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Optimizing Antibiotic Pharmacodynamics for Clinical Practice

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Abstract

With an absence of new antibiotics in the pipeline to address increasing resistance among gram-positive and gram-negative bacteria, new strategies are needed to retain utilization of currently available agents. As recommended in current guidelines for antimicrobial stewardship, dosage optimization through consideration of antibiotic pharmacodynamics provides a formidable approach to making good antibiotics better. Knowledge of the relationship between antibiotic concentration to microbiological potency and its effect on antibacterial activity leads to the design of dosing regimens that optimize killing of bacteria in the clinical setting. The activity of aminoglycosides is dependent on maximizing peak free drug concentrations in relation to their minimum inhibitory concentration (MIC), so giving larger doses less frequently has become the gold-standard strategy for optimizing their pharmacodynamics. In contrast, the activity of β-lactam antibiotics is dependent on maximizing the time that free drug concentrations remain above the MIC; numerous approaches including continuous and prolonged infusion of these agents enable optimization of this pharmacodynamics parameter and improve clinical outcomes. This review discussed pharmacodynamics concepts as applied clinically for aminoglycosides, β-lactams, and other classes of antibiotics.

Keywords: Antibiotics; Pharmacodynamics; Optimization; Aminoglycoside; Beta-Lactams; Prolonged Infusion; Continuous infusion; Stewardship

Introduction

In recent decades, emerging bacterial resistance is defying the efficacy of currently available antibiotics. Of the approximate 1.7 million hospital acquired infections in the US annually, a staggering 350,000 infections can be attributed to just a few multi-drug resistant pathogens [1-3]. Current consensus indicates *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* species, affectionately dubbed the "ESKAPE" pathogens, to be overwhelmingly responsible for the majority of antibiotic resistant infections found in US hospitals [4,5]. In the US alone, methicillin resistant *S. aureus* (MRSA) infections have been linked to higher mortality rates than HIV/AIDS and tuberculosis combined [6,7]. In addition to increased morbidity and mortality, figures from the Centers for Disease Control and Prevention (CDC) associate drug-resistant infections with an economic burden of approximately US$3.5 billion per year [2,3].

Given current trends in infectious disease, it's unfortunate that the scientific, regulatory, and economic challenges of antibiotic research have led to a decline in the approval of new agents [4,5,8-13]. Today, there are few new antibiotics in late stage development offering activity against the most dangerous hospital acquired gram-negative pathogens [14-16]. Of 90 antibacterial agents in development with *in vitro* activity reviewed by The European Centre for Disease Prevention and Control/European Medicines Agency, only 66 were considered "new agents" of which only 27 showed potential benefits over current agents. Furthermore, just 15 of the 27 agents could be systemically administered, with only 2 agents exhibiting activity against gram-negative pathogens via a new mechanism [14]. Presently there are 6 antibiotics in Phase II-III trials, 3 of which demonstrate activity against *Pseudomonas aeruginosa*: MK-7655/imipenem-cilastatin (Merck), ceftazidime/avibactam (Astra Zeneca/Forest), and ceftolozane/tazobactam (Cubist) [15,16].

By limiting inappropriate antimicrobial use and enhancing the selection, dose, route, and duration of therapy, institutions with ongoing antimicrobial stewardship programs are bridging the gap between resistance and optimizing available therapies for favorable clinical outcomes [17-19]. Techniques employed by stewardship teams may include formulary restriction, implementation of specialized order sets, treatment algorithms and guidelines designed specifically for the institution, education of practitioners, pharmacy dosing programs, and pharmacodynamic dose optimization [18]. The last strategy, of which this review will focus, describes the use of pharmacodynamic principles to guide the selection and optimization of the dosing regimen. This review will describe strategies to optimize dosing of some currently available antibiotic classes through the incorporation of pharmacodynamic principles in clinical practice.

Basic Principles of Pharmacodynamics

A true understanding of the pharmacodynamics begins with a few basic principles. First, administering a fixed dose of drug to a large number of patients will result in substantially different profiles of changing concentrations of the drug over time (i.e., variability in pharmacokinetics). Second, the shape of the curve describing the concentration-time profile can have a direct impact on the effect of a particular drug dose (i.e., different drugs have different pharmacodynamic properties). Only free (non-protein bound) drug is microbiologically active. The higher the value of the measure of the potency of the drug [e.g., the minimum inhibitory concentration (MIC)] for the pathogen, the less effect a fixed drug exposure will have, and finally, it is the drug exposure at the site of the infection which is responsible for the antimicrobial effect. With respect to the latter,

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most pharmacodynamic studies reference drug exposure in blood to an effect that takes place at the site of infection (e.g., lung epithelial lining fluid, tissue, bone, etc). For most antibiotics, including β-lactams, the exposure at the site of infection is similar to that of blood, and therefore, blood is a reasonable surrogate marker for exposure. However, one must consider each antibiotics pharmacokinetic characteristic to determine if this relationship will hold true. For example, macrolide antibiotics such as azithromycin have low blood concentrations, a large volume of distribution, and penetrate widely into lung alveolar macrophages; therefore, the exposure in blood is only a correlate for the required exposure needed to achieve an antimicrobial effect in the lung.

