Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on β-Lactam Antibiotics

Insights from the Society of Infectious Diseases Pharmacists

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In recent years there have been tremendous strides in understanding the relationship between the pharmacodynamics of β-lactams and microbiologic response. For β-lactams, in vitro and animal studies suggest that the amount of time in which free or non–protein-bound antimicrobial concentration exceeds the minimum inhibitory concentration (MIC) of the organism (fT>MIC) is the best predictor of bacterial killing and microbiologic response. Using population pharmacokinetic modeling and Monte Carlo simulation, it is possible to integrate pharmacokinetics, a pharmacodynamic target, and microbiologic surveillance data to generate empiric β-lactam dosing strategies that maximize the likelihood of achieving fT>MIC associated with near-maximal bactericidal effect against the range of pathogens encountered in clinical practice. At Albany Medical Center Hospital, these mathematical modeling techniques were used to devise alternative dosing schemes for piperacillin-tazobactam, meropenem, and cefepime. These alternative schemes optimized fT>MIC at a lower total daily dose than would be employed with traditional dosing methods. Moreover, they achieved the targeted fT>MIC with less administration time/day than would be needed for continuous infusion.

Key Words: pharmacokinetics, pharmacodynamics, Monte Carlo simulation, antibiotics, β-lactams.

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Antimicrobial pharmacodynamics describe the relationship between drug exposure and antimicrobial activity. Over the past 20 years, there have been tremendous strides in understanding the relationship between pharmacodynamics and microbiologic response. Specifically, the pharmacodynamic target associated with maximal effect has been identified for most antimicrobials, including the β-lactams. With advances in computer technology and mathematical modeling (population pharmacokinetics and Monte Carlo simulation), it is now possible to apply pharmacodynamic principles to clinical practice. Specifically, mathematical modeling techniques can determine the probability that an antibiotic dosing regimen will achieve the pharmacodynamic target associated with maximal effect. Moreover, these techniques...
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make it possible to design antimicrobial regimens that optimize the probability of achieving this target. 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.

Un fortunately, most β-lactam antibiotics that are widely used were developed before our current understanding of β-lactam pharmacodynamics. It is not surprising that many conventional β-lactam dosing schemes are suboptimal; these schemes often provide a concentration-time profile with a low probability of achieving the pharmacodynamic end point linked with a favorable outcome in the targeted patient population. In an effort to maximize the pharmacodynamic profile of β-lactam antibiotics and ensure the highest probability of the desired patient response, alternative dosing schemes for piperacillin-tazobactam, meropenem, and ceferpine derived from population pharmacokinetic modeling and Monte Carlo simulation were adopted into clinical practice at Albany Medical Center Hospital (AMCH).

Antimicrobial Pharmacodynamics: An Evolving Science

Historically, the measure most often used to characterize antimicrobial activity is the minimum inhibitory concentration (MIC), which is the antimicrobial concentration that inhibits visible microbial growth in artificial media after a fixed time of incubation. Although the MIC is a useful parameter, it is often viewed as an “all or none” (growth vs no growth) phenomenon and does not provide information on the time course of antimicrobial activity; that is, because the MIC is determined after exposure to fixed concentrations of drug, MIC values fail to account for the fact that drug concentrations change throughout the dosing interval. More important, since the MIC concentration is fixed, it does not capture interpatient pharmacokinetic variability. It is well known that if a number of patients are given an antibiotic, there will be considerable dispersion in the observed concentration-time profiles.

In addition, the MIC does not provide information on the potential for persistent antinefctive activity after drug concentration at the site has dropped below the MIC or on the additive effects of the immune system with the drug. The MIC does not reflect the rate at which bacteria are killed, nor does it shed light on whether bactericidal activity is further enhanced at higher concentrations. 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.

Integration of pharmacokinetic parameters with the MIC surmounts many limitations of the MIC and provides a more reliable predictor of outcomes than the MIC alone. Recent years have witnessed great strides in understanding the relationship between the pharmacodynamics of β-lactams and microbiologic response. In contrast to the aminoglycosides and fluoroquinolones, β-lactams exhibit little concentration-dependent bacterial killing. This phenomenon was observed in the earliest Staphylococcus aureus time-kill studies, which demonstrated that the rate of bacterial kill was not improved by increasing the concentration of penicillin.

