concentration (MIC) ratio, the free area under the curve ($fAUC/MIC$) ratio and the duration of time the free concentration exceeds the MIC ($fT>MIC$). Utilization of known pharmacokinetic/ pharmacodynamic surrogate relationships should help to optimize treatment outcome, especially in the face of emerging resistance among Gram-positive and Gram-negative bacteria. Clinical studies in the field of antibacterial PD are still relatively scarce, and much information is needed to enable relevant dosing strategies for all types of antibiotics against all common infections and microorganisms. In this review, the distinctive patterns of antimicrobial activity based on PD parameters are discussed. Various antibiotics and bacterial pathogens can be used as models to demonstrate the utility of PD parameters in predicting the *in vivo* efficacy of antimicrobial therapy. And finally, the use of computer modeling with Monte Carlo population simulations can further enhance the predictability of antimicrobial efficacy when using PD parameters.

Keywords: antibiotic, bacteria, pharmacodynamics, resistance

INTRODUCTION

Since the availability of antimicrobial chemotherapy, scientists and clinicians have sought and debated the most appropriate method to administer antibiotics with the purpose of optimizing the killing of microorganisms, while minimizing toxicity to the patient. The discipline of studying this interaction between antibiotics and their effects on pathogens is referred to antimicrobial pharmacodynamics (19). Some of the earliest documentation of antimicrobial pharmacodynamics dates back to studies with penicillin, where it was noted that maintaining concentrations via the use of continuous infusion improved the bactericidal activity compared with a bolus or 'discontinuous' dosing regimen (22). Today, these concepts are applied to

currently available antibiotics and are a critical part of the development process for all new antimicrobial agents (14). During development, *in vitro*, *in vivo* animal, and human pharmacodynamic studies are employed to support dosage selection and for determination of susceptibility breakpoints (21). Unfortunately, the call for new antimicrobial agents with novel mechanisms of action and activity against certain multidrug resistant bacteria has been largely unmet by the pharmaceutical industry. As a result, pharmacodynamic study designs can be utilized to optimize the dosage regimens of already clinically available antibiotics and, in essence, "make good drugs better".

Increasing antimicrobial resistance within both Gram-positive and Gram-negative bacteria has further prompted a reevaluation of the selection of antimicrobial dosing regimens in terms of

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their pharmacokinetic and pharmacodynamic properties. In this review article, we summarize contemporary resistance data among the most common clinically relevant pathogens in Latin America, review pharmacodynamic concepts for currently available antimicrobials, and discuss various methods to optimize pharmacodynamics that may aid the reader in combating the resistance trends he or she face in clinical practice.

Gram-Positive Resistance

Among Gram-positive organisms, resistance within *Staphylococcus aureus* and coagulase negative staphylococci is most concerning. Methicillin resistance is the most clinically observed phenotype, and is also common worldwide. Rates of methicillin resistant *S. aureus* (MRSA) in South America are similar or slightly lower than North America, Europe, and Asia. Data from the SENTRY Antimicrobial Surveillance Program conducted in Latin America during 2000 and 2001 found 38.6% of *S. aureus* and 78.1% of coagulase negative staphylococci to be methicillin resistant (28). However, culture source is an important consideration as an earlier assessment from the same group found 46.2% MRSA among respiratory isolates between 1997 and 2000 (29). MRSA rates, obviously, can also differ from region to region and among institutions; rates were as high as 63% in some hospitals in Columbia (2). More recently, MRSA strains that are still susceptible to non- β -lactam antibiotics such as tetracyclines and trimethoprim-sulfamethoxazole, have been isolated with increasing frequency in the hospitalized population (18). These stains are similar to what is currently referred to as “community-acquired MRSA” in the United States, as they all produce a type IV staphylococcal cassette chromosome (SCC) *mec* gene (32).

Although vancomycin has been considered the antibiotic of choice for most MRSA infections, overuse of this compound has prompted development of vancomycin or glycopeptide intermediate resistant *S. aureus* (VISA or GISA) on many continents (Asia, Europe, North America), and the development of full vancomycin resistance (VRSA) in isolated cases in the United States (13,48). The prevalence of these resistance phenotypes in Latin America is not currently well elucidated. Fortunately, antibiotics from other classes, such as linezolid, daptomycin, and tigecycline, are now available that have activity against MRSA, GISA, and VRSA, thereby providing treatment options for these resistant pathogens.