One of the first studies elucidating the relationship between drug concentration (i.e., pharmacokinetics) and microbiological effect (i.e., pharmacodynamics) can be traced back to the 1940s when Eagle and colleagues observed the antibacterial properties of penicillin to be related to time and those of streptomycin to be concentration [20]. This concept of time and concentration in relation to drug exposure are paramount to distinguishing the bactericidal activity of antibiotics. Furthermore, this concentration/time exposure profile can be further quantified by characterizing a mathematical relationship with antibacterial effect and the maximum free drug concentration (fC_{max})/MIC ratio, the area under the free drug concentration-time curve (*f*AUC)/MIC ratio, or the time in which free drug concentrations exceed the MIC (*f*T>MIC) with microbiological outcome (Figure 1) [21-23].

At clinically relevant concentrations, antibiotics like β-lactams (penicillins, cephalosporins, carbapenems, and monobactams), lincosamides, macrolides, oxazolidinones, vancomycin and tigecycline exhibit time-dependent microbiological effects, whereby increases in concentration alone relative to the MIC do not add to enhanced killing of bacteria. For some agents, such as the β-lactams, optimized killing is obtained when a specific *f*T>MIC exposure is achieved against the pathogen. This exposure varies by type of β-lactam, as well as by bacteria. In general, members of the penicillin class require approximately 50% *f*T>MIC for maximal exposure, the cephalosporins require 50-70% *f*T>MIC, and carbapenems require 30-40% *f*T>MIC

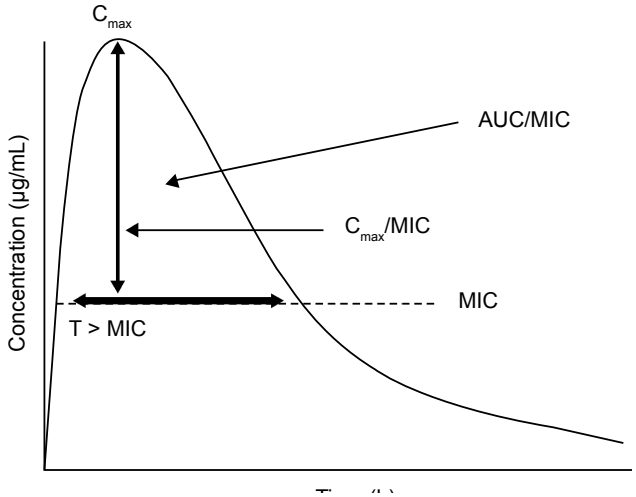

Figure 1: Pharmacokinetic / pharmacodynamic indices that describe antimicrobial effects. Cmax = maximum concentration; AUC/MIC = area under the curve / minimum inhibitory concentration; T>MIC = time above the MIC.

[21,22]. Additionally, the *f*T>MIC exposure required for maximal killing of Gram-negative bacteria is often greater than that achieved for Gram-positives [22]. For example, the newest member of the carbapenem class, doripenem, required 27.3% ± 11.7% *f*T>MIC to achieve a 2-log reduction against *Streptococcus pneumoniae*, 35.4% ± 5.0% *f*T>MIC against *S. aureus* and 43.7% ± 7.1% against Gram-negatives when tested in the classic murine in vivo thigh infection model [24]. The goal for this class of antibiotics is then to achieve the greatest amount of time during a dosing interval in order to achieve free drug concentrations above the MIC. This can be accomplished using several methods clinically [25]. The dosage of the antibiotic can be increased or more doses can be administered over a 24 hour period (i.e., shorten the dosing interval). Both of these methods increase T>MIC but does so inefficiently. Alternatively, the infusion duration for β-lactams can be increased, either by administering the entire daily dose continuously over a 24 hour period (i.e., continuous infusion), or by increasing the infusion duration enough to maximize the likelihood of achieving the pharmacodynamic target and the repeating this using the standard dosing interval. This latter concept, referred to as prolonged or extended-infusion β-lactam therapy has become quite popular over the recent decade due to its ability to increase the *f*T>MIC efficiently, while still providing an antibiotic free interval to administer other agents. These concepts will be discussed in greater detail later in this review.

