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REVIEW

Use of Pharmacodynamic Principles to Inform β-Lactam Dosing: "S" Does Not Always Mean Success

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Dose optimization is one of the key strategies for enhancing antimicrobial stewardship. There have been tremendous strides in our understanding of antibiotic exposure-response relationships over the past 25 years. For many antibiotics, the "pharmacodynamic" or the exposure variable associated with outcome has been identified. With advances in mathematical modeling, it is possible to apply our understanding of antimicrobial pharmacodynamics (PD) into clinical practice and design empirical regimens that have a high probability of achieving the PD target linked to effect. By optimizing antibiotic doses to achieve PD targets predictive of efficacy, clinicians can improve care and minimize drug toxicity. For β-lactams, the PD parameter most predictive of maximal bactericidal activity is the duration of time free drug concentrations remain above the minimum inhibitory concentration (MIC) during the dosing interval ($fT > MIC$). Unfortunately, the conventional intermittent β-lactam dosing schemes often used in practice have suboptimal PD profiles. Prolonging the infusion time of β-lactams is one method to maximize the probability of achieving concentrations in excess of the MIC for the majority of the dosing interval, especially against pathogens with elevated MIC values. Prolonged infusions of intravenous β-lactams are not only associated with improved probability of target attainment (PTA) profiles but offer possible cost savings and greater potential for reducing emergence of resistance relative to intermittent infusions. ***Journal of Hospital Medicine*** **2011;6:S16–S23.** © *2011 Society of Hospital Medicine.*

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Tremendous strides have been made over the last 25 years in understanding the relationship between antimicrobial exposure and response.[1–4] Many clinicians consider antimicrobial drug pharmacokinetics (PK) and pharmacodynamics (PD) a rather esoteric or academic topic without practical applicability or clinical utility. However, it is becoming increasingly clear, particularly as less-susceptible pathogens emerge, that consideration of PK/PD in dose selection is essential for optimizing antimicrobial therapy and, as such, is a core component of effective antimicrobial stewardship and patient care. Antimicrobial therapy can fail if an appropriate agent is selected but the dosing regimen does not provide adequate exposure against the infecting pathogens, especially at the site of infection.[5,6]

The 2007 guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) for developing institutional antimicrobial stewardship programs highlight dose optimization as one of the key strategies for enhancing antimicrobial stewardship.[7] More specifically, they recommend optimizing dosing by focusing on individual patient characteristics, causative organism and site of infection, and the PK/PD characteristics of the drug. With advances in mathematical modeling (Monte Carlo simulation), it is possible to apply our understanding of PK/PD to clinical practice and design empiric regimens that have a high probability of achieving the PD target linked to effect. These mathematical modeling techniques have an array of other utilities and have become the standard methodologies for assessing the clinical viability of both experimental and approved antimicrobials.[8,9] Furthermore, the Clinical and Laboratory Standards Institute (CLSI) has recently begun to incorporate results from PK/PD analyses in determining MIC breakpoints.[10] This paper provides a general overview of antimicrobial PD before demonstrating how to apply PD principles to clinical practice through the use of Monte Carlo simulation (MCS). Piperacillin/tazobactam (TZP) is used as a motivating example for this latter purpose.

Pharmacokinetics and Pharmacodynamics: Parameters and Principles

Pharmacokinetics describes the actions of the body on an administered drug, whereas PD describes the actions of the administered drug on the body. In essence, PK refers to the movement of the drug within the body, including absorption, distribution, metabolism, and excretion. Conversely, PD refers to the effects of the drug on the body, or its physiologic actions. A drug's PD is defined by its mechanism of action, and includes both desired and undesired effects. Typically, PK and PD work together to best define or predict

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the full range of effects of an administered drug on an individual patient, as described in greater detail below.

The Minimum Inhibitory Concentration

The MIC is the PD parameter most often used to describe the relationship between antimicrobial drug and physiologic activity. The MIC is defined as the lowest or minimum antimicrobial concentration that inhibits visible microbial growth in artificial medium after a fixed incubation time.[10,11] This is typically determined by placing a known quantity of bacteria (or other microorganism) into multiple test tubes, and then adding increasing concentrations of a particular antibiotic, typically in $\log_2$ dilution, into consecutive tubes. The lowest antibiotic concentration that inhibits bacterial growth is then defined as the MIC for that drug-pathogen pairing.

