Pharmacodynamic Target Attainment for Cefepime, Meropenem, and Piperacillin-Tazobactam Using a Pharmacokinetic/Pharmacodynamic-Based Dosing Calculator in Critically Ill Patients

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ABSTRACT This was a prospective study to determine if pharmacokinetic/pharmacodynamic (PK/PD)-based antibiotic dosing software aids in achieving concentration targets in critically ill patients receiving cefepime (n = 10), meropenem (n = 20), or piperacillin-tazobactam (n = 19). Antibiotic calculator doses targeting a ≥90% probability of target attainment (PTA) differed from package insert doses for 22.4% (11/49) of patients. Target attainment was achieved for 98% of patients (48/49). A PK/PD-based antibiotic dosing calculator provides beta-lactam doses with a high PTA in critically ill patients.

KEYWORDS beta-lactam, critically ill, pharmacodynamic, pharmacokinetic

The rapid increase in antibiotic resistance highlights the urgent need to maximize the effectiveness of currently available antibiotics, especially within the critically ill population, which has high clinical failure rates and is disproportionately affected by multidrug-resistant organisms (1–3). While therapeutic drug monitoring (TDM) is commonplace for vancomycin and aminoglycosides, TDM for beta-lactams is not routinely available at most institutions (4, 5). However, PK/PD-based antibiotic dosing software offers a way to individualize dosing using patient-specific data in conjunction with population pharmacokinetic models in the absence of individual drug concentration data (3).

The objective of this prospective cohort study was to determine if measured beta-lactam concentrations in a critically ill population help us to achieve predefined therapeutic concentrations (pharmacodynamic target attainment) as predicted by an individualized antibiotic dosing program. The secondary objective was to assess the frequency at which the use of an individualized antibiotic dosing program results in a change in recommended dosing compared with that from traditional package labeling.

Hospitalized adult (≥18 years of age) patients in the intensive care unit (ICU) receiving piperacillin-tazobactam, cefepime, or meropenem were screened, and those patients with a culture-positive Gram-negative infection were eligible to consent for study inclusion. Standard empirical doses used at our institution for patients with
normal renal function are 3.375 g of intravenous (i.v.) piperacillin-tazobactam every 6 h (q6h), 2 g of i.v. cefepime every 8 hours (q8h), or 1 g of i.v. meropenem q8h, each infused over 30 min per dose. A culture-proven infection was defined as a positive culture from a sterile site(s) (e.g., blood, cerebrospinal fluid) and/or a respiratory sample (e.g., sputum, bronchoalveolar lavage fluid) that meets the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSH) definition for pneumonia (6), with an identified pathogen and susceptibility results available. The Vitek 2 system (bioMérieux, Durham, NC) is used for organism identification and to determine susceptibility for Enterobacteriaceae spp., and Kirby-Bauer disc diffusion is used to determine susceptibility of non-lactose-fermenting Gram-negative organisms, with MICs determined via Etest (bioMérieux) available on request. For patients with a non-lactose-fermenting Gram-negative organism for which the MIC was unavailable, the highest MIC for susceptible bacteria based on Clinical and Laboratory Standards Institute breakpoints to the antibiotic was assumed to represent a worst-case scenario of bacterial susceptibility (7).

Patients receiving extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) were excluded, as the pharmacokinetic model in the PK/PD dosing program was not available for these populations.

Once consented, the participants’ antibiotic dose was assessed by the primary investigator (PI) using the ID-ODS system (Optimum Dosing Strategies, Bloomingdale, NJ). The ID-ODS program performs an individualized pharmacokinetic assessment using a Bayesian parametric approach and Monte Carlo simulation (3, 8–10). The patients’ antibiotic was evaluated in the context of the MIC of the infecting organism, and dose adjustments were made by the PI in conjunction with each patient’s primary care team to achieve a 90% probability of target attainment (PTA; unbound concentrations of antibiotic above the MIC \( f_{T>MIC} \), 50% for piperacillin, 40% for meropenem, and 60% for cefepime) for the cultured organism (11). Two antibiotic levels were drawn, one midpoint (50% of the dosing interval) and one trough at the end of the dosing interval once the patient was at steady state on that dose. The samples were frozen and batched for analysis at the Center for Anti-infective Research and Development by validated chromatographic methods (12–14). Total concentrations were corrected for protein binding, which is considered adequate for the prediction of unbound concentrations for these drugs with relatively low protein binding (15).