In contrast to β-lactams, other time-dependent antibiotics can have persistent effects and when combined with small MIC ranges for pathogenic bacteria, the pharmacodynamic parameter best correlated with outcome becomes the AUC/MIC ratio. For example, although vancomycin is considered a time-dependent antimicrobial agent and trough concentrations are often analyzed clinically for therapeutic drug monitoring, it exhibits maximal bactericidal activity against *S. aureus* when the AUC/MIC (total drug) ratio is ≥ 400 [26,27]. A trough of 15-20 µg/mL correlates with this AUC/MIC exposure when the MIC is 1 µg/mL of less; therefore, therapeutic drug monitoring by use of trough concentrations are clinically useful for predicting pharmacodynamic exposure attainment [27]. For tigecycline, a time-dependent glyclcycline antibiotic, the *f*AUC/MIC ratio is also most predictive of efficacy against *S. aureus* and Enterobacteriaceae [28,29]. The dosing strategy for these time-dependent antibiotics is to provide an overall daily dose that achieves the requisite AUC/MIC ratio without decreasing tolerability or increasing adverse events. For newer antibiotic agents such as tigecycline, the approved dosing regimen has often been selected with an understanding of pharmacodynamic requirements for common susceptible bacteria [23]. However, infections such as hospital acquired pneumonia, or bacteria such as *A. baumannii*, for which the drug is not approved, may require higher dosing regimens due to different pharmacodynamic targets, elevated MICs against the pathogen, or penetration to the site of infection. [30,31]. In contrast, concentration-dependent killing antibiotics achieve more rapid and greater antimicrobial effects when the free peak concentration is maximized in relationship with the MIC [21]. The pharmacodynamic parameters predictive of efficacy for these agents are the fC_{max}/MIC, the *f*AUC/MIC, or both. At clinically relevant concentrations, concentration-dependent killing antibiotics include the aminoglycosides, fluoroquinolones, daptomycin, polymyxin antibiotics, and metronidazole. Aminoglycosides are considered the classic concentration-dependent killing antibiotic class and achieve maximal bactericidal activity when their fC_{max}/MIC is greater than 10-12 [32,33]. A total drug AUC/MIC of at least 156 was also highly predictive of temperature resolution by day 7 for patients with hospital

acquired pneumonia [33]. Therefore, clinical dosing regimens to optimize pharmacodynamics should attempt to maximize the *f*C_{max}/MIC or AUC/MIC by increasing the individual dose and extending the dosing interval to prevent accumulation. Fluoroquinolone antibiotics are also concentration dependent, and the pharmacodynamic parameter best correlated with efficacy is an *f*Cmax/MIC ratio of 12 or AUC/MIC (total drug) of 100-125 against Gram-negative bacteria, or a *f*AUC/MIC ratio of at least 30-50 against gram-positive bacteria such as *S. pneumoniae* [34-36]. More recently, the pharmacodynamics of the older polymyxin class of antibiotics has been found to observe concentration-dependent killing, where the *f*AUC/MIC ratio is predictive of antibacterial effect against Gram-negative bacteria [37]. *in vitro* and in vivo thigh infection studies indicate that the *f*AUC/MIC required for 1- to 2- log reductions against *P. aeruginosa* range from 15.6 to 22.8 and from 27.6 to 36.1, respectively; in the lung infection model, those requirements ranged from 12.2 to 16.7 and 36.9 to 45.9, respectively [38]. Similar targets were required for 1-log reduction against *A. baumannii* isolates, although more variability was noted in the lung infection models [37].

Optimizing Antibiotics

Using the above knowledge, novel dosing strategies can be proposed to optimize the treatment of serious infections in hospitalized patients. Table 1 provides a list of common antibiotic classes, their pharmacodynamic parameter and target exposure, and strategies to optimize dosing for use in clinical practice. Of note, most of the dosing strategies discussed below are not approved by the Food and Drug Administration (FDA), as the science of pharmacodynamics has evolved greatly since the approval of many older antibiotics. Fortunately, many newer antibiotics today are designed with an understanding of pharmacodynamic principles and dosage regimens are selected based on the ability to optimize exposure against pathogens of interest for approved indications.

Aminoglycosides

Traditional or conventional dosing regimens of aminoglycosides call for two to three divided daily doses administered daily at doses of 1 to 1.5 mg/kg (gentamicin and tobramycin) or 7.5 mg/kg (amikacin) [39,40]. This method of dosing results in peak concentrations well below that needed to achieve the requisite pharmacodynamic thresholds against current bacteria and has notoriously been associated with nephro- and oto-toxicity due to higher average concentrations over a 24 hour period [41]. The alternative dosing regimen to this is known as high-dose, extended-interval or high-dose, once-daily aminoglycoside therapy.

Using a fixed 7 mg/kg intravenous dose of gentamicin and a dosing interval nomogram based on estimated creatinine clearance of patients, Nicolau et al. evaluated a once daily aminoglycoside dosing algorithm (referred to as the Hartford Nomogram) in 2,184 adult patients [42]. The investigators observed similar clinical response rates to historical data, but a reduced incidence of nephrotoxicity, which was 1.2% while using the Hartford Nomogram versus 3-5% historically. Notably, the 7 mg/kg dose selected was based on several of our institution specific factors. The MIC_{90} for gentamicin against *P. aeruginosa* was 2 mcg/ml in the hospital, and based on a population pharmacokinetic model from our patients, a 7 mg/kg daily dose was required to achieve an average peak of 20 mcg/ml, approximately 10 times the MIC. Today, tobramycin is employed instead of gentamicin at our hospital; because it's MIC_{90} for *P. aeruginosa* remains about 2 MIC dilutions lower than gentamicin and still enables use of the 7 mg/kg dosing algorithm.