Increasing vancomycin use has also encouraged the development of vancomycin resistance among *Enterococcus* species, particularly within *E. faecium*. In Latin American countries, *E. faecalis* is significantly more common than the *faecium* species (ratio of 17:1 compared with 3:1 to 5:1 in other parts of the world); furthermore, *E. faecalis* is rarely associated with vancomycin resistance.⁶¹ As a result, the overall prevalence of glycopeptide resistance in Latin America was only 4% during the 1997-2000 SENTRY Antimicrobial Surveillance Program.

More recent data from separate surveillance studies have observed vancomycin resistance rates in the range of 7% to 12% among all enterococci species globally (17,68). While South American countries participated in these studies, the reports did not differentiate resistance rates by country or continent.

Streptococcus pneumoniae is a common cause of community-acquired infections in adults and pediatrics, most notably pneumonia, meningitis, and upper respiratory tract infections. Resistance to penicillin is the hallmark epidemiological measurement. In Latin American countries, penicillin non-susceptibility was approximately 30% during the 1997-2001 SENTRY study.¹² However, high level penicillin resistance (MIC ≥ 2 μ g/ml) was only 11.9%. Macrolide resistance (i.e., erythromycin) was also approximately 13% during that same time period; those isolates that displayed high-level resistance to penicillin were more likely to be non-susceptible to macrolides and trimethoprim-sulfamethoxazole. Subsequent years (up to 2003) from the SENTRY studies have demonstrated no increases in penicillin non-susceptibility or high-level resistance in these countries (33). Similar observations were seen in other surveillance studies (11,56). Fluoroquinolone resistance, which has been increasing in Asia and Canada, remains less than 0.5% in Latin America. Nevertheless, emerging reports globally have indicated that as many of 29.9% of *Streptococcus pneumoniae* (including those that are fluoroquinolone susceptible) may harbor a first step mutation in *ParC*.⁹ Although, the clinical significance of this observation is not well known yet, reports of fluoroquinolone failures have been associated with the presence of this resistance mechanism (5,38).

Gram-negative Resistance

Resistance among gram-negative bacteria, particularly *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and certain Enterobacteriaceae is of great concern in Latin American countries. During a recent review of global data collected during the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program, South America had the lowest susceptibility rates among tested β -lactams, fluoroquinolones, and aminoglycosides against *Acinetobacter* and *P. aeruginosa* compared with any other participating region of the world (79).

Acinetobacter baumannii and other *Acinetobacter* species are emerging opportunistic pathogens due to the ability for these organisms to produce numerous simultaneous resistance mechanisms. During the MYSTIC study (2002-2004), antibiotic susceptibilities were greatest for the carbapenems (71.5% and 71.9% for meropenem and imipenem), followed distantly by gentamicin (48.0%) and other antibiotic classes (79). Carbapenem resistance in one study, however, appeared to be highest among isolates from Argentina compared with other Latin America, thus it is apparent that clonal resistance that differs regionally is an important determinant of local resistance rates (77). In Brazil, *Acinetobacter baumannii* presented susceptibility rates

to meropenem of 97.1% and 73% to tobramycin during the 2003 MYSTIC study (39). While the carbapenems (imipenem and meropenem) are still considered the antibiotics of choice for *Acinetobacter* infections, the occurrence of metallo- β -lactamases are increasing in frequency and cause high-level (MIC > 32 $\mu\text{g/ml}$) resistance to these agents (66). They also efficiently hydrolyze other β -lactam antibiotics and are often resistant to fluoroquinolones and aminoglycosides via plasmid mediated resistance. These enzymes are fortunately still rare, but are more prevalent in certain Latin America countries compared with other regions of the world (66).

P. aeruginosa is one of the most common pathogenic Gram-negatives occurring in Latin America. Like *Acinetobacter*, it too, has the ability to develop numerous resistance mechanisms making it a problematic pathogen to treat. Antibiotic susceptibility during the 2002-2004 MYSTIC studies were 57.5%, 56.9%, 52.1%, 47.3%, 45.6% and 44.4% for piperacillin/tazobactam, meropenem, imipenem, ceftazidime, ciprofloxacin, and gentamicin against 1159 *P. aeruginosa* from South America, respectively (79). These susceptibility rates were similar to those observed during the Brazilian analysis of MYSTIC (2003) as well as later years of the SENTRY Antimicrobial Surveillance Program in Latin America (circa 2001) (7,39). In all of these analyses, the carbapenems, piperacillin/tazobactam, and the aminoglycosides (specifically, amikacin) had the greatest susceptibility rates. Nevertheless, resistance rates were still high for these compounds, and often the best agent had no better than 60-70% susceptibility against these strains. Like *Acinetobacter*, *P. aeruginosa* was also a culprit in the emerging production of carbapenemases and metallo- β -lactamases in Latin America (66).