The level of patient illness severity was calculated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores (16, 17). Infection-related mortality was defined as death that could be attributed to infectious disease as either the immediate or underlying cause. Positive clinical outcome was defined as in the Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study (4), that is, the completion of an antibiotic treatment course without a change or addition of antibiotic therapy and with no additional antibiotics commenced within 48 h of cessation. Descriptive statistics were used for data analysis.

Forty-nine patients were included in the study; 20 (41%) patients received meropenem, 19 (39%) piperacillin-tazobactam, and 10 (20%) cefepime (Table 1). Drug-specific target attainment was achieved for 48/49 (98%) patients, with one patient not achieving target attainment in the piperacillin-tazobactam group.

Drug concentrations remained above the MIC for the entire dosing interval in 47/49 (95.9%) patients; both patients in whom drug concentrations dropped below the MIC before the end of the dosing interval were receiving piperacillin-tazobactam. MIC values were relatively low in the cohort, with only two patients with an organism MIC by Etest outside the susceptibility range for the antibiotic they were receiving, one patient on cefepime for Pseudomonas aeruginosa with an MIC of 16 µg/ml, and one patient on piperacillin-tazobactam for P. aeruginosa with an MIC of 32/4 µg/ml. Median antibiotic concentrations and MICs are reported in Table 2. When a goal target attainment of 100% \( f_{T>MIC} \) was considered, target attainment decreased to 65% (32/49), with 8/10 (80%) for cefepime, 17/20 (85%) for meropenem, and 7/19 (37%) for piperacillin-tazobactam. Doses recommended based on the antibiotic dosing calculator differed from those based on the...
Our study found that doses predicted by an antibiotic dosing calculator to achieve pharmacodynamic targets relative to the organism MIC ≥90% of the time actually achieved these targets in 98% of the patients. Currently, antibiotic dose recommendations from tertiary drug information resources (e.g., Lexicomp, Micromedex) and package labeling fit a “one dose fits all” paradigm, with renal function being the primary driver of dose adjustments. However, optimization of antibiotic dosing in critically ill patients requires an individualized approach that accounts for the MIC of the antibiotic for the cultured organism and provides a dosing regimen that can attain the PK/PD ratio predictive of treatment success. The concept of individualized dosing of antibiotics using TDM has long been available for known narrow therapeutic index drugs, such as vancomycin and the aminoglycosides, but it is a relatively new approach for beta-lactams (18). Individualized dosing based on population models represents a feasible alternative until point-of-care TDM for beta-lactams becomes more widely available.

Critical illness can substantially change antibiotic concentrations, potentially predisposing patients to treatment failure, emergence of antibiotic resistance, and excess drug toxicity (19). Optimizing the pharmacokinetic exposure of antibiotics in critically ill
patients could improve infection-related outcomes (20). For example, a study of patients with nosocomial pneumonia performed assays of antibiotic concentrations and adjusted doses to achieve a goal peak/MIC of $\geq 4 \mu g/ml$ and time above the MIC of unbound antibiotic ($fT_{>MIC}$) of at least 70%. Patients with individualized doses were more likely to have an eradication of the causative pathogen (21).