While useful as a quantitative measure of drug activity or potency, the MIC is not without limitations.[12] The MIC does not mimic physiologic conditions. The MIC is a static measure (fixed concentration of drug in an artificial growth medium for a fixed period of time) and is not reflective of the concentration-time profile one would typically observe in patients; drug concentrations change throughout the dosing interval. Because the MIC only measures growth inhibition, it does not reflect the rate at which bacteria are killed, nor can it identify if a dose–kill response relationship exists for a particular antibiotic-pathogen pairing. Furthermore, the MIC only quantifies net growth over an 18–24-hour observation period. Killing and regrowth may well occur during this period, as long as the net growth is zero. Finally, the MIC does not account for the post-antibiotic effects of antibiotics. Most antibiotics, depending on the pathogen and drug class, exhibit some persistence of bacteriostatic or bactericidal activity after the drug concentration at the target site has dropped below the MIC. This activity has been described as the post-antibiotic effect,[13–15] post-antibiotic sub-MIC effect,[13–17] or post-antibiotic leukocyte enhancement effect.[18,19]

Common Pharmacodynamic Measures

Examination of PK measures of drug exposure (eg, serum/tissue concentrations) in relation to the MIC surmounts many of the limitations of the MIC and provides much better prediction of antimicrobial effect than the MIC or exposure profile alone. The 3 most common PK/PD indices (sometimes abbreviated as PD measures) used to predict drug response are: 1) the ratio of the maximal free drug concentration to the MIC (fC$_{max}$:MIC), 2) the ratio of the free area under the concentration-time curve to the MIC (fAUC:MIC), and 3) the duration of time free drug concentrations remain above the MIC (fT>MIC).[2–4,20,21] The PD parameter most predictive of outcomes varies by drug class (Table 1).[20]

Certain antibiotics exhibit concentration-dependent bactericidal activity, while others exhibit time-dependent activity (Table 1).[2–4,20] For concentration-dependent antibiotics, a dose–response relationship exists and the therapeutic goal is to maximize exposure at the target site. Alternatively, the activity of time-dependent antibiotics is not dependent on the intensity of exposure but is a function of the duration of time concentrations are above the MIC during the dosing interval. For the time-dependent antibiotics like the β-lactams, concentrations do not have to remain above the MIC for the entire dosing interval, and the fraction of the dosing interval required for maximal bacterial effect varies for the different types of β-lactams. Although the precise fT > MIC varies for different drug–bacteria combinations, bacteriostatic effects are typically observed when the free drug concentration exceeds the MIC for 35–40%, 30%, and 20% of the dosing interval for the cephalosporins, penicillins, and carbapenems, respectively. Near-maximal bactericidal effects require 60–70%, 50%, and 40% fT > MIC, respectively, for these β-lactam classes.[3,4]

TABLE 1. PD Parameters by Drug Class

Antibiotic	Optimal PD measure(s)
Aminoglycosides	Cmax:MIC; AUC:MIC
β-lactams	
Penicillins	T>MIC
Cephalosporins	T>MIC
Carbapenems	T>MIC
Monobactams	T>MIC
Clindamycin	AUC:MIC
Fluoroquinolones	AUC:MIC, Cmax:MIC
Glycopeptides/lipopeptides	
Daptomycin	AUC:MIC, Cmax:MIC
Oritavancin	T>MIC, Cmax:MIC
Vancomycin	AUC:MIC
Linezolid	AUC:MIC
Macrolides	
Azithromycin	AUC:MIC
Clarithromycin	AUC:MIC
Telithromycin	AUC:MIC
Metronidazole	AUC:MIC, Cmax:MIC
Tetracyclines	
Doxycycline	AUC:MIC
Tigecycline	AUC:MIC

AUC:MIC, ratio of the area under the concentration-time curve at 24 hours to the MIC; C_{max}:MIC, ratio of the maximal drug concentration to the MIC; T > MIC, duration of time a drug concentration remains above the MIC.
Abbreviations: AUC, area under the curve; MIC, minimum inhibitory concentration; PD, pharmacodynamics.

It is important to note that it is the free (or unbound) fraction of drug that determines its ability to penetrate tissues and exert its microbiological effect.[3,4,22] This was demonstrated as early as the 1940s with penicillin. There are occasionally exceptions, mostly with the therapy of gram-positive infections. Daptomycin is one such example; protein binding is approximately 90–92% (free drug 8–10%), but the agent behaves as if the drug is approximately 75% bound (25% free).[23] Nonetheless, the guiding principle is that protein binding can have an adverse impact on the PD and microbiological activity of an antibacterial agent.