For β-lactams, in vitro and animal studies have demonstrated that the amount of time in which the free or non–protein-bound drug concentration exceeds the MIC of the organism (fT>MIC) is the best predictor of bacterial killing and microbiologic response. These studies have consistently shown that free β-lactam concentrations do not have to remain above the MIC for the entire dosing interval. They have also demonstrated that 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.

Population Pharmacokinetic Modeling and Monte Carlo Simulation: Integration of Pharmacokinetics, Pharmacodynamics, and Microbiologic Data

With advances in computer technology and software, it is now possible to integrate pharmacokinetics, a pharmacodynamic target, and microbiologic surveillance data to determine the probability of pharmacodynamic target attainment for a specific antibiotic regimen. More
important, it is possible to generate empiric antibiotic dosing strategies that maximize the likelihood that an antibiotic regimen will achieve the desired pharmacodynamic target (e.g., 50% \( f/T > \text{MIC} \), AUC:MIC > 125) against the range of pathogens encountered clinically in the patient population of interest.\(^{14, 17, 18, 23, 24}\)

This integration process begins with obtaining estimates and associated dispersions of the pharmacokinetic parameters for the patient group. The two methods primarily used to estimate pharmacokinetic parameters are the standard two-stage pharmacokinetic modeling approach and population pharmacokinetic modeling. The two-stage approach of pharmacokinetic modeling has been the traditional method for generating pharmacokinetic values, and it has the advantage of being much less computationally intensive than population pharmacokinetic modeling. However, population pharmacokinetic modeling provides several distinct advantages over the standard two-stage modeling approach. Its major advantage is that it deals with populations of patients rather than individual patients and aims to estimate the distribution of parameters. In other words, population pharmacokinetics explicitly estimates between-patient variability in pharmacokinetic parameters for the population pharmacokinetic model. Population modeling also seeks to estimate covariance among the pharmacokinetic parameters.

The standard two-stage approach first determines the pharmacokinetic estimates for each patient and then uses descriptive statistics to generate the dispersion surrounding pharmacokinetic estimates. While fitting an individual subject, the standard two-stage approach ignores the existence of all other individuals within the population. Mean estimates of parameters are usually unbiased, but random effects (variance and covariance) are likely to be overestimated in realistic situations. As a result, estimates of dispersion of model parameters and simulated drug exposures are often substantially reduced by the population-modeling technique.\(^{25}\)

Another advantage of population pharmacokinetic modeling over the standard two-stage approach is its improved ability to estimate population pharmacokinetic parameters for subjects with limited sampling times. The ability of the standard two-stage approach to accurately estimate all pharmacokinetic parameters is highly suspect for subjects with limited sampling times. Population pharmacokinetic modeling surmounts this limitation by incorporating data from other subjects when estimating the mean parameter vector and its associated dispersions. In essence, population modeling “borrows” pharmacokinetic information from other subjects within the dataset to estimate the most likely population parameters. Because of these methodologic differences, population pharmacokinetic modeling has become the standard pharmacokinetic methodology for estimating population pharmacokinetic parameters and associated dispersions.\(^{23, 26}\)

Once the values for pharmacokinetic parameters and their dispersion are estimated, Monte Carlo simulation is used to characterize the pharmacodynamic profile of the antibiotic. If a number of volunteers or patients are given an antibiotic, there will be true variability in the observed concentration-time profiles. For example, peak serum concentrations and drug clearance will vary between individuals. Monte Carlo simulation is a mathematical modeling technique that simulates the dispersion or full spread of values (e.g., peak concentration, area under the curve) that would be seen in a large population after administration of a specific drug dose.\(^2, 11\)