Data vary on the precise PK/PD target for beta-lactams; however, achieving the PK/PD target of at least 50% $fT_{>MIC}$ for the beta-lactams has been associated with maximal bacterial killing, improved clinical cure, and improved microbiologic cure (22–29). This is of particular importance for pathogens with an MIC at or near the resistance breakpoints where a standard regimen could lead to underdosing. It is also important to account for MIC variation, as there is inherent assay variation in the MIC test and differences in MIC determination methods (30). In our study, we applied the drug-specific PK/PD targets from Craig (11), but these should be considered minimum targets. Had we utilized a more aggressive target, such as 100% $fT_{>4\times MIC}$, only 65% of the patients would have achieved these target concentrations, driven largely by piperacillin-tazobactam.

Despite the altered pharmacokinetics that result from critical illness, the vast majority of patients in our study still achieved adequate drug concentrations. Conversely, in some patients, the antibiotic concentrations were excessively high and could have contributed to toxicity. For example, cefepime trough concentrations exceeding $\geq 22 \mu g/ml$ have been shown to be an independent predictor of neurologic toxicity (31). This concentration was exceeded in 2 of our 10 cefepime patients; although neither of these patients experienced any antibiotic-related adverse effects, it is plausible that a lower dose could have been administered given the low MICs of their cultured organisms.

This study has notable limitations, including the relatively narrow range of infecting-

### TABLE 2 Meropenem, piperacillin, and cefepime concentrations adjusted for protein binding and corresponding organism MICs

<table>
<thead>
<tr>
<th>Antibiotic (no. of patients)</th>
<th>Antibiotic concn (µg/ml)</th>
<th>Median (IQR)</th>
<th>Low value</th>
<th>High value</th>
<th>Median (range) organism MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.25–4)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>10.9 (11.9)</td>
<td>3.86</td>
<td>41.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trough</td>
<td>5.4 (2.9)</td>
<td>1.36</td>
<td>26.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin (n = 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 (4–32)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>64.3 (61.0)</td>
<td>14.51</td>
<td>311.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trough</td>
<td>35.6 (37.2)</td>
<td>0.79</td>
<td>269.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime (n = 10)</td>
<td></td>
<td>1.5 (1–16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midpoint</td>
<td>24.9 (10.7)</td>
<td>8.5</td>
<td>57.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trough</td>
<td>16.0 (9.9)</td>
<td>6.3</td>
<td>45.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3 Target attainment and clinical outcomes

<table>
<thead>
<tr>
<th>Target attainment (n = 49)</th>
<th>Value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculator doses that differed from package insert doses (no. [%])</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>PTA (no. [%])</td>
<td></td>
</tr>
<tr>
<td>Midpoint level</td>
<td>48 (98)</td>
</tr>
<tr>
<td>Trough level</td>
<td>47 (95.9)</td>
</tr>
<tr>
<td>Drug specifica</td>
<td>48 (98)</td>
</tr>
<tr>
<td>Clinical outcomes (n = 49) (no. [%])</td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>41 (83.7)</td>
</tr>
<tr>
<td>30-day mortality rate</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Infection-related mortality rate</td>
<td>5 (10.2)</td>
</tr>
<tr>
<td>Mean hospital length of stay (days)</td>
<td>43</td>
</tr>
<tr>
<td>Mean ICU length of stay (days)</td>
<td>31</td>
</tr>
</tbody>
</table>

a$fT_{>MIC}$ of 50% for piperacillin, 40% for meropenem, and 60% for cefepime.
organism MICs. Individualization of beta-lactam doses is likely to have a greater impact in patients in whom an organism’s MIC approaches or exceeds susceptibility thresholds. We had a small sample size that did not allow for formal statistical analysis of clinical outcomes associated with antibiotic concentrations, and we collected only 2 beta-lactam concentrations at steady state for these patients, which represents only a snapshot of serum drug concentrations and does not account for drug concentrations at the site of infection.

PK/PD-based antibiotic dosing software can provide individualized beta-lactam doses that result in high attainment of target concentrations in critically ill patients. This is likely to be of particular importance with organisms such as E. coli, with MICs approaching or exceeding the susceptibility breakpoint for the antibiotic of choice. Future research is needed to review the relevance of PK/PD-based dose adjustments for clinical outcomes.

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REFERENCES