Monte Carlo Simulation

"With advances in mathematical modeling, it is possible to apply our understanding of antimicrobial PD to clinical

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practice."[12] In particular, MCS can be used to integrate PK, PD, and local microbiologic surveillance data to design antibiotic regimens that have a high probability of achieving the PD target linked to effect against the range of pathogens encountered in clinical practice. In short, MCS is a technique that incorporates the variability in PK among potential patients (between-patient variability) when predicting antibiotic exposures, and allows calculation of the probability for obtaining a critical target exposure for the range of possible MIC values.[12] If a number of volunteers or patients are given an antibiotic, there will be true variability in the observed concentration time profiles between people. For example, the peak serum concentrations and $AUC_{0\text{-}24h}$ will vary between individuals. In essence, MCS is a mathematical modeling technique that "simulates" the dispersion or full spread of concentration-time exposure values (eg, peak concentration, area under the curve) that would be seen in a large population after administration of a specific drug dose or regimen. Once the distribution in concentration-time profiles is determined, the probability of achieving the PD target at each MIC value for a given MIC range (ie, probability of target attainment [PTA] profile) is ascertained.

There are several steps in the MCS process. First, a PK model for the antibiotic under study is embedded into the MCS. The mean PK parameters (eg, volume, clearance, intercompartmental transfer constant) and associated variability (variance and covariance) from the selected PK model are used to create a multivariate distribution of PK parameters. From this multivariate distribution, the MCS randomly selects a set of PK parameters, and these randomly selected PK parameters are used to simulate a concentration-time profile for a "virtual" subject based on the desired antibiotic dosing regimen. This process is repeated a specified number of times (eg, 5000, 1000) to simulate the distribution of concentration-time profiles one would expect to see in the population. Once the specified number of virtual patients has been simulated (eg, 10,000 virtual patients), the proportion of the simulated population that achieves the critical exposure target (eg, 50% $fT > MIC$) at each MIC value for a given MIC range can be calculated. Because the relationship between drug exposure and effect is expressed as a ratio (eg, AUC:MIC, C_{max}:MIC, T:MIC), a unique drug exposure:MIC ratio and PTA exists for each unique MIC value within the distribution.[12]

In clinical practice, a distribution of MIC values exists for a given organism or infection. Therefore, the final step is determining the overall PTA for the distribution of organisms encountered clinically. As previously mentioned, the PTA is determined at each MIC value within a given MIC range. Because the fraction of organisms collected at each MIC value is known, the overall or weighted PTA average can be calculated by multiplying the PTA for a specific MIC and the proportion of isolates with that MIC. This product is calculated for each MIC value within the MIC distribution. The overall PTA is then calculated by summing the products (PTA at a given MIC value x proportion of isolates with that MIC value) of the MIC values encountered within the distribution.[12]

A key element for these simulations is the estimation of the PK parameters and their associated dispersion (variance and covariance). Pharmacokinetic data, especially for new compounds, are usually limited to data from healthy volunteer studies. Caution should be exercised when generalizing the results of volunteer studies to the population of interest. Volunteer studies are often considered as the most conservative evaluation of a new drug; volunteers are young and healthy, likely to have the highest drug clearances and shortest half lives. However, when one performs MCS, the measure of central tendency (high drug clearance, short half-lives) is only part of the story. Because MCS are explicitly creating a distribution, it is important to understand the measure of dispersion. Secondary to the limited variation surrounding PK parameters from healthy volunteer studies, it is possible that they overestimate the PTA. Applicability to the target population must always be considered.[12]

Motivating Example: Piperacillin-tazobactam

Piperacillin-tazobactam (TZP) is an acylureido-penicillin–beta-lactamase inhibitor combination and is frequently used as first-line empirical therapy for healthcare-associated infections. Like all β-lactams, the PD parameter most predictive of its efficacy is $fT > MIC$, and its activity is optimized when free drug concentrations exceed the MIC for 50% of the dosing interval (50% $fT > MIC$). Because it is used empirically, it is critical that the TZP regimens used in practice have a high probability of achieving 50% $fT > MIC$ against the range of MIC values likely to be encountered in a given institution.

Since the MIC of the infecting pathogen is often not available at the start of therapy, clinicians frequently rely on the hospital antibiogram to determine the utility of an antibiotic as an empiric agent. The range of MIC values reported as "susceptible" in clinical practice is based on the CLSI susceptibility interpretive criteria. For TZP, *Enterobacteriaceae* and *Acinetobacter baumannii* isolates with MIC values $\leq$16 mg/L are considered susceptible. The CLSI breakpoint for *Pseudomonas aeruginosa* is higher and isolates with MIC values $\leq$64/4 mg/L are considered susceptible.[11]

It is important to recognize that these CLSI TZP susceptibility breakpoints were established prior to our current understanding of β-lactam PD and are higher relative to other β-lactams. It was not until sometime after the establishment of the TZP susceptibility interpretive criteria were MCS studies performed to determine the ability of the US Food and Drug Administration (FDA)-approved TZP dosing regimens in achieving 50% $fT > MIC$ against the range of MICs deemed susceptible by CLSI.