Several steps are involved in the Monte Carlo simulation process. First, the mean pharmacokinetic parameters and their associated variability (variance and covariance) are used to create a multivariate distribution of pharmacokinetic parameters. From this multivariate distribution, Monte Carlo simulation randomly draws a set of pharmacokinetic parameters for a single subject (this is why it is extremely important to have reasonable estimates of the dispersion surrounding pharmacokinetic parameters). Second, these randomly selected parameters are used to simulate a concentration-time profile for that subject based on the desired antibiotic dosing regimen. Based on this simulated concentration-time profile, one determines whether the target was reached or not in this virtual patient (e.g., 50% \( f/T > \text{MIC} \) for different MICs). This process is repeated a specified number of times (e.g., 10,000 times) to simulate concentration-time profiles for a virtual patient population. Once the prespecified number of virtual patients has been simulated (e.g., 10,000 virtual patients), it is possible to determine the number of virtual patients who reach the target at each MIC value over the specified MIC range. This information is used to estimate the probability of pharmacodynamic target attainment (e.g., 50%
In clinical practice, a distribution of MICs is encountered for a given organism and/or infection. The final step, therefore, is to determine the overall probability of target attainment for the distribution of organisms encountered clinically. Because the fraction of organism collection at each MIC is known, one can calculate a weighted average (expectation) of target attainment rates. This is done by multiplying the probability of target attainment for a specific MIC by the frequency of occurrence for that MIC. This product is calculated for each MIC of interest. The overall probability of target attainment for the MIC distribution is then calculated by summing the product of probability of target attainment and the probability of MIC occurrence for each respective MIC.

Monte Carlo simulation has been used by several investigators for various functions. It has been used to determine the pharmacodynamic profile of both approved and study antimicrobials, to optimize antimicrobial dosing against a known or suspected MIC distribution of organism(s), to establish the optimal dosage for a new compound, and to estimate the ability of antimicrobials to penetrate the site of infection.\cite{1-20, 21, 22, 23, 24, 25, 26, 27}

Monte Carlo simulation is considered by the Clinical Laboratory Standards Institute (CLSI; formerly known as National Committee for Clinical Laboratory Standards) to establish antibiotic susceptibility breakpoints for new antibiotics and assess the validity of existing breakpoints for United States Food and Drug Administration–approved antibiotics.\cite{20, 28, 29}

A key element for Monte Carlo simulations is input of estimates of the pharmacokinetic parameter and associated dispersion (variance and covariance). Pharmacokinetic data, especially for new compounds, are usually limited to data from studies of healthy volunteers. Young, healthy volunteers should be viewed as a worst case scenario, since they represent a group with rapid elimination and have much lower variability in pharmacokinetic estimates than sick patients. In theory, severely ill patients would be expected to eliminate the same drug more slowly than healthy patients. Care must always be taken and appropriate consideration given to applying available data to the actual target population.

### Transitioning the New Dosing Schemes into Practice

The AMCH antibiotic subcommittee provided the impetus for generating novel β-lactam dosing schemes and incorporating them into clinical practice. Physicians and doctors of pharmacy on this subcommittee applied their extensive knowledge of β-lactam dose optimization strategies, population pharmacokinetic modeling, and Monte Carlo simulation to devise alternative dosing schemes for piperacillin-tazobactam, meropenem, and cefepime.\cite{16, 17, 23} Mathematical modeling techniques also provided the subcommittee with a method for predicting the likelihood of the proposed changes to result in successful patient outcomes. To minimize heterogeneity in dosing practices, the subcommittee implemented an automatic substitution program with a preprinted antibiotic order sheet (Figure 1) to ensure that all providers would use the new dosing schemes. Preprinted antibiotic order sheets had been used in the past at AMCH for therapeutic substitutions and were well accepted by both the medical attending and house staff. If a prescriber failed to use the specified dose and frequency, the preprinted antibiotic order sheets allowed the pharmacy to automatically convert written orders to the newly adapted protocols. This feature was critical because it avoided dosing discrepancies and potential delays in therapy.