Therefore, not all hospital's employing a once daily aminoglycoside dosing strategy requires use of a 7 mg/kg daily dose. Hospitals with lower gentamicin or tobramycin MICs against *P. aeruginosa* may be able to use lower dosing regimens to achieve the pharmacodynamic threshold. Conversely, larger doses would be needed to treat MICs higher than 2 mcg/ml. A pharmacokinetic/pharmacodynamics

Antibiotic class	Pharmacodynamic (PD) profile	PD parameter	Clinical optimization strategy
Aminoglyosides	concentration-dependent	*f*Cmax/MIC ≥ 10 to 12; total AUC/MIC ≥ 156	High-dose, once-daily or extended interval dosing; dosing strategy can use a nomogram (Hartford Nomogram) or be individualized using therapeutic drug monitoring and MIC
β-lactams penicillins carbapenems cephalosporins	 time-dependent time-dependent time-dependent	 *f*T>MIC ≥ 50 *f*T>MIC ≥ 30-40 *f*T>MIC ≥ 50-70	Continuous or prolonged infusion; can be combined with greater doses to treat higher MIC organisms
Fluoroquinolones	concentration-dependent	*f*Cmax/MIC ≥ 10 to 12; total AUC/MIC > 125 for gram-negatives; *f*AUC/MIC > 30-50 for gram-positives	Increase dose related to MIC; however careful of increases in toxicity associated with higher concentrations; Use the most potent agent (i.e., lowest MIC) to maximize AUC/MIC ratio
Glycopeptides/Lipopeptides daptomycin vancomycin	 concentration-dependent time-dependent	 *f*AUC/MIC; *f*Cmax/MIC * total AUC/MIC > 400	 Maximize dose in relation to MIC Maximize over daily dose in relation to MIC; target trough concentrations of 15-20 mcg/ml
Macrolides/Azalides	time-dependent	AUC/MIC *	N/A
Oxazolidinone (linezolid)	time-dependent	total AUC/MIC > 110	Maximize overall daily dose in relation to MIC; standard dose optimized for most susceptible bacteria up to MIC of 2 mcg/ml.
Polymyxins	concentration-dependent	*f*AUC/MIC > 12 to 15; total AUC/MIC > 60	Maximize overall daily dose in relation to MIC while considering nephrotoxicity; Consider algorithm for loading and maintenance doses by Garonzik (70)
Tetracyclines/Glycylcyclines doxycycline tigecycline	 time-dependent time-dependent	 AUC/MIC * *f*AUC/MIC	 N/A Approved dosage optimized for most susceptible bacteria in intra-abdominal infections and complicated skin infections; if tolerated, increase overall daily dose to 200mg daily to maximize pharmacodynamics for more serious infections or *Acinetobacter* spp.

*Clinically relevant AUC/MIC targets for these antibiotics have not been well established

Table 1: Summary of antibiotic classes, pharmacodynamics parameter, exposure threshold and strategy to optimize pharmacodynamics.

simulation study recently conducted by Drusano and Louie observed that the probability of day 7 temperature resolution using a 10 mg/kg daily dose against an organism with an MIC of 4 mcg/ml was 79.7%, with an estimated probability of nephrotoxicity well below 1% [41]. In contrast, a 5 mg/kg dose administered every 12 hours provided a 53.6% likelihood of effect against an MIC of 4 mcg/ml, with a 24.6% likelihood of nephrotoxicity. Additionally, patient populations with altered pharmacokinetics may require lower or larger doses depending on individual clearance or volume of distribution, as well as MIC. In a study by Rea et al. in 102 critically ill patients, due to a larger volume of distribution [mean of 53 L (95% confidence interval: 38-67 L)], a 7 mg/kg dose in the investigator's population had a 10% likelihood of achieving a C_{max}/MIC of 10 against *P. aeruginosa* with an MIC of 2 mcg/ml [43]. This likelihood increased to 50% and 88% at MICs of 1 mcg/ml and 0.5 mcg/ml respectively. Conflicting literature exists as to whether critically ill patients require larger doses of aminoglycosides then 7 mg/kg to achieve the threshold *f*C_{max}/MIC ratio of at least 10 [44-47].

An alternate approach to a nomogram designed dose is to employ individualized dosing in specific patients based on the results of multiple serum concentrations, the resulting or estimated peak concentration and the MIC of the pathogen [48,49]. Although this provides a highly individualized and accurate approach, this may be time-consuming and burdensome in some hospitals if applied to all patients. Additionally, the MIC of the pathogen is the greatest factor in this equation since it lies in the denominator of the pharmacodynamic equation (*f*C_{max}/MIC or *f*AUC/MIC). Thus one-dilution changes in the MIC result in doubling or halving of the pharmacodynamics exposure. Indeed, for isolates with lower MICs (below 2 mcg/ml), the nomogram approach is very reliable in obtaining the requisite exposure, while greater MICs and more variable pharmacokinetic profiles (i.e., variations in renal function) may benefit from a more individualized approach.