The first study to characterize the ability of standard TZP dosing (0.5-hour infusion of 3.375 g every 6 hours) in achieving 50% $T > MIC$ in its targeted population for the range of MIC values deemed susceptible by CLSI was published in 2004 by our group. Employing a population PK model derived in hospitalized patients, TZP 3.375 grams administered every 6 h provided high PTA rates for MICs of $\leq$8/4 mg/L (ie, 8 mg/

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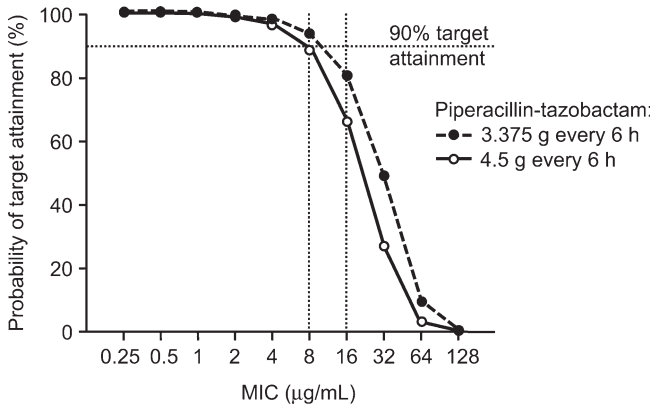

FIGURE 1. Probability of achieving 50% fT > MIC for piperacillin/tazobactam 3.375 g administered every 6 hours as a 0.5-hour infusion and piperacillin/tazobactam 4.5 g administered every 6 hours as a 0.5-hour infusion (modified from Lodise, 2004[24] and DeRyke, 2007.[25] Original magnification: 160 × 99 mm (300 × 300 DPI). Abbreviations: MIC, minimum inhibitory concentration; DPI, dots per inch.

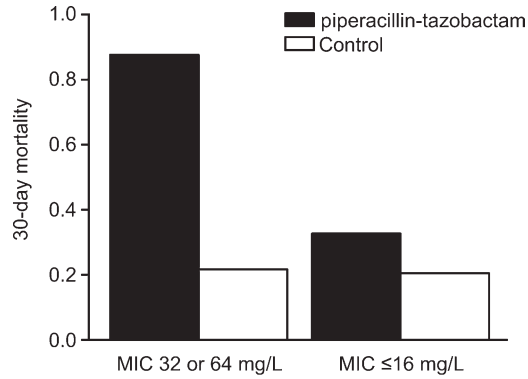

FIGURE 2. 30-day mortality among patients with *Pseudomonas aeruginosa* bacteremia (reprinted by permission from Tam et al, 2008).[26] Control patients received alternative empiric therapy (in doses appropriate for renal function as recommended by the manufacturer) within 24 hours of the first positive blood culture result to which the isolate was found to be susceptible using current CLSI susceptibility breakpoints. Original magnification: 132 × 93 mm (300 × 300 DPI). Abbreviations: MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute (CLSI); DPI: dots per inch.

L for piperacillin and 4 mg/L for tazobactam) when hospitalized-patient data were used (Figure 1).[24] In clinical situations in which the MICs are expected to be ≥16/4 mg/L, the results of the MCS indicate that caution should be exercised when using standard TZP dosing. More recently, DeRyke et al evaluated the PD profile of the TZP nosocomial dosing scheme (0.5-hour infusion of 4.5 g every 6 hours). Using the same population PK model employed as our study, DeRyke and colleagues noted a slightly improved PTA profile at a MIC value of 16/4 mg/L with the TZP nosocomial pneumonia dosing scheme relative to standard dosing. However, the PTA was still suboptimal for MIC values ≥ 32/4 mg/L (Figure 1).[25]