Once a consensus agreement on the novel β-lactam dosing protocols and procedures was achieved, it was presented to the pharmacy and therapeutics committee and the medical executive committee for approval. This gained the support of hospital administration and medical attending staff and minimized any potential liability issues or concerns that may have occurred on the practitioner level. The final component of the implementation process was pharmacy and medical staff education. House staff education was performed on a regular basis to ensure compliance with and understanding of the new protocols. Because of the thoughtfully planned approach, implementation into practice met with minimal resistance and AMCH completely converted to the new dosing schemes shortly after approval by the committees. It is important to note that these novel β-lactam dosing schemes were adopted into practice solely based on the results of Monte Carlo simulation studies. No pilot data were collected before implementation. Because of the collective expertise in pharmacokinetics and pharmacodynamics on the antibiotic subcommittee, the pharmacy and therapeutics and medical executive committees were highly supportive of the new β-
lactam dosing protocols.
For each antibiotic addressed by the protocols, we provide detailed reviews of the Monte Carlo simulation and supporting outcomes data (if available), focusing primarily on piperacillin-tazobactam. The approach and thought processes were similar for meropenem and cefepime. Other researchers have used similar methodologies to develop specific protocols for their institutions. 30, 31

Piperacillin-Tazobactam
A major goal was to explore ways of altering drug administration to maximize fT>MIC. Piperacillin-tazobactam is frequently used as

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**Figure 1.** Albany Medical Center Hospital dosing protocols for piperacillin-tazobactam, meropenem, and cefepime.
first-line empiric therapy for patients with documented or suspected *Pseudomonas aeruginosa* infections. The AMCH antibiogram identifies piperacillin-tazobactam as a suitable agent for this pathogen. However, the subcommittee questioned whether the most commonly used dosing strategy of 3.375 g every 4 or 6 hours as a 0.5-hour infusion would attain 50% \( f_{T>MIC} \) for the full range of MICs deemed susceptible by the CLSI. These concerns stemmed from the current

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**PHARMACY THERAPEUTIC SUBSTITUTION ORDER SHEET**

**Instructions:**

1. Imprint patient’s plate before placing in chart
2. Sign bottom of form.
3. Kardex order as substitution.

**ALLERGIES:**

**WEIGHT**

<table>
<thead>
<tr>
<th>lb.</th>
<th>kg.</th>
<th>HEIGHT</th>
<th>cm</th>
<th>BSA: m²</th>
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</thead>
</table>

**ANTIBIOTIC Therapeutic Substitution**

**Meropenem - Imipenem/Cilastatin (Adult & Pediatric)**

**BY DIRECTION OF THE ALBANY MEDICAL CENTER FORMULARY COMMITTEE, THESE AGENTS ARE DESIGNATED THERAPEUTIC EQUIVALENTS FOR AUTOMATIC SUBSTITUTION.**

**Nursing – Please discontinue:**

- Imipenem/cilastatin (Primaxin®) (dose) (frequency)
- Meropenem (Merrem®) 1 g IV q6h

**Nursing – Please start:**

- Meropenem (Merrem®) □ 500 mg IV over 30 min □ 1 g over 3 h □ 2 g over 3 h □ q6h □ q8h □ q12h for ___ days
- Meropenem ____ mg (___ mg/kg) IV over 30 min □ q6h □ q8h □ q12h □ q24h for ___ days

Pharmacist Signature: __________________________ Date: ________ Time: ________

Print Name: __________________________

RN Signature: __________________________ Date: ________ Time: ________

Print Name: __________________________

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**FOR REFERENCE ONLY**

Renal Impairment dose adjustment for adults and children (not neonates):

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<th>CrCl (ml/min)</th>
<th>26-50</th>
<th>10-25</th>
<th>Under 10, peritoneal, hemodialysis</th>
<th>CRRT</th>
</tr>
</thead>
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<td>Adult Dose:</td>
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<td>250 mg q8h</td>
<td>500 mg q6h</td>
<td>500 mg q12h</td>
</tr>
<tr>
<td>Pediatric Dose:</td>
<td>Normal dose q6h</td>
<td>Normal dose q8h</td>
<td>Normal dose q12h</td>
<td>Normal dose q24h</td>
</tr>
</tbody>
</table>

Normal dose (Adult): 500 mg IV q6h

**NOTE:** Adult patients ordered on meropenem 1 g IV q6h should be substituted to 500 mg q6h except in CF and Meningitis

For cystic fibrosis patients: 1 g over 3 h IV q6h max (normal renal function)

For meningitis: 2 g over 3 h IV q6h max (normal renal function)