As a result of such high levels of resistance among these non-fermenting Gram-negatives, therapeutic options based on microbiology alone are few. In such cases, polymixin, an old member of the polypeptide antibiotic class, may still serve some utility. Tested against 54,731 Gram-negative bacilli worldwide, polymixin resistance remained surprisingly low, even in Latin America (30). Resistance rates were only 1.1% and 1.7% against *P. aeruginosa* and *Acinetobacter* spp., respectively. However, susceptibility against other notable resistant non-fermenting Gram-negative bacteria was variable: *Stenotrophomonas maltophilia* (72.4%), *Burkholderia cepacia* (11.8%).

Among common Enterobacteriaceae, the most concerning resistance mechanisms include the production of Extended Spectrum β -lactamases (ESBLs) and derepression of the AmpC cephalosporinase. ESBL resistance is most notable within *Klebsiella* spp. and *Escherichia coli*, while AmpC resistance is frequent among *Enterobacter* spp. Although the ESBL rate for *Klebsiella* spp. has been steady over the last decade, it has been high. Between 1997-2000, 26.7% to 49.6% of *Klebsiella* spp. produced an ESBL; furthermore, most of the countries participating reported rates in the 40th percentile (29,67). Meanwhile, ESBL rates in *E. coli* have observed slight increases

over that time period, from 4.7% in 1997 to 9.4% in 2000 (67). One study from Columbia observed similar ESBL rates for *Klebsiella* spp. and *E. coli* in 2002, although prevalence varied substantially among the 8 participating hospitals (81). These investigators also went on to characterize the ESBLs and found that 59% and 34% of *Klebsiella pneumoniae* and *E. coli*, respectively, produced multiple enzymes. These included TEM, SHV and most frequently, CTX-M enzymes. While *Enterobacter* spp. can also produce ESBLs, expression of the chromosomally mediated AmpC cephalosporinase is more common. Such pathogens display poor susceptibility to ceftazidime (68.4%), as well as β -lactam/ β -lactamase inhibitors such as piperacillin/tazobactam (68%) and ticarcillin/clavulanate (56.5%) (67). However, cefepime remained very active against this pathogen in Latin America (91.5% susceptible). In general, carbapenems retained activity for both these ESBL producing Enterobacteriaceae and those with derepressed AmpC.

Of particular concern is the increasing resistance of Gram-negatives to fluoroquinolone antibiotics. Ciprofloxacin susceptibility within *Acinetobacter* spp. and *Pseudomonas* are commonly less than 50% and 70% across Latin American countries. Resistance to other fluoroquinolones, such as levofloxacin and gatifloxacin, are even higher for these non-fermentors. Additionally, fluoroquinolone resistance within *E. coli* is rising (67). Susceptibility was approximately 85% in 2000 for these antibiotics; resistance is now over 20% in some countries (2,67). Furthermore, in an analysis of various continents across the world that participated in both SENTRY and MYSTIC, Latin America was independently associated with ciprofloxacin non-susceptible *E. coli* and had the highest resistance rates compared with Northern Europe, Southern Europe, North America, and the Western Pacific (71). Fluoroquinolones, therefore, may not be a viable option for the treatment of many Gram-negative infections in the near future.

Pharmacodynamic Principles

In light of increasing resistance among Gram-positive and Gram-negative bacteria, opportunities exist to optimize antibiotic therapy against these organisms based on the knowledge of pharmacodynamics, i.e., how the drugs and bugs interact. First, it is imperative to realize some consistencies among the pharmacodynamic relationships discussed below. Foremost, it is the free or unbound antibiotic that is responsible for antibacterial activity (19). Drug that is bound to human proteins, routinely albumin, cannot effectively bind to their site of action on the bacteria and induce their antimicrobial activity. In cases where an antibiotic has low protein binding, the total drug concentrations are a reasonable indicator of exposure, but in cases of highly bound drugs, a correction factor should be utilized. Second, antibiotic concentrations in the human body are often referenced to the blood because it is easiest to determine concentrations at this site. However, it should be

emphasized that the antibiotic must get to the site of the infection, and therefore tissue penetration should be considered. In some cases, antibiotics do not penetrate completely to the site of infection (β -lactam penetration into the epithelial lining fluid [ELF] of the lung, or any antibiotic into the cerebral spinal fluid), thus the knowledge of blood concentrations only may lead to an overestimation of the actual tissue concentrations. In contrast, other antibiotics may accumulate at the site of infection and therefore concentrations are several fold higher than they are in blood (e.g., macrolides, ketolides and fluoroquinolones in the ELF, or β -lactams in the urine).