These findings are concerning because the TZP CLSI susceptibility breakpoint for non-lactose fermenting Gram-negative bacteria is ≤ 64/4 mg/L.[11] In essence, the conventional and nosocomial pneumonia TZP dosing schemes provide a suboptimal PD profile for a substantial portion of the MIC distribution deemed susceptible by CLSI. The clinical relevance of this is highlighted by a study by Tam and coworkers examining the efficacy of TZP in hospitalized patients with bacteremia due to *P. aeruginosa* (Figure 2).[26] This retrospective cohort study examined 30-day mortality among patients who received appropriate empiric therapy between 2002 and 2006. Therapy was defined as appropriate if: 1) β-lactam treatment (in doses appropriate for renal function as recommended by the manufacturer) was started within 24 hours of blood culture collection, and 2) the isolate was found to be susceptible to the β-lactam agent selected. The cohort was stratified by the TZP piperacillin MIC (32–64 mg/L vs. ≤16 mg/L) and 30-day mortality rates were compared within MIC strata between patients who received TZP or an alternative β-lactam with activity against *Pseudomonas aeruginosa*. A total of 34 episodes with MICs of 32 or 64 mg/L were identified. Seven of these cases were empirically treated with TZP, while the remaining 27 received other β-lactam agents. Forty-nine episodes of *P. aeruginosa* bacteremias had MIC values ≤16 mg/L. Of these 49, 10 were empirically treated with TZP and the remaining 39 were treated with other β-lactams. The results showed that the 30-day mortality rate was significantly higher among patients treated with TZP versus control-treated patients with isolates possessing a MIC of either 32 or 64 mg/L (86% vs. 22%, P value = 0.004), while there was no significant difference between the two treatment groups for isolates with a MIC of up to 16 mg/L (30% vs. 21%, $P = 0.673$). Interestingly, patients treated with a non-TZP β-lactam antibiotic had 30-day mortality rates of ≈21%, regardless of the TZP MIC value. Collectively, these findings and the results of the TZP MCS studies highlight the importance of considering PTA data when evaluating the utility of an antibiotic dosing scheme. These data also cast uncertainty on the appropriateness of the current TZP CLSI susceptibility breakpoint in connection with the conventional dosing TZP strategies. The current CLSI interpretation of TZP susceptibility for non-lactose-fermenting gram-negatives may inadvertently provide misleading guidance to clinicians for optimal patient care.

Dosing Strategies to Improve the Probability of Target Attainment Profile of β-lactams

Three potential dosing strategies used to improve the PTA of a β-lactam against the range of pathogens encountered in various clinical situations include: 1) increasing the dose, 2) increasing the dosing frequency, or 3) increasing the duration of infusion.[12] Intuitively, it makes sense to simply increase the drug dose. However, as demonstrated in the aforementioned TZP MCS studies, increasing the TZP dose from 3.375 grams to 4.5 grams every 6 hours had a minimal impact on the PTA profile.[24,25] To increase *f*T >MIC by 1

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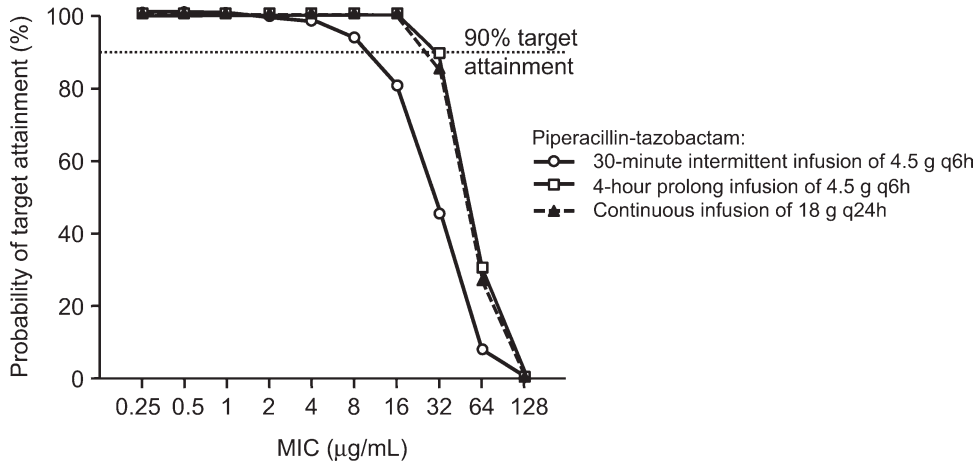

FIGURE 3. Probability of target attainment at doubling MIC dilutions for piperacillin/tazobactam regimens containing piperacillin 16 g/day (reproduced from Kim et al, 2007).[31] Original magnification: 205 × 99 mm (300 × 300 DPI). Abbreviations: MIC, minimum inhibitory concentration; DPI: dots per inch.

half-life, the dose would need to be doubled. Since most β-lactams have a half-life of 30 minutes to 1 hour, doubling the dose only provides an extra 30 minutes or hour above the MIC, which would not be expected to have much clinical impact. In addition, doubling the dose is not cost effective since it doubles drug acquisition costs.[12,27]

Increasing the dosing frequency is a viable option and may be the optimal strategy in certain situations.[12] However, it is often associated with increased drug acquisition costs (more doses per day) relative to the parent regimen and may not be a viable option from a nursing and pharmacy perspective due to increased administration and preparation time. In addition, there may be a higher potential for toxicity because a greater amount of drug is given per day.