Regardless of which approach to high-dose, once-daily or extended-interval dosing of aminoglycoside is employed, this pharmacodynamic dosing strategy is today the standard of practice for aminoglycoside dosing. In a national survey of 500 acute care hospitals, 3 of every 4 hospitals have now adopted the use of this strategy which correlates to a 4-fold increase in use since 1993, when a similar survey of 336 acute care hospitals resulted in a mere 19% reporting the use of pharmacodynamics based dosing [50].

β-lactams

Traditional dosing for β-lactam antibiotics typically involves administering smaller doses over 15-30 minute infusions 2-4 times daily, depending on the serum half-life of the antibiotic and the patient's kidney. This strategy often does not achieve the requisite *f*T>MIC thresholds for all susceptible bacteria. DeRyke et al. used Monte Carlo simulation to arrive at a likelihood of achieving *f*T>MIC targets using current susceptibility breakpoints versus that of pharmacodynamics derived breakpoints for 7 β-lactams [51]. As demonstrated in table 2, susceptibility breakpoints are traditionally set for a single dosing regimen against an organism, while pharmacodynamics breakpoints are dosing regimen specific. A higher susceptibility breakpoint (i.e., more organisms in the population would be defined as susceptible and considered 'treatable') can be justified if larger doses administered more frequently were employed. Importantly, standard clinical doses for most of the tested β-lactams were unable to achieve the requisite *f*T>MIC threshold at the susceptibility breakpoint, as noted by lower pharmacodynamics breakpoints for these regimens. For example, a standard cefepime regimen of 2 g every 12 hours administered as a 30 minute infusion achieves a high likelihood of achieving 50% *f*T>MIC only up to a MIC of 4 mcg/ml, while *P. aeruginosa* with a MIC of 8 mcg/ml would still be considered susceptible. This puts patients receiving these standard regimens against organisms with MICs at or near the breakpoint at risk for clinical failure or the development of resistance because the *f*T>MIC threshold may not have been achieved clinically. The solution to such a scenario is to either reduce the susceptibility breakpoint in line with these data, as was recently done for piperacillin/tazobactam and *P. aeruginosa* (i.e., the breakpoint is now 16 mcg/ml instead of 64 mcg/ml), or modify the dosing strategy to increase the likelihood of obtaining *f*T>MIC against higher MIC organisms.

Drug regimen (all 30 minute infusions)	Susceptibility breakpoint MIC (mcg/ml)	
	CLSI	Pharmacodynamic
Cefepime 1 g q12 h	8	2
Cefepime 2 g q12 h	8	4
Cefepime 2 g q8 h	8	16
Ceftazidime 1 g q8 h	8	8
Ceftazidime 2 g q8 h	8	16
Imipenem 1 g q8 h	4[a]	2
Meropenem 1 g q8 h	4[a]	2
Piperacillin/tazobactam 3.375 g q6 h	64[b]	8
Piperacillin/tazobactam 4.5 g q6 h	64[b]	8

[a]CLSI susceptibility breakpoints for imipenem and meropenem against *P. aeruginosa* were reduced to 2 mcg/ml in 2012
[b]CLSI susceptibility breakpoints for piperacillin/tazobactam against *P. aeruginosa* were reduced to 16 mcg/ml in 2012

Table 2: Clinical Laboratory Standards Institute (CLSI) susceptibility breakpoints for several β̃lactam antibiotics against *Pseudomonas aeruginosa* versus pharmacodynamics derived breakpoints, which are based on the ability for a dosing regimen to attain the *f*T>MIC exposure threshold for all bacteria defined as susceptible. Derived from DeRyke and colleagues [51].

Various methods have been employed to optimize the pharmacodynamics of the β-lactams, including giving higher dosages, administering the drugs more often, and prolonging the infusion time (either to 3-4 hours depending on room temperature stability or continuously over 24 hours). In general, the most effective way to optimize these agents, particularly for higher MIC organisms, is to both increase the administered dose and prolong the infusion, thereby maintaining a concentration above higher MICs for the required bactericidal exposure time. This has been applied to β-lactams such as cefepime and meropenem in clinical studies [52,53] Dosages of 2 grams every 8 hours (each dose administered as a 3 hour prolonged infusion) in patients with normal kidney function achieve a high probability of treating organisms considered resistant with MICs of 16 μg/ml and 32 μg/ml for meropenem and cefepime, respectively, which is significantly greater than if the same dosage regimen were infused over the standard 30 minutes.

Perhaps the most common β-lactam that these concepts have been applied to clinically is piperacillin/tazobactam. Both continuous and prolonged infusion techniques have been evaluated to optimize pharmacodynamics in several studies [54-57]. Using Monte Carlo simulation, Kim et al. found that a 4.5 g every 6 hour dose (with each dose infused over 3 hours) would achieve a similar pharmacodynamic exposure to the same daily dose (18.0 g) administered as a continuous infusion, and both would have higher probabilities of target attainment than the standard 4.5 g every 6 hour (30 minute infusion) dose at MICs ranging from 16 mcg/ml to 64 mcg/ml [55]. Importantly, the likelihood of achieving 50% *f*T>MIC at a MIC of 64 mcg/ml remained less than 30% for these regimens, further justifying the reduction in the CLSI susceptibility breakpoint to 16 mcg/ml for *P. aeruginosa*.