Antimicrobial killing is dependent on both the concentration of drug in relation to the MIC and the time that this exposure is maintained (Fig. 1) (14,19). When the effect of concentration predominates over that of time, the antimicrobial is said to be

concentration-dependent and bactericidal effects are associated with an optimal free drug maximum concentration to MIC ratio (fC_{max}/MIC). When the effect of time is greater, the antibiotic displays time-dependent antibiotic activity, and bacterial outcomes are associated with free drug concentrations above the MIC for a defined portion of the dosing interval, or time above the MIC ($fT>MIC$) (78). A summary of currently available antibiotics and their respective pharmacodynamic categories is listed in Table 1.

At standard doses, concentration-dependent antimicrobials include the aminoglycosides, fluoroquinolones, daptomycin, metronidazole and colistin (14,17,47,70). The goal when dosing concentration-dependent antimicrobials is to achieve a C_{max}/MIC of approximately 10 to 12 (59, 60, 64). Thus, a pharmacodynamic approach to administering the aminoglycosides would be to give

Table 1. Summary of antibiotics that display concentration-dependent or time-dependent killing characteristic and the requisite pharmacodynamic exposure.

Antibiotic Class - <i>Antibiotic</i>	Killing Characteristic	Pharmacodynamic Parameter*
Aminoglycosides <i>amikacin, gentamicin, tobramycin</i>	Concentration Dependent	$fC_{max}/MIC > 10 - 12$ (Gram-negatives)
β -lactams carbapenems (<i>ertapenem, imipenem, meropenem</i>) cephalosporins (e.g., <i>ceftazidime, cefepime</i>) penicillins (e.g., <i>penicillin, oxacillin, piperacillin/tazobactam</i>)	Time Dependent	40% $fT>MIC$ (bactericidal activity, Gram-negatives) 40% - 70% $fT>MIC$ (bactericidal activity, Gram-negatives) 50% $fT>MIC$ (bactericidal activity, Gram-negatives)
Fluoroquinolones <i>ciprofloxacin, levofloxacin, moxifloxacin</i>	Concentration Dependent	$AUC/MIC > 125$ (Gram-negatives) $fAUC/MIC > 30 - 50$ (Gram-positives)
Glycopeptides <i>vancomycin</i>	Time Dependent	$AUC/MIC > 345$
Glycylcyclines <i>tigecycline</i>	Time Dependent	$AUC/MIC \geq 6.96$ (Gram-negatives) $AUC/MIC \geq 12.5 - 17.9$ (Gram-positives)
Ketolides <i>telithromycin</i>	Concentration Dependent	$AUC/MIC \geq 3.375$
Lipopeptides <i>daptomycin</i>	Concentration Dependent	$fAUC/MIC 12 - 36$ (<i>Staphylococcus aureus</i>) $fAUC/MIC 5-13$ (<i>Enterococcus</i> spp.)
Macrolides <i>azithromycin, clarithromycin</i>	Time Dependent	$AUC/MIC > 254$ 40% - 50% $T>MIC$
Nitroimidazoles <i>metronidazole</i>	Concentration Dependent	$AUC/MIC > 70$ (<i>Bacteroides fragilis</i>)
Oxazolidinones <i>linezolid</i>	Time Dependent	$AUC/MIC > 39 - 167$ (<i>Staphylococcus aureus</i>)

* Exposures are total drug unless otherwise noted

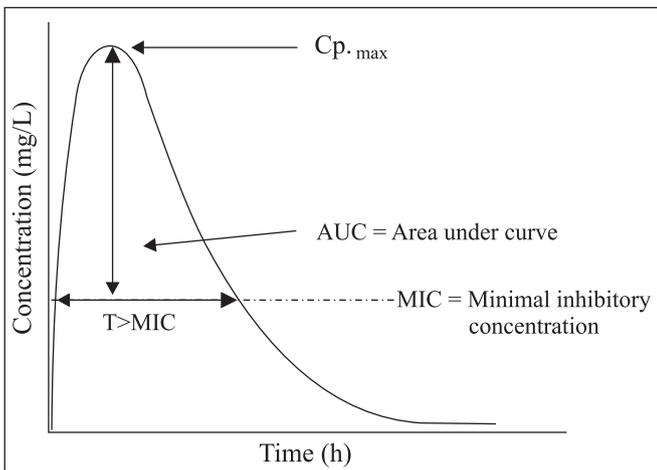


Figure 1. Depiction of pharmacodynamic parameters over a concentration time profile

a very large dose once daily in order to maximize the C_{\max}/MIC (26). While fluoroquinolones are concentration-dependent antimicrobials, the maximum dose that can be given is limited by dose-related toxicity, thus a C_{\max}/MIC of 10 to 12 cannot be achieved for many pathogens and time must be considered to maximize response. Therefore, in many pharmacodynamic studies, the bactericidal effect has been correlated with the area under the curve (AUC) to MIC (45). Against Gram-negative bacteria an $AUC/MIC \geq 125$ is required for maximal effect, while Gram-positive bacteria, such as *Streptococcus pneumoniae*, require an $AUC/MIC \geq 30$ (83).