Extending the infusion time is another β-lactam dose optimization strategy that is becoming more commonly used in clinical practice. "Administering a dose of a β-lactam agent as an infusion longer than the conventional 0.5–1.0-hour infusion duration has 2 main effects. First, it produces a lower peak concentration of the drug."[24] Because the bacterial kill rate for these agents is not concentration-dependent, this does not present a major disadvantage.[3,4,28–30] Second, the drug concentrations remain in excess of the MIC for a longer period of time. Because this is what drives antibacterial effect for β-lactams, this will yield a more favorable PTA profile. It should also be noted that this can be done with less frequent drug dosing.[27]

Extending the infusion time can be accomplished by either prolonging the infusion time for a major portion of the dosing interval (prolonged infusion) or administering continuously throughout the day (continuous infusion). From a PD profiling viewpoint, the two infusion methodologies yield nearly identical PTA profiles. This was highlighted in the 2007 study by Kim et al, which compared PTA rates between intermittent (0.5 hour), prolonged (4 hours), and continuous infusions of TZP (Figure 3). In their study, the PTA curves for prolonged and continuous infusion TZP were superimposable and superior to the intermittent infusion regimen for MIC values in excess of 4 mg/L.[31]

There are several practicalities to consider when differentiating prolonged and continuous infusion methods. The principle advantages of continuous infusion are once-daily administration and reduced costs for labor, supplies, and administration.[12,27] The major disadvantages of continuous infusion are the need for a dedicated line for infusion (which often leads to drug compatibility issues), issues of drug stability and waste, and lack of ambulation for the patient. The need for a dedicated infusion line is particularly impractical for patients with limited intravenous access or those requiring multiple daily infusions. In addition, continuous infusion often requires insertion of a central line, which places patients at unnecessary risk of secondary catheter-related infection.[12] Continuous infusion solutions are typically prepared as 24-hour infusions containing the total daily amount of drug. Considerable drug wastage can occur with early discontinuation of therapy; all drug within the solution needs to be wasted and cannot be reused if the order is discontinued prior to scheduled completion.

Prolonged infusion provides many of the benefits of intermittent dosing, but with the PD advantages of continuous infusion. Administration of the infusion for a prolonged time, but not continuously, obviates the need to have a dedicated intravenous line just for β-lactam continuous infusion. It also achieves the targeted $fT > MIC$ at a total daily dose less than standard β-lactam dosing methods. Drug wastage is also minimized because the intermittent administration formulations are used; there is no need to prepare antibiotic solutions for 24-hour periods. Prolonged infusion also allows the patient to be ambulatory for much of the day. The potential disadvantages of prolonged infusion relative to continuous infusion include the increased use of labor, supplies, and administration resources. Although minimized, there is still the need to schedule or time the administration of incompatible drugs.[12,27]

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Data Examining the Outcomes Associated With Prolonged and Continuous β-lactam Infusions

Over the years, a number of randomized controlled trials (RCTs) and observational studies have compared outcomes between extended and intermittent β-lactam infusions. These studies, mostly small scale in nature, involved a number of different β-lactam antibiotics and various infectious etiologies. To ascertain if there are any clinical benefits in extending the infusion duration (prolonged and continuous), Roberts and colleagues performed a systematic review of available data on PubMed (January 1950 to November 2007), EMBASE (1966 to November 2007), and the Cochrane Controlled Trial Register (updated November 2007).[32] Randomized controlled trials were meta-analyzed, and observational studies were reviewed. Among a total of 59 potentially RCTs, 14 involving a total of 846 patients from nine countries were deemed appropriate for meta-analysis. The use of continuous infusion of a β-lactam antibiotic was not associated with an improvement in clinical cure (n=755 patients; odds ratio: 1.04, 95% confidence interval: 0.74–1.46, $P = 0.83$) or mortality (n=541 patients; odds ratio: 1.00, 95% confidence interval: 0.48–2.06, $P = 1.00$). In contrast, the observational studies showed that β-lactam administration by extended or continuous infusion confers an improvement in clinical cure and this was most pronounced in critically ill patients being treated for gram-negative bacterial infections.