Clinically, continuous infusion piperacillin/tazobactam has been employed at the authors' institution since 1999 with good success using dosages ranging from 9 grams daily to 18 grams daily depending on the type of infection (e.g., higher dosages for pneumonia and bacteremia versus intra-abdominal and complicated skin and skin structure infections) and the patient's kidney function [54]. Benefits of a continuous infusion modality for piperacillin/tazobactam include its once daily administration, a reduction in daily dose for less severe infections leading to lower drug costs, and optimal time above the MIC. However, a 24 hour continuous infusion does require a dedicated intravenous site if other drugs with compatibility issues also require co-administration.

Circa 2005, Lodise et al. implemented a piperacillin/tazobactam dosing regimen at their medical center whereby all piperacillin/tazobactam orders were changed to 3.375 g every 8 hours (4 hour prolonged infusions) and compared the mortality and length of stay of this regimen with a historic control of patients who received 3.375g every 6 hours (as 30 minute infusion) for *P. aeruginosa* infections [56]. Patients receiving the prolonged infusion had a lower 14-day mortality rate (12.2% *vs.* 31.6%, p=0.04) and shorter hospital stay (21 days vs. 38 days, p=0.02) that reached statistical significance when limited to critically-ill patients with an APACHE II score of ≥17. These data confirm that, like continuous infusion, prolonged infusion is also a viable option for maximizing the outcomes of piperacillin/tazobactam against *P. aeruginosa*, and can do so while permitting a 4 hour window each dosing interval to administer other intravenous medications. However, according to pharmacodynamic models, the 3.375 g every 8 hour (4 hour infusion) regimen would be inadequate for isolates with MICs ≥ 32 μg/mL, thus it would be beneficial to know the piperacillin/tazobactam MIC distribution of the *P. aeruginosa* population in one's institution before implementing this dosage regimen [55]. Similarly, in a multicenter, retrospective medical record review, the RECEIPT Study evaluated 359 adult patients treated for gram-negative infections with either a 4-hour extended-infusion piperacillin-tazobactam (n=186) or non-extended-infusions of cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam (n=173). The primary outcome measured was mortality rate between the two groups respectively with secondary outcomes of hospital length of stay, ICU length of stay, and total duration of antibiotic therapy. Although baseline characteristics of the cohorts were slightly different, the investigators observed similar rates of antibiotic duration, hospital length of stay, and ICU length of stay, but in-hospital mortality was significantly less in the extended-infusion piperacillin-tazobactam group versus the comparators (9.7% *vs.* 17.9%, p=0.02). A multivariate analysis revealed the extended infusion group prolonged survival by 2.77 days (p<0.01) and reduced the risk of mortality (odds ratio 0.43, p=0.05) [57].

Recently, a systematic review and meta-analysis of observation studies assessing the clinical outcomes of extended or continuous infusion carbapenems or piperacillin/tazobactam versus standard infusion demonstrated a significant advantage to this pharmacodynamics strategy [58]. Mortality was lower among patients receiving extended or continuous infusion [relative risk (RR), 0.59; 95% confidence interval (CI), 0.41-0.83]. This was most notable among patients with pneumonia (RR, 0.50; 95% CI, 0.26-0.96) suggesting these dosage strategies may provide the greatest benefits for critically ill patients, or patients likely to be infected with more resistant organisms. Indeed, in the same issue of Clinical Infectious Diseases, investigators from Australia and Hong Kong presented the first prospective, double-blind, randomized controlled trial of continuous versus standard infusion β-lactam therapy in patients with severe sepsis [59]. Sixty patients from 5 different intensive care units were randomized to receive piperacillin/tazobactam, meropenem, or ticarcillin/clavulanate as continuous or standard 30 minute infusion regimens. The investigators observed plasma concentrations for the continuous infusion cohort to exceed the MIC in 82% of patients versus only 29% of the standard intermittent infusion cohort (p=0.001). Clinical cure was also higher in the continuous infusion group (70% *vs.* 43%, p=0.037); however, there was no observed difference in survival. These observations are similar to other small non-randomized studies that reported greater clinical success rates with continuous infusion piperacillin/tazobactam, meropenem, and ceftriaxone versus that of standard infusion in critically ill patients [60-62]. Finally, a double-blind, randomized controlled study of doripenem 500 mg q8h as a 4 hour prolonged infusion versus standard infusion imipenem-cilastatin in patients with ventilator-associated pneumonia demonstrated non-inferiority between dosing regimens; however, clinical success against the small population of patients infected with *P. aeruginosa* was numerically in favor of the prolonged infusion regimen [80% (16/20) *vs.* 43% (6/14)] [63]. Unfortunately, these results could not be replicated in a randomized controlled trial evaluating shorter courses of a higher dose prolonged infusion doripenem [64].