Unlike many other classes of antimicrobials, the fluoroquinolone and aminoglycoside pharmacodynamic breakpoints have been validated in human trials, as opposed to only *in vitro* and *in vivo* animal studies. This was done with the aminoglycosides during the 1980's and more recently with fluoroquinolones against both Gram-negative and Gram-positive pathogens (3,20,25,57,60,64). In a study of 74 patients receiving ciprofloxacin for serious nosocomial infections, an AUC/MIC below 125 was associated with a lower probability of clinical and microbiologic response (25). Additionally, an AUC/MIC above 125 and above 250 were significantly associated with shorter median times to eradication ($AUC/MIC < 125$: 32 days, 125-250: 6.6 days, > 250 : 1.9 days, $P < 0.005$). However, it is important to acknowledge that the majority of patients included were infected with Gram-negative bacteria and that the authors did not consider the protein binding of ciprofloxacin in their analysis. In another study, a levofloxacin total drug AUC/MIC exposure greater than or equal to 87 was prospectively determined to be an important factor in predicting eradication in 47 patients with nosocomial pneumonia (20). This study included both Gram-positive and Gram-negative pathogens, as

well as the use of combination therapy for *Pseudomonas aeruginosa*. These variables along with slightly different methodologies, including consideration of protein binding or not, may partially explain why the pharmacodynamic breakpoints among these studies do not agree.

In a separate study evaluating gatifloxacin and levofloxacin pharmacodynamics against *S. pneumoniae*, Ambrose and colleagues found that a free drug AUC/MIC greater than 33.7 was a significant predictor of clinical and microbiological response in patients with lower respiratory tract infections (3). While providing important information regarding the *in vivo* pharmacodynamic profiling for these agents, this study did not appear to include isolates with varying fluoroquinolone genotypic resistance profiles such as *ParC*. Moreover, recently derived *in vitro* pharmacodynamic data with isolates containing these genotypic mutations have suggested that considerably higher exposures (i.e., AUC/MIC) are required to produce bactericidal outcomes and prevent the emergence of further resistance (1,24). Similar observations have been documented against *P. aeruginosa*, suggesting that an AUC/MIC of 125 may not be great enough to prevent resistance (34, 72).

Time-dependent antimicrobials include β -lactams, vancomycin, some macrolides, tigecycline, and clindamycin. In general, β -lactam antibiotics require $fT > MIC$ for 50% of the dosing interval; however, exposure can vary by the specific β -lactam class. For instance, while the penicillins commonly require approximately 50% $fT > MIC$ for bactericidal effects, discordance among exposures for the cephalosporins has been reported with a requirement between 50% and 70% $fT > MIC$ for bactericidal activity (78). Additionally, *in vivo* animal studies with the fourth generation cephalosporin, cefepime, have demonstrated bactericidal effects at free drug exposures as low as 40% $fT > MIC$ for *Escherichia coli* irrespective of the production of extended-spectrum β -lactamases (ESBLs) (53). The carbapenem class (i.e., imipenem, meropenem, ertapenem) of antibiotics are generally thought to require less $T > MIC$ because of their post-antimicrobial effect against Gram-negative bacteria and their high affinity for penicillin binding proteins (54). Bacteriostatic and bactericidal effects are observed at 20% and 40% $fT > MIC$, respectively.

In contrast to the aminoglycosides and fluoroquinolones, little data in humans are available to directly validate these pharmacodynamic endpoints for β -lactams. Instead, numerous studies have linked clinical response with MIC ; a detailed review of these studies has been published (78). In a separate review, a quantitative relationship between time above the MIC_{90} in serum and bacteriologic success for a variety of β -lactams (penicillins and cephalosporins) in the treatment of otitis media and acute maxillary sinusitis was demonstrated (16). The authors demonstrated that bacteriologic success was greatest when the $T > MIC$ was at least 50% of the dosing interval. More recently, the pharmacodynamics of cefepime were determined

in 20 patients with *P. aeruginosa* infections (74). These investigators observed a strong link between microbiological success and $T > MIC$. Success was 89% when $T > MIC$ was 100% compared with 0% when $T > MIC$ was less than 100%, $p=0.032$. A minimum concentration (C_{min})/MIC > 4.3 , however, was independently predictive of response. A similar analysis of 101 adults with lower respiratory tract infections receiving meropenem demonstrated that while all pharmacodynamic parameters could be linked to response, the fC_{min}/MIC was most predictive; a ratio greater than 5 was required to predict microbiological eradication (46). Although these were small studies and had their limitations, the data suggest that higher pharmacodynamic targets than previously documented from *in vitro* and animal studies may be needed in the clinical setting.