<table>
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<th>Normal dose: Pediatrics:</th>
<th>Sepsis and other indications</th>
<th>Meningitis</th>
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</thead>
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<td>Neonates under 7 days</td>
<td>20 mg/kg/dose q12h</td>
<td>40 mg/kg/dose IV q12h</td>
</tr>
<tr>
<td>Neonates 7 days and over</td>
<td>20 mg/kg/dose q8h</td>
<td>40 mg/kg/dose (max 2 g) IV q8h</td>
</tr>
<tr>
<td>Children</td>
<td>15 mg/kg/dose (max 500 mg) q6h</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 1. Albany Medical Center Hospital dosing protocols for piperacillin-tazobactam, meropenem, and cefepime (continued).
CLSI susceptibility breakpoints for *P. aeruginosa* (susceptible ≤ 64 mg/L, intermediate 128 mg/L, and resistant ≥ 256 mg/L) and were validated by our Monte Carlo simulation (Figure 2A). The subcommittee did not believe its jurisdiction encompassed adjustment of susceptibility.

**Figure 1.** Albany Medical Center Hospital dosing protocols for piperacillin-tazobactam, meropenem, and cefepime (continued).
breakpoints set by the CLSI, a global, standards-developing organization within the health care community. Therefore, it decided to explore strategies for optimizing the pharmacodynamic profile of piperacillin-tazobactam against the range of MICs considered susceptible by CLSI. We recognized that optimal target attainment against nonlactose fermentors, for which the susceptibility breakpoint is 64 mg/L, would be difficult, but we hoped to achieve better results than were possible with intravenous piperacillin-tazobactam 3.375 g administered every 4 hours.

To maximize the pharmacodynamic profile of piperacillin-tazobactam, the subcommittee considered several dose-optimization strategies. These included markedly increasing the dose by doubling it, increasing the frequency of dosing, and prolonging antibiotic infusion time (continuous and extended infusion). As shown in Figure 3, increasing the dose is ineffective because it only raises T>MIC by one half-life, which is typically 1 or 2 hours for most β-lactams, including piperacillin. More frequent dosing of piperacillin-tazobactam was rejected due to nursing and pharmacy concerns (administration and preparation time) because piperacillin-tazobactam was already dosed 4–6 times/day. The use of continuous infusion was also considered secondary to its ability to provide a high probability of target fT>MIC with a total daily dose less than the optimization dosing strategies mentioned above.

Although continuous infusion is a rational method for optimizing fT>MIC, it has several drawbacks. For example, an intravenous line or the lumen of an intravenous catheter must be dedicated to infuse the antibiotic, and this is not always practical, especially for patients with limited intravenous access or patients requiring multiple daily infusions (with other concerns such as compatibility and access site issues). Continuous infusion often requires insertion of a central line because of difficulties in maintaining the patency of a peripheral intravenous access site for prolonged periods of time. Insertion of a central line for the sole purpose of delivering an antibiotic places patients at unnecessary risk for a secondary nosocomial intravenous catheter-related infection. It is also inconvenient to ambulatory patients because it imposes limits on mobility and often restricts them to bed.

Extension of the infusion time has been suggested as the most practical way of maximizing fT>MIC and minimizing drug expenditures. This approach circumvents many of the practical liabilities of continuous infusion while achieving the targeted fT>MIC at a total

![Figure 2](link-to-figure2.png)

Figure 2. Probabilities of target attainment with piperacillin-tazobactam (A), meropenem (B), and cefepime (C). MIC = minimum inhibitory concentration.
daily dose less than that administered with traditional dosing methods. At AMCH, as with most health care institutions, piperacillin-tazobactam was being infused over 0.5 hour. This methodology provides a high peak concentration, but it is associated with a precipitous drop in serum piperacillin levels secondary to its short half-life. Prolonging the infusion time ensured a more consistent serum level during the dosing interval (Figure 3), thereby maximizing fT>MIC. It also provided an antibiotic free window during which other drugs could be administered.