Collectively, these data suggest that continuous or prolonged infusion dosing strategies are effective in optimizing β-lactam pharmacodynamics and may result in a clinically superior dosing modality compared with standard infusion, particularly for critically ill patients or those infected with higher MIC pathogens. Selection of which antibiotic to apply these strategies to and at what dose depends on several factors, one of which is drug stability. Most beta-lactam antibiotics are stable for at least 24 hours at room temperature, and thus can be administered as a 24 hour continuous infusion or as prolonged infusion. However, certain beta-lactams including the carbapenems (imipenem, meropenem, doripenem), ampicillin, and the newest cephalosporin, ceftaroline, are not stable at room temperature for a full 24 hours. As a result, these antibiotics are better suited for administration as a prolonged infusion to enhance pharmacodynamic exposure while retaining room temperature stability requirements. Additional factors include the available antibiotics in one's hospital, the severity of illness of patients to receive these agents, and most importantly, the MIC distribution of target pathogens.

For example, the authors employed a strategic process to identify the most likely pathogens causing ventilator associated pneumonia in their intensive care units (ICUs), the MIC distributions for the most common Gram-negative (i.e., *P. aeruginosa*), and pharmacodynamics modeling to select the antibiotic and dosing regimen to empirically treat patients [65]. Due to substantial differences in MIC distributions for *P. aeruginosa* between the three included ICUs, different antibiotic regimens were implemented as empiric therapy. These included prolonged infusion regimens of meropenem (2 g q8h, 3 h infusion), cefepime (2 g q8h, 3 h infusion), and piperacillin/tazobactam (18 g continuous infusion) for patients with normal kidney function. After one year of implementing this program, appropriate antibiotic therapy was significantly increased in the intervention cohort and infection-related mortality was reduced by 69% (8.5% *vs.* 21.6%, p=0.029).

Clinical Pharmacodynamics of Other Antibiotic Classes

We refer the reader to table 1 for pharmacodynamic strategies for various other antibiotic classes. For newer antibiotic agents (i.e., those approved over the last decade), pharmacodynamics has typically

been considered in dosing regimen selection. As a result, for most susceptible bacteria listed in the approved indications, these antibiotics at approved dosages (e.g., linezolid 600 mg q12h, daptomycin 4-6 mg/kg q24h, tigecyline 50 mg q12h, etc.) have a high likelihood of obtaining pharmacodynamic exposure thresholds. We will, therefore, focus our remaining discussion on older antibiotic classes where standard dosing regimens likely did not consider pharmacodynamic theory.

Fluoroquinolones

While fluoroquinolone antibiotics are widely utilized and listed in the guidelines for the treatment of various infections (pneumonia, community and hospital-acquired; urinary tract infections; etc.), the poor susceptibilities for many gram-negative organisms that potentially cause these infections should make them second line considerations [20]. From a pharmacodynamic perspective, fluoroquinolones are unable to achieve bactericidal exposure (AUC/MIC > 125) at standard dosages for not only bacteria considered resistant, but also a number of bacteria that the microbiology laboratory would classify as susceptible [51]. This is a result of a higher than acceptable breakpoint used to define susceptibility for Gram-negatives (≤ 1 μg/ml for ciprofloxacin and ≤ 2 μg/ml for levofloxacin). Pharmacodynamic simulation studies suggest the proper breakpoints should be 0.25 μg/ml and 0.5 μg/ml, respectively, which would significantly increase resistance rates further at most hospitals. As a result, ciprofloxacin 400 mg every 8 hour and levofloxacin 750 mg every 24 hour regimens historically have achieved low probabilities of attaining the required pharmacodynamic exposure against *P. aeruginosa* isolates, as well as for the empiric treatment of hospital acquired pneumonia [66,67]. The pharmacodynamic strategy for fluoroquinolones against Gram-negatives is to; therefore, maximize the overall daily exposure through dosage increases in relation to the MIC. However, fluoroquinolones may not be tolerated at higher doses because peak concentrations are related to central nervous stimulation and gastrointestinal side effects. Thus the optimal fluoroquinolone dosing regimen is the maximum tolerated dose of the agent with the lowest MIC, so as to maximize AUC/MIC. If this exposure threshold cannot be obtained, these agents should be reserved for combination therapy regimens.

Against *S. pneumoniae* causing community acquired respiratory tract infections; a *f*AUC/MIC of at least 33.7 was required to optimize clinical response. Levofloxacin (intravenous and oral), moxifloxacin (intravenous and oral), and gemifloxacin (oral only) are currently the only available fluoroquinolones in the United States with sufficient microbiological activity against *S. pneumoniae*. Currently, resistance to these 'respiratory' fluoroquinolones is rare and standard dosage regimens (levofloxacin 750 mg once daily, moxifloxacin 400 mg once daily, and gemifloxacin 320 mg once daily) provide a high likelihood of achieving *f*AUC/MIC ratios of at least 30 against this organism in most patients [68,69].