There are several possible explanations for the discrepancy in results between the meta-analysis and observational studies. First, disease severity in the studies included in the meta-analysis was generally low, as evidenced by low mortality rates in the majority of studies. Second, a diverse group of patients and infection types were included in the RCTs, which increased the heterogeneity of the cohort analyzed. Third, a higher antibiotic dose was used in the intermittent administration group in all RCTs except one. Fourth, microbiologic and PK/PD data were not available for the majority of RCTs. Collectively, the null result from the meta-analysis and positive data from the nonrandomized studies suggest that prolonged or continuous infusion β-lactams is unlikely to be advantageous for all hospitalized patient populations, but may be beneficial for specific groups, such as critically ill patients with higher MIC pathogens.

The benefits of prolonged β-lactam infusion among critically ill patients were highlighted by the study performed at Albany Medical Center Hospital.[27] Based on a MCS, prolonged infusion TZP (3.375 grams administered over a 4-hour period every 8 hours) was identified as an alternative means to the intermittent TZP dosing (3.375 grams administered over 30 minutes every 4 or 6 hours) and adopted as the standard TZP dosing scheme in February 2002. Prior to February 2002, all patients received traditional infusion TZP; after this time, all patients received prolonged infusion TZP. To evaluate the impact of the automatic dose substitution program, 14-day mortality and hospital length of stay post-culture collection were compared between patients who received either intermittent or prolonged TZP infusion for a TZP-susceptible *P. aeruginosa* infection between 2000 and 2004.[27] The study was restricted to *P. aeruginosa* infections for several reasons. First, patients with *P. aeruginosa* represented a relatively homogenous patient population; this attribute minimized confounding and increased the ability to detect differences between treatment groups according to intervention. Second, patients with *P. aeruginosa* infections are more dependent on antimicrobial therapy than other populations, since patients infected with *P. aeruginosa* are frequently critically ill and often have an impaired innate immune system.[33,34] Third, *P. aeruginosa* isolates typically have a higher range of MICs to TZP than other organisms, and the benefits of optimizing *f*T>MIC were thought to be better elucidated in this patient population.[35,36]

In patients who were identified as having the greatest risk for 14-day mortality (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≥17), there was a significantly lower 14-day mortality rate and a shorter median hospital LOS after culture sample collection for patients who received prolonged infusion, compared with patients who received intermittent infusion (Figure 4). No differences between prolonged infusion and intermittent infusion of TZP were observed with respect to outcome in patients at lowest risk for death (APACHE II score <17). These findings support the notion that critically ill patients who have *P. aeruginosa* infection are most dependent upon drug exposure for good clinical outcomes. The results also suggest that improved outcomes can be achieved by optimizing antibiotic PD in this population. Furthermore, the results highlight the importance of examining the influence of treatment within a population at greatest risk for the outcome of interest.[27]

In addition to potential clinical benefits, prolonged infusions can provide cost savings by minimizing the amount of drug used per day. Prolonged infusion typically achieves the targeted *f*T > MIC at a total daily dose less than standard β-lactam dosing methods. For example, TZP purchases totaled $275,000 the year before conversion at Albany Medical Center Hospital. Switching to the prolonged infusion strategy reduced the total daily dose by 25%–50% (by 1–3 doses per day) representing a savings of $68,750–$135,750 in annual direct drug acquisition costs.[27]

Additional Pharmacokinetic and Pharmacodynamic Considerations

When assessing the PK/PD of an antibiotic, it is also important to consider concentrations achieved at the site of infection. Most MCS studies have focused on free concentrations in plasma. Whereas free concentrations in plasma are often viewed as an acceptable approximation for free concentrations at the site of infection, this is not always the case. Of particular concern is in the treatment of lower respiratory tract infections. For β-lactams, it was commonly believed that plasma and epithelial lining fluid (ELF) of the alveolar space concentrations were comparable; antibiotic concentrations in ELF are currently used to estimate the penetration of antibiotics into the respiratory tract. However, the median ELF/plasma penetration ratio for meropenem among patients with ventilator-associated pneumonia (VAP) is only 25%.[37] The only way to achieve a favorable *f*T > MIC PD profile at the site of infection with meropenem is to