Based on a Monte Carlo simulation that used pharmacokinetic data from healthy male volunteers, piperacillin-tazobactam 3.375 g infused over a 4-hour period every 8 hours (extended infusion) was identified as an alternative to the traditional dosing regimen of piperacillin-tazobactam 3.375 g infused over 30 minutes every 4 or 6 hours (Figure 2A). The pharmacodynamic end point selected for this simulation, 50% fT>MIC, correlated with maximal bactericidal activity for penicillins. Monte Carlo simulation revealed that the probability of target attainment for extended infusion piperacillin-tazobactam was 92% at 16 mg/L and 100% for lower MICs. In contrast, with a 30-minute infusion of piperacillin-tazobactam every 4 hours, the probability of target attainment was greater than 90% only for MIC values of 8 mg/L or less; with higher MICs, the likelihood of target attainment was substantially below 90%. For a 30-minute infusion of piperacillin-tazobactam every 6 hours, the probability of target attainment was more than 90% only for an MIC value of 1 mg/L. For MICs of 32 mg/L or greater, no regimen was optimal.

Given the low probabilities of target attainment for MICs of 32 mg/L or greater, the subcommittee evaluated several regimens in which piperacillin-tazobactam 3.375 was administered every 6 hours with extended infusions ranging from 2–6 hours. For all regimens examined, the probability of target attainment was less than 50% for MICs of 32 mg/L or greater (data not shown). Given the minimal gain in probability of target attainment and higher drug acquisition costs and workload associated with more frequent dosing, the committee decided to endorse piperacillin-tazobactam 3.375 g every 8 hours as a 4-hour infusion as the preferred piperacillin-tazobactam dosing strategy. It is important to note that only the piperacillin component of piperacillin-tazobactam was simulated. The pharmacodynamic profile of tazobactam was not examined because recommended doses of tazobactam in the piperacillin-tazobactam formulation have been shown to be sufficient for an antibacterial effect when the target is fT>MIC.

The extended-infusion dosing strategy for piperacillin-tazobactam offered two benefits in addition to its superior pharmacodynamic profile. First, this regimen allowed 4 hours within each 8-hour dosing interval in which other agents could be administered through the same intravenous line. Second, it provided an economic benefit by reducing the amount of doses/patient/day by one or three. During 2000, piperacillin-tazobactam purchases totaled approximately $275,000 at the AMCH. Reducing the total daily dose by 25–50% represented a potential savings of approximately $68,750–137,500 in direct drug acquisition costs/year. In February 2002, a hospitalwide, automatic substitution program was implemented to allow automatic conversion of written orders for intermittent infusion of piperacillin-tazobactam to orders for extended infusion.

We formally assessed the overall impact of the program on mortality and hospital length of stay. For the outcomes analyses, all patients who received piperacillin-tazobactam between August 2000 and August 2003 at AMCH were eligible. Before February 2002, all patients received traditional 30-minute infusions of piperacillin-tazobactam. After that date, virtually all patients given this drug received extended (4-hr) infusions.

The study included patients who were at least...
18 years old, were nonneutropenic (absolute neutrophil count at least 1000 cells/mm³), had a positive culture for *P. aeruginosa* meeting the Centers for Disease Control and Prevention criteria for infection, were administered piperacillin-tazobactam within the first 72 hours of the onset of *P. aeruginosa* infection, and received piperacillin-tazobactam for 48 hours or longer. Patients were excluded if they received more than 1 day of intermittent infusion of piperacillin-tazobactam before conversion to the extended-infusion protocol, if the *P. aeruginosa* isolate was resistant to piperacillin-tazobactam, if they received a solid organ or bone marrow transplant, and if they were diagnosed with cystic fibrosis. For patients with multiple *P. aeruginosa* clinical cultures, only the first set of cultures was considered for the study.

The outcomes analysis was restricted to patients with *P. aeruginosa* for several reasons. Outcomes of patients with *P. aeruginosa* infections are more dependent on antimicrobial therapy than other populations because these patients are usually critically ill and often have an impaired innate immune system. An impaired immune system places a greater emphasis on the activity of the antimicrobial therapy. Isolates of *P. aeruginosa* typically have higher MICs to piperacillin-tazobactam than other organisms, and the benefits of optimizing T>MIC will be better elucidated in this subset of patients.

