Extended-Infusion Cefepime Reduces Mortality in Patients with Pseudomonas aeruginosa Infections

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In an era of escalating resistance and a lack of new antimicrobial discovery, stewardship programs must utilize knowledge of pharmacodynamics to achieve maximal exposure in the treatment of Pseudomonas aeruginosa infections. We evaluated the clinical and economic outcomes associated with extended-infusion cefepime in the treatment of P. aeruginosa infections. This single-center study compared inpatients who received cefepime for bacteremia and/or pneumonia admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h) to those admitted from 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h). The overall mortality was significantly lower in the group that received extended-infusion treatment (20% versus 3%; P = 0.03). The mean length of stay was 3.5 days less for patients who received extended infusion (P = 0.36), and for patients admitted to the intensive care unit the mean length of stay was significantly less in the extended-infusion group (18.5 days versus 8 days; P = 0.04). Hospital costs were $23,183 less per patient, favoring the extended-infusion treatment group (P = 0.13). We conclude that extended-infusion treatment with cefepime provides increased clinical and economic benefits in the treatment of invasive P. aeruginosa infections.

Antimicrobial resistance has emerged as a global health crisis, gaining the attention of the World Health Organization and the U.S. Department of Health and Human Services (1). As antimicrobial resistance continues to emerge and new antimicrobial development stagnates, antimicrobial stewardship programs are being implemented worldwide. The goal of antimicrobial stewardship is to optimize antimicrobial therapy with maximal impact on the subsequent development of resistance (2–4). The Healthcare Infection Control Practices Advisory Committee, in partnership with the U.S. Department of Health and Human Services, lists antimicrobial stewardship as a top 5 message for health care workers (5).

Pseudomonas aeruginosa infections constitute a tremendous burden on hospitals in the United States in terms of morbidity, mortality, and health care costs. P. aeruginosa infections are associated with a mortality rate of 18 to 60%, and the cost of treatment is substantial, ranging from $20,000 to $80,000 per infection (6–11). Antimicrobial therapy for P. aeruginosa is limited because of the organism’s multiple resistance mechanisms, often resulting in higher MICs (12–14).

Cefepime is a “fourth-generation” cephalosporin with activity against Gram-positive and Gram-negative organisms, including P. aeruginosa. Because of its broad activity, cefepime is used as empirical antibiotic therapy for serious infections, including pneumonia and bacteremia. Like other β-lactam antibiotics, cefepime displays time-dependent bactericidal activity, and its efficacy is optimized when free drug concentrations exceed the MIC (fT > MIC) for at least 60 to 70% of the dosing interval (15–18). Recent evidence suggests that conventional regimens may not attain this fT > MIC (19–21). Recognizing the difficulties associated with the treatment of P. aeruginosa infections, the Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America recognize extended infusion of β-lactams as a viable method in optimizing antibiotic therapy (2).

This study compares a cefepime 30-min infusion to a 4-h infusion to determine whether the extended-infusion strategy results in decreased mortality in the treatment of P. aeruginosa pneumonia and/or bacteremia.

(This work was presented in part at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 17 to 20 September 2011.)

MATERIALS AND METHODS

Pharmacodynamic analysis. Prior to the evaluation of clinical outcomes, 64 consecutive blood or respiratory isolates from unique patients were tested for MIC by the Center for Anti-Infective Research and Development at Hartford Hospital using broth microdilution techniques according to the current Clinical and Laboratory Standards Institute (CLSI) interpretive criteria for cefepime susceptibility of an MIC at ≤8 μg/ml. The in vitro potency was evaluated by determining the MIC50 and MIC90 and by calculating the overall percent susceptibility. The cefepime regimen was simulated as a 30-min or 4-h infusion. A pharmacokinetic model was developed and used with Monte Carlo simulation to evaluate the ability of cefepime to achieve bactericidal activity against the organism. The model and its pharmacokinetic parameters are described in detail elsewhere (22). Pharmacodynamic exposures for the simulated cefepime were assessed at 60% fT > MIC.

The probability of target attainment (PTA) was calculated for each dosing regimen over a range of doubling MICs between 0.008 and 256 μg/ml. The PTA results were used to calculate the cumulative fraction of response (CFR) for each regimen at the appropriate bactericidal breakpoint. A CFR of ≥90% was applied for defining a regimen as optimal against the bacterial population.