Although vancomycin success for Gram-positive infections has historically been thought to be associated with $T > MIC$, data actually suggest that the AUC/MIC ratio best predicts outcomes for this time-dependent antibiotic (65). Studies in patients with pulmonary infections caused by *S. aureus* observed that vancomycin response was associated with a total drug AUC/MIC > 345 , and microbiological eradication was associated with an AUC/MIC > 400 (57, 58). Assuming about 50% protein binding, these total drug targets are similar to the $fAUC/MIC$ targets found in the original *in vivo* murine thigh infection models required for a static effect (65). Alternative supportive data are provided by studies suggesting that outcomes for *S. aureus* bacteremia were very low when the MIC was $> 1 \mu\text{g/ml}$; at this MIC, the standard vancomycin dose (1g q12h) does not attain these AUC/MIC exposures in patients with reasonable renal function (69). Pharmacodynamic data for teicoplanin, another glycopeptide, is not available yet, but should be similar to vancomycin targets.

As newer antibiotics become clinically available, the determination of pharmacodynamic endpoints for these agents is also conducted. When the pharmacodynamics of the novel ketolide, telithromycin, was examined in murine infection models, it was noted to display concentration-dependent killing, with the free AUC/MIC being most predictive of bacterial load reduction (76). This finding is in discordance with older macrolides, which are better described as time-dependent killing antibiotics (37). More recently, telithromycin pharmacodynamics were examined in 115 patients with community-acquired pneumonia caused by extracellular pathogens, most of which were *Haemophilus influenzae* and *S. pneumoniae* (50). An AUC/MIC ≥ 3.375 was associated 90.8% positive predictive value for eradication, while values below this breakpoint were associated with 23.5% negative predictive value. This means that the determined breakpoint was highly sensitive for identifying eradication, but not specific for it, so that a patient not obtaining an AUC/MIC of 3.375 would not necessarily always fail therapy, but might be more likely to do so. Linezolid is the first in class oxazolidinone. The pharmacodynamics of this agent have been

assess in a murine thigh infection model, and a total AUC/MIC of 39 to 167 (mean = 83) was required to produce a static effect against *S. aureus*, including a methicillin resistant strain (6). Half the exposure was required against *S. pneumoniae*. Daptomycin pharmacodynamics were concentration-dependent in murine infection models against *S. aureus* and enterococci; a free AUC/MIC ratio of 12 to 36 and 5 to 13, respectively, were associated with static effects (17,51). Finally, the pharmacodynamics of tigecycline, a novel glycylycine antibiotic derived from minocycline were analyzed in patients with complicated skin and skin structure infections and complicated intra-abdominal infections. Tigecycline displays time-dependent activity, and a total AUC/MIC ≥ 6.96 and ≥ 12.5 - 17.9 for Gram-negative and Gram-positive bacteria, respectively, was predictive of successful clinical responses (55,63,80).

Optimizing Pharmacodynamics

New antibiotics are needed to combat the emerging resistance in Latin American countries. While novel Gram-positive antibiotics have been introduced that have activity against MRSA, VRE, and penicillin-resistant *S. pneumoniae*, antibiotics with activity against multidrug-resistant *Acinetobacter* spp. and *P. aeruginosa* are many years from clinical development. As a result, we must look to our currently available antibiotic armamentarium for clinical use against these organisms. Pharmacodynamic concepts can be utilized to develop strategies to optimize the dosing of these antibiotics, in many cases, without sacrificing patient safety.

Aminoglycosides (tobramycin, gentamicin, and amikacin) are an important therapeutic option for non-fermenting Gram negative infections, especially in combination with other antibiotic classes. Because these antibiotics are concentration-dependent and the C_{max}/MIC ratio is associated with positive outcomes, increasing the administered dose of these drugs should be considered. Moreover, because higher concentrations are obtained, the dosing interval can be extended to prevent aminoglycoside accumulation and associated nephro- and ototoxicity. This dosing strategy has been termed Once Daily or Extended Interval Aminoglycoside Dosing. Numerous data support the use of extended interval aminoglycosides, and some reports have suggested less toxicity with this regimen (26). Individualized pharmacokinetic monitoring has been proposed as the most accurate method to achieve the target C_{max}/MIC of 10 to 12 (35,82). However, one must consider the cost of multiple drug samples, the potential for impractical dosing schedules, the requirement for a significant understanding of pharmacokinetic principles by the clinician, and the expertise and time associated with using pharmacokinetic computer software to calculate kinetic parameters. Moreover, the denominator in the C_{max}/MIC ratio is seldom available to the practicing clinician, thus the economic benefit of potentially administering lower doses for bacteria with a lower aminoglycoside MIC is rarely realized. This individualized

approach, however, is the most appropriate method for administering the agent to patients with unusual pharmacokinetics, such as pregnant women, burn patients, or patients with ascites, etc. Another approach to extended-interval aminoglycoside administration has been through the use of population kinetics and institution specific dosing nomograms (4,31,62).

The dose of an aminoglycoside should be based on the MIC of the causative pathogen, when available. If using a nomogram, the ideal dose should be one that is based on the aminoglycoside MIC₉₀ for the most common pathogen targeted at that specific institution (e.g., *P. aeruginosa*). Some nomograms have suggested doses of 5 mg/kg instead of 7 mg/kg once daily. In many instances a dose of 5 mg/kg is more than adequate to achieve a C_{max}/MIC ratio of 10 to 12. In other cases, a dose higher than 7 mg/kg may be necessary if the MIC is greater than 2 µg/mL. Continued monitoring of MIC distribution changes is necessary to assure appropriate use of nomogram dosing.

Due to their activity against many multidrug-resistant non-fermenting Gram-negative rods, colistin (polymyxin E) or polymyxin B remain potential treatment options (23). Unfortunately, the pharmacodynamics of these agents are not well established and clinicians are not likely using appropriate dosing based on pharmacodynamic concepts; moreover, one must consider the potential for nephrotoxicity and peripheral neuropathy with this antibiotics. One in vitro study that linked AUC/MIC to the development of resistance observed that a dose 8 times greater than the standard 2.5mg/kg dose was required to maintain bactericidal activity at 24 hours (1). They suggested further studies with higher, but less frequent polymyxin B dosing, similarly to what is done with the aminoglycosides.

Manipulation of the dosage of β-lactams offers among the broadest spectrum of possibilities for optimizing pharmacodynamics. This is further supported by the safety of these compounds at higher doses, as well as their popularity as antibiotic workhorses in many hospitals. Since the β-lactams are time-dependent killing agents, maximizing the $fT > MIC$ is necessary for optimal bacterial load reduction. Accordingly, numerous strategies such as prolonging the infusion time over several hours, or administering the antibiotics as a continuous infusion over the entire day, have been advocated (15,54). Both prolonged and continuous infusion dosing concepts require less antibiotic to achieve similar exposures to standard intermittent infusions and thus may provide an economic benefit; however, it is the ability to use high doses along with these dosing strategies to pursue treatment of less susceptible pathogens (10,37,43,49).

Numerous β-lactams have been studied as continuous infusions, the majority of which would otherwise require numerous daily dosing because of short serum half-lives, such as piperacillin/tazobactam, ceftazidime, cefepime, oxacillin, and nafcillin. The only caveats to continuous infusion are the

requirement of room temperature stability for the 24 hours and dedicated line access. In the case of poor stability, continuous infusion can still be conducted if the bag is changed within the required time frame or if the infusion bag is surrounded by freezer packs to maintain stability (54). Alternatively, the prolonged infusion strategy may be adopted. This concept involves infusing the β-lactam for only a few hours (e.g., 3. to 4 hours) on a standard every 6 to 8 hour schedule. The majority of data with prolonged infusion have been conducted with carbapenems due to their poor stability at room temperature; however, logistically, this can be applied to any β-lactam. Data with piperacillin/tazobactam and cefepime are available (49,73).

Unfortunately, unlike aminoglycosides and vancomycin, most hospitals do not have the resources to conduct β-lactam concentration monitoring; therefore, it is more difficult to individualize dosing strategies for these antibiotics. In the absence of concentration data, population pharmacokinetic models and Monte Carlo simulation can be utilized to estimate the likelihood of different dosage regimens achieving the requisite pharmacodynamic target (8). Monte Carlo simulation is a stochastic model that considers the variability in patient pharmacokinetic parameters as well as the likelihood of infection with an organism with a specific MIC (44). Combined with local or national surveillance MIC data, these models can assist in choosing among antibiotic regimens empirically, and determining optimal dosage regimens to employ against less susceptible bacteria (42,44). This technique was utilized to assess differing antibiotic regimens against Gram-negative bacteria collected from the MYSTIC Program in South America (41). The simulations suggested that meropenem and imipenem had the greatest likelihood of achieving bactericidal exposure against the non-fermenting Gram-negative bacteria, although neither regimen attained high probabilities. Thus, combination therapy was advocated. Additionally, the simulations pointed to discrepancies between susceptibility and pharmacodynamic attainment against *P. aeruginosa*, specifically for piperacillin/tazobactam 4.5g q8h and ciprofloxacin 400 mg q12h. Whereas susceptibility was approximately 67% and 55%, respectively, target attainment was only 26% and 33%, suggesting that standard dosages for these antibiotics may be too low for even susceptible bacteria.