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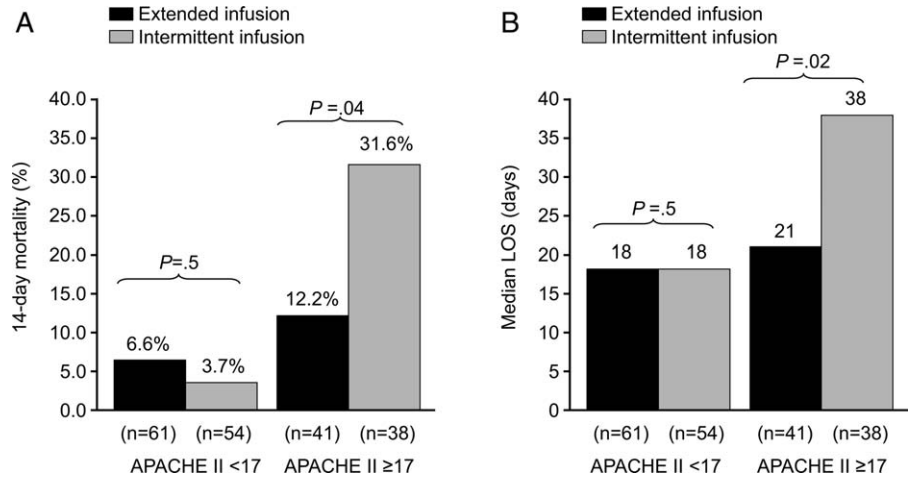

FIGURE 4. Comparison of (A) 14 day mortality rate and (B) Median LOS of patients with APACHE II scores $\geq$ 17 and patients with APACHE II scores <17 who received either a prolonged (4 hours) or intermittent infusion (0.5 hour) of piperacillin/tazobactam. Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; LOS, length of stay. [a]Excludes patients dying within 14 days of collection of *P. aeruginosa*-positive culture sample. Comparison between patients with APACHE II score below 17 and APACHE II score of 17 or above was $P < 0.05$. Comparison between prolonged and intermittent infusion group was $P < 0.05$. (Reproduced from Lodise et al., 2007)[27] 233 × 124 mm (300 × 300 DPI).

administer higher doses over prolonged periods of time (Figure 4). In light of the meropenem ELF data, data available on concentrations at the site of infection, particularly difficult-to-penetrate sites, such as ELF and cerebrospinal fluid, should be considered before designing dosing scheme for implementation into clinical practice.

Up to this point, this review has been focused on PD targets of clinical success. The next frontier in PK/PD is identifying antibiotic dosing schemes and drug combinations that minimize the emergence of resistance. Data available to date suggest that PD targets for resistance prevention are typically 2–4-fold higher than PD targets for success. Tam et al showed that for meropenem, the PD target needed to suppress the emergence of resistance in *P. aeruginosa* was a C_{min}:MIC ratio of 1.7.[38] Further study is still needed in the area of resistance suppression but the current data suggest that obtaining the PK/PD target against the range of MIC encountered clinically is not likely with conventional β-lactam dosing and will most likely require more intensive regimens administered over extended periods of time.[38]

Arguments Against Extended β-lactam Infusions

Limited clinical trial data and lack of FDA approval are frequently cited as the major clinical barriers for implementing extended β-lactam infusions into practice. Unfortunately, there is a relative dearth of large-scale randomized clinical data supporting extending the infusion of β-lactam therapy. In addition, the package inserts for the various β-lactam antibiotics do not provide support for these prolonged infusion dosing.

While these are valid concerns, the clinical support for intermittent β-lactam infusions is also limited. The clinical data are largely limited to complicated intra-abdominal infections, complicated skin and soft tissue infections, complicated urinary tract infections, and community-acquired pneumonia. None of the intermittently administered β-lactams currently have an indication for bacteremia (except imipenem for bacterial septicemia), and there are only limited indications for hospital-acquired pneumonia (HAP) or VAP (imipenem for lower respiratory tract infections and TZP in combination with an aminoglycoside for HAP). In addition, the clinical trials of intermittent β-lactam infusion regimens have commonly assessed clinical response at the test-of-cure visit or after completion of therapy. Arguably, this is not a very clinically meaningful endpoint for the types of infections commonly encountered on a day-to-day basis in today's world, where mixed diagnoses and infecting pathogens are often seen. Most important, the bacteria have evolved since the early clinical trials used to obtain FDA approval, and those outdated studies do not address the resistance profiles currently observed in clinical practice.

Conclusions

Understanding exposure-response relationships is critical when designing antibiotic dosing schemes. In the absence of therapeutic drug monitoring, MCS can be used to design antibiotic regimens that have a high probability of attaining the PD target linked to effect against the range of MICs likely to be encountered in clinical practice. When considering β-lactam therapy for critically ill patients likely infected with high-MIC or reduced-susceptibility pathogens, a prolonged or continuous infusion regimen should be considered. Compared with intermittent dosing, prolonged infusion of β-lactams is typically associated with improved PTA, as potential benefits of cost savings, and an enhanced PD profile at the site of infection.

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