Polymyxins

The polymyxin class of antibiotics includes polymyxin B and polymyxin E (colistin), the latter of which is administered clinically as colistin methane sulfate intravenously. Although an older class of antibiotics, their use has been revitalized by the multi-drug and pan-resistant strains of *P. aeruginosa*, *A. baumannii*, and carbapenem-resistant Enterobacteriaceae that has arisen over the last decade [37]. Notably, these agents were shelved in the early 1970's because of high rates of nephrotoxicity and neurotoxicity relative to other available antibiotic agents. Their pharmacokinetic/pharmacodynamic properties have only recently begun to be elucidated, and antimicrobial effect is correlated with *f*AUC/MIC exposures. To date, these experiments have largely been undertaken *in vitro* or in animal infection models. As previously mentioned, 1-log reductions in colony forming unit require *f*AUC/MIC ratios of approximately 12.2 to 22.8 in both thigh- and lung-infection murine models [37]. Unfortunately, the protein binding of colistin in humans, particularly critically ill patients, has not been established; therefore, for dosing strategies, a total AUC/MIC ratio of approximately 60 has been used to target drug concentrations [70]. Garonzik et al. used a population pharmacokinetic model from 105 critically ill patients receiving various clinical doses of colistin methane sulfate to derive recommendations for loading and maintenance doses. We refer the reader to the original reference for details on the weight-based, MIC-based dosing algorithm [70]. The investigators note, however, that because colistin methane sulfate, which is eliminated in the kidney, must be converted to active colistin for microbiological activity, and therefore obtaining therapeutic concentrations needed to achieve the AUC/MIC target would be unlikely in patients with a creatinine clearance (CrCL) greater than 70 ml/min or against an MIC greater than 0.5 mcg/ml, without increasing risk for nephrotoxicity. Based on pharmacokinetic and pharmacodynamic data, the most reasonable approach for polymyxins is to use them as part of a highly active antibiotic combination.

Vancomycin

Vancomycin, a glycopeptide, has long been considered a time-dependent killing antibiotic, and therefore therapeutic drug concentration monitoring by using peak concentrations, troughs, or both, has been practiced for years. Therapeutic drug monitoring for vancomycin has also been largely debated for the same amount of time. [71]. Current consensus for treatment of serious *S. aureus* infections is that vancomycin is a slowly-cidal, time-dependent killing antibiotic [72]. However, AUC/MIC, not T>MIC, is the most predictive pharmacodynamic parameter [26,27]. This concept, unfortunately, is directly opposed to guidelines that indicate that a trough of 15-20 mcg/ml is sufficient for therapeutic drug monitoring of the drug [72]. First, a trough alone is insufficient to estimate a patient's 24 hour AUC, unless incorporated into a population pharmacokinetic model using a Bayesian approach. Even so, an additional, often a peak, concentration is required to generate a more accurate estimate of clearance and AUC. Second, not all patients who obtain troughs of 15-20 mcg/ml obtain 24 hour AUCs sufficient to achieve an AUC/MIC of at least 400 [73]. Finally, the MIC is once again in the denominator for this pharmacodynamic parameter, and a single dilution in each direction will affect exposure significantly. Currently, standard dosing regimens of vancomycin aimed at obtaining troughs of 15-20 mcg/ml are not adequate to achieve the target AUC/MIC of 400 when the vancomycin MIC is above 1 mcg/ml [73]. Thus, based on this model, *S. aureus* with a vancomycin MIC of 2 mcg/ml are considered 'untreatable', yet remain susceptible given the current CLSI breakpoints. Although numerous studies have linked higher MICs with clinical failure and mortality, many patients receiving vancomycin against organisms at an MIC of 2 mcg/ml do well [74]. It is also well known that higher doses of vancomycin (upwards of 4 grams per day) cause a significant increase in nephrotoxocity, and in some patient populations it is not possible to achieve a trough of 15-20 mcg/ml without using dosages that result in toxicity [73,75]. Despite years of use and clinical studies, the optimal dosing strategy for vancomycin that optimized kill of *S. aureus* while minimizing nephrotoxicity has yet to be established [76]. Until then, clinicians are advised to at the very least continue to aim for trough concentrations of 15-20 mcg/ml, or collect sufficient information to calculate the AUC/MIC ratio, which would be several plasma concentrations and a MIC [72,73].

Conclusions

In the absence of new antibiotics to treat current pathogenic bacteria, the incorporation of pharmacodynamic principles into designing optimal dosing regimens for clinical practice is paramount. Knowledge of the relationship between antibiotic concentration to microbiological potency and its effect on antibacterial activity can lead to the design of dosing regimens that optimize killing of bacteria in the clinical setting. Fortunately, these optimal dosing strategies are now defined for many of the available antibiotics we use frequently, including aminoglycosides and β-lactams. Pharmacodynamic strategies for other antibiotic classes continue to evolve.

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