If local susceptibility data are known, dosing strategies such as prolonged or continuous infusion can be implemented to increase the likelihood of target attainment against less susceptible bacteria. An assessment of the bacteria implicated in consecutive infections in one hospital's intensive care unit in Brazil demonstrated that standard dosing regimens might not be ideal empirically due to high resistance rates (40). *P. aeruginosa* was the most commonly isolated organism, and a high dose, prolonged infusion regimen of meropenem (2g q8h as a 3 hour infusion) achieved 88% likelihood, while the standard 1g q8h (30 minute infusion) regimen achieved only 80.7%. This

pharmacodynamically optimized regimen for meropenem can achieve $\geq 40\% fT > MIC$ against organism considered meropenem intermediate (MIC = 8 $\mu\text{g/ml}$) and those considered resistant (MIC = 16 $\mu\text{g/ml}$) (42,73). Similarly, a high dose prolonged infusion of cefepime (2g q8h as a 3-4 hour infusion) can achieve $\geq 50\% fT > MIC$ against organisms considered cefepime intermediate (MIC = 16 $\mu\text{g/ml}$) and resistant (MIC = 32 mg/ml) (52,73). In the unfortunate case that organisms with these MIC values exist in one's hospital population, these optimized dosing regimens should be advocated empirically until susceptibility data are available.

CONCLUSIONS

Antimicrobial resistance among Gram-positive and Gram-negative bacteria in Latin American countries is increasing. Since few novel antibiotics are near market entrance, specifically against Gram-negatives such as *P. aeruginosa* and *Acinetobacter* spp., we must optimize the dosing of currently available agents. Pharmacodynamic studies in essentially all antibiotics are available demonstrating relationships between concentration, MIC, and microbiological effects. Furthermore, quantitative targets can help clinicians and researchers design dosing regimens that have a high likelihood of obtaining requisite exposures for use in daily clinical practice. In some instances, novel administration strategies including high-dose extended intervals for aminoglycosides and prolonged or continuous infusion for β -lactams will be required to optimize antibiotic pharmacodynamics against these less susceptible pathogens.

RESUMO

Utilização de princípios de farmacocinética e farmacodinâmica na otimização do tratamento antimicrobiano com relação à resistência emergente

A eficácia antimicrobiana *in vivo* não pode ser definida exclusivamente pela atividade de um antibiótico determinada por um teste de sensibilidade *in vitro*. O conhecimento da farmacocinética e farmacodinâmica dos antimicrobianos, assim como de todos os fenômenos que ocorrem entre agentes antimicrobianos e microrganismos é fundamental na interpretação de alguns resultados. Os parâmetros farmacodinâmicos (PD) mais frequentemente usados nos estudos do efeito dos antibióticos incluem os seguintes relacionamentos: a concentração livre máxima (fC_{max}) com relação à concentração inibitória mínima (CIM), a área livre sob a curva ($fAUC/CIM$) e a duração do tempo em que a concentração livre excede a CIM ($fT > CIM$). A utilização dos dados conhecidos de farmacocinética/farmacodinâmica devem ajudar a otimizar o resultado dos tratamentos adotados, especialmente com relação à resistência emergente entre as bactérias Gram-positivas e Gram-negativas. Os estudos clínicos

no campo da farmacodinâmica dos antimicrobianos ainda são relativamente escassos, e muita informação é necessária para permitir estratégias de dosagem relevantes para todos os tipos de antibióticos contra a todas as infecções e microrganismos comuns. Nesta revisão, os padrões distintos da atividade antimicrobiana baseado em parâmetros de farmacodinâmica são discutidos. Vários antibióticos e patógenos bacterianos podem ser usados como modelos para demonstrar a utilidade de parâmetros de farmacodinâmica em prever a eficácia *in vivo* da terapia antimicrobiana. E finalmente, o uso da modelagem computadorizada utilizando a simulação de Monte Carlo em determinadas populações podem realçar ainda mais o valor preditivo e a eficácia antimicrobiana quando se utilizam parâmetros de farmacodinâmica nas interpretações.

Palavras chave: antibiótico, bactérias, farmacodinâmica, resistência

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