Study design. This was a retrospective quasi-experimental study of all hospitalized adult patients who received cefepime for a positive respira-
tory or blood culture with a Gram-negative organism admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h) and 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h) at The Ohio State University Medical Center (OSUMC), a 1,150-bed tertiary-care facility located in Columbus, OH. A planned subgroup analysis of patients with P. aeruginosa infections was completed. The study was approved by the Office of Responsible Research Practices Institutional Review Board, with a waiver of consent granted. All patients receiving ceftazidime on or after 1 July 2010 regardless of renal function automatically received extended infusion. The dosing frequency was adjusted per protocol using the Cockcroft Gault equation to calculate the creatinine clearance (Cl_{Cr}): <60 ml/min (2 g every 12 h) and <30 ml/min (2 g every 24 h). There were no additional changes in dosing regimens except for the infusion time between the study periods. Only the first episode per study period was analyzed.

**Inclusion criteria.** Patients were included if all of the following criteria were met: (i) age ≥ 18 years, (ii) discharge diagnosis of bacteremia and/or pneumonia, (iii) culture with in vitro susceptibility to ceftazidime based on the CLSI MIC of ≤8 μg/ml, (iv) ceftazidime therapy administered within the first 72 h of the onset of Gram-negative infection, and (v) receipt of ceftazidime for ≥48 days.

**Exclusion criteria.** Patients were excluded if they met any of the following criteria: (i) receipt of concurrent β-lactam antibiotic with activity against a Gram-negative organism within 2 days of the initiation of ceftazidime therapy, (ii) incarceration, or (iii) patients who received both intermittent- and extended-infusion ceftazidime.

**Data.** Demographic and clinical outcomes data were collected from the patient’s electronic medical record and OSUMC’s Information Warehouse (IW). Cost data were obtained from the IW. The data obtained included: age, sex, hospital service, Charlson comorbidity index (23), duration of hospitalization prior to culture collection, intensive care unit (ICU) admission, location in the ICU at the time of culture collection, mechanical ventilator status at culture collection, APACHE (acute physiology and chronic health evaluation) II score (24), microbiologic data, antibiotics administered and treatment duration, Infectious Diseases (ID) consult, hospital costs, and discharge disposition. The APACHE II score was defined as the worst physiological score calculated during the initial 24 h after culture collection. Microbiological data included all respiratory or blood cultures positive for a Gram-negative organism and the date at which the culture sample was collected. Susceptibility testing was performed using the MicroScan WalkAway System (Siemens Diagnostics). Treatment data included information about antimicrobials administered for the Gram-negative infection. Comitant therapy with an aminoglycoside, fluoroquinolone, or colistin was considered combination therapy if it was administered within 72 h of the positive culture, for ≥24 h, and the organism was susceptible to the agent.

Clinical outcomes included duration of mechanical ventilation, length of hospital stay (LOS), infection-related LOS, ICU LOS, and hospital mortality. LOS was calculated as the difference between the admission and the discharge date. Infection-related LOS was calculated as the difference between ceftazidime administration and discontinuation or discharge date whichever was sooner. Cost was based on the actual costs accrued by the patient, independent of reimbursement. In an effort to explain costs related to infection, we assessed hospital costs incurred only during ceftazidime administration. Costs were inflated to calendar year 2011 by using the medical component of the Consumer Price Index (25).

**Statistical analysis.** Categorical variables were compared using the chi-square test or the Fisher exact test; continuous variables were compared by using the Student t test or the Wilcoxon rank-sum test. A two-tailed P value of 0.05 was considered statistically significant. The data are presented as a number (%), mean (standard deviation), or median (interquartile range) as appropriate. Exact logistic regression was performed to determine predictors of hospital mortality. Variables with a P value of ≤0.20 on univariate analysis were considered for inclusion in the multivariable model. Regression model data are presented as odds ratios (OR) and 95% confidence intervals (95% CI). Stata, version 11 (StatCorp LP, College Station, TX), was used for all calculations.

**RESULTS**

In the pharmacodynamic analysis, the ceftazidime MICs ranged from 1 to 32 μg/ml for P. aeruginosa. The MIC90 was 4 μg/ml, and the MIC90 was 8 μg/ml (Fig. 1). At the current CLSI-defined breakpoint of 8 μg/ml, only the regimen 2 g every 8 h as a 4-h infusion had a 90% likelihood of achieving at least 60% T>MIC. Based on the pharmacodynamic analysis, extended infusion was implemented, and clinical outcomes were evaluated.

During the study period, 1,433 patients were screened for study inclusion. We identified 592 patients with a positive blood and/or respiratory