During the specified enrollment period, 111 patients satisfied the study criteria. There were 54 patients in the extended-infusion group and 57 patients in the traditional-infusion group. No significant differences in baseline characteristics, source of infection, or use of combination therapy were noted between the groups. Comparisons of 14-day and 30-day mortality rates are shown in Figure 4. Although the rates of 14- and 30-day mortality were higher in the traditional infusion group, these differences were not significant. Median length of hospital stay from the start of piperacillin-tazobactam until discharge or death was comparable between the extended-infusion group and the traditional-infusion group (14 vs 17 days, p=0.2). These findings persisted in the multivariate analyses.

Based on results from AMCH and similar evaluations performed by other research groups, extended-infusion piperacillin-tazobactam was deemed a safe and effective alternative dosing strategy compared with traditional piperacillin-tazobactam intermittent dosing. The program continued based on the similar outcomes between patient groups and the substantial cost savings associated with extended infusion.

**Meropenem**

In 2001, conventional imipenem-cilastatin dosing was switched to meropenem 500 mg every 8 hours as a 30-minute infusion or 1000 mg every 8 hours as a 3-hour infusion (extended-infusion meropenem). A Monte Carlo simulation using pharmacokinetic data from healthy volunteers showed that extended-infusion meropenem provided more robust probabilities of target attainment than either conventional meropenem dosing regimens or imipenem 500 mg every 6 hours administered as a 1-hour infusion. Using the global Meropenem Yearly Susceptibility Testing Information Collection (MYSTIC) surveillance data as the measure of MIC distribution and frequency, the subcommittee calculated the overall probability of target attainment for various nosocomial pathogens (Table 1). Meropenem 500 mg every 8 hours (1- and 3-hr infusions) had excellent coverage against all nosocomial pathogens examined except *P. aeruginosa* and *Acinetobacter* species. For these pathogens, meropenem 1000 mg every 8 hours, administered by 3-hour infusion, provided higher probabilities of target attainment. Based on these results, conventional meropenem dosing was changed to meropenem 500 mg every 8 hours (1-hr infusion). The regimen of meropenem 1 g every 8 hours as a 3-hour infusion was reserved for documented or
suspected infections with either *P. aeruginosa* or *Acinetobacter* species. For situations in which these pathogens were not suspected, the antibiotic subcommittee opted for 1-hour infusion of meropenem 500 mg every 8 hours because this regimen had a similar probability of target attainment and required less administration time than the alternative regimen. The subcommittee did not evaluate prolonged infusion for imipenem-cilastatin because of stability issues cited in the package insert.

After gaining approval from the pharmacy and therapeutics and medical committees in April 2001, a hospitalwide automatic substitution program was implemented to allow automatic conversion of written orders for conventional infusion of meropenem and imipenem-cilastatin to orders for extended infusion of meropenem. This program continued until the national meropenem shortage in February 2004. During the meropenem shortage, meropenem orders were changed to imipenem-cilastatin 500 mg intravenously every 8 hours. Once the meropenem shortage was lifted, the hospital began converting orders for imipenem-cilastatin to orders for meropenem 500 mg intravenously every 6 hours, with an infusion time of 0.5 hour. The current AMCH dosing protocol for meropenem is shown in Figure 1B.

There were several reasons for converting from extended-infusion meropenem to meropenem 500 mg every 6 hours as a 0.5-hour infusion. This second regimen had a high likelihood of achieving 40% $f_{T>MIC}$ for the full range of MICs deemed susceptible by CLSI (Figure 2C). In addition, several published reports supported the results of the AMCH’s Monte Carlo simulation for meropenem 500 mg intravenously every 6 hours. A published Monte Carlo simulation revealed that meropenem 500 mg every 6 hours and meropenem 1 g every 8 hours achieved similar percentages of $f_{T>MIC}$. A separate Monte Carlo simulation found similar probabilities of target attainment ($f_{T>MIC}$ 50% or 70%) for meropenem 500 mg every 6 hours and meropenem 1 g every 8 hours against clinical isolates of *P. aeruginosa*. Using data obtained from neutropenic patients, a third research group observed similar $T>MIC$ between meropenem 500 mg every 6 hours and meropenem 1000 mg every 8 hours.

A third reason for conversion to meropenem 500 mg intravenously every 6 hours was the shorter infusion time (0.5 hr). Although extended infusion circumvents many of the practical limitations of continuous infusion, extended infusion nevertheless requires a dedicated line for most of the day. As mentioned above, use of an intravenous line for the sole purpose of delivering antibiotics carries certain infection risks and presents difficulties for patients and the hospital pharmacy. Prolonged infusion, therefore, is only justifiable when the benefits outweigh the risks. After reviewing the Monte Carlo simulation data, the AMCH antibiotic subcommittee decided that the slightly higher probability of target attainment observed with extended-infusion meropenem did not merit these additional risks (Figure 2C).

The fourth and final reason that factored into the decision-making process was the projected daily drug cost savings (of 1 g/patient/day) compared with meropenem 1000 mg intravenously every 8 hours. When drug acquisition costs were projected over the year, the cost savings of 1 g/patient/day were substantial (in excess of $40,000/yr). Of greater importance, clinical data suggested that

<table>
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<th>Organism</th>
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<th>Meropenem 500 mg q8h (1-hr infusion)</th>
<th>Meropenem 500 mg q8h (3-hr infusion)</th>
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<td>77.1%</td>
<td>83.0%</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>73.0%</td>
<td>76.0%</td>
<td>79.3%</td>
<td>86.4%</td>
</tr>
</tbody>
</table>

$40\% f_{T>MIC} =$ amount of time that non–protein-bound (free) antimicrobial concentration exceeds the minimum inhibitory concentration of the pathogen for 40% of the dosing interval.

*Organisms were isolated by the Meropenem Yearly Susceptibility Testing Information Collection (MYSTIC) surveillance program. From reference 17.*
meropenem 500 mg intravenously every 6 hours was a suitable alternative to meropenem 1000 mg intravenously every 8 hours. A published outcomes study found that clinical and microbiologic success rates were similar between patients who received meropenem 500 mg intravenously every 6 hours versus those receiving meropenem 1000 mg intravenously every 8 hours. In the same study, level one costs (drug-related costs) were reduced by $406/patient in the treatment arm that provided meropenem 500 mg intravenously every 6 hours. Outcomes of the meropenem dosing program at AMCH are currently being assessed.

Cefepime

Using 67% fT>MIC as the pharmacodynamic target, cefepime 1000 mg every 6 hours as a 0.5-hour infusion was identified as an alternative to conventional cefepime dosing (Figure 2C). Multiple extended-infusion regimens were evaluated, and all cefepime dosing schemes provided high probability of target attainment against the range of MICs deemed susceptible by the CLSI.

Cefepime 1000 mg every 6 hours as a 0.5-hour infusion was adopted as the new dosing strategy for several reasons. First, this regimen provided more robust probabilities of target attainment than conventional cefepime dosing (1000 mg every 12 hrs as a 0.5-hr infusion). Second, the new regimen (cefepime 1000 mg intravenously every 6 hrs) had a similar probability of target attainment profile as maximal cefepime dosing (2000 mg every 8 hrs as a 0.5-hr infusion), but it optimized fT>MIC while using a smaller amount of drug (2 g/day less). Given that cefepime costs approximately $12.50/g, the projected drug acquisition cost savings were considerable. Finally, cefepime 1000 mg intravenously every 6 hours achieved the targeted fT>MIC with less administration time/day than prolonged infusion or continuous infusion. Again, prolonged infusion is only justifiable when its benefits outweigh its risks; the antibiotic subcommittee decided that the slightly higher probability of target attainment observed with extended-infusion cefepime did not merit the additional risks. In 2004, AMCH converted from conventional cefepime dosing to cefepime 1000 mg every 6 hours as a 0.5-hour infusion. The outcomes of this program are being evaluated. We are unaware of any supporting clinical data from other institutions.

Conclusion

Population pharmacokinetic modeling and Monte Carlo simulations can generate new dosing strategies that optimize the pharmacodynamic profiles of β-lactam antibiotics and can be applied directly into clinical practice. At AMCH, these mathematical modeling techniques were used to devise new dosing schemes for piperacillin-tazobactam, meropenem, and cefepime. Even though pharmacodynamic simulations can never replace well-controlled clinical studies, they can be used to assess the desirability of proceeding with a new agent or a new dosing method. They can also be used to compare antimicrobial regimens with each other or with findings from published data. In the end, the advantages of simulations should be evaluated in the clinical setting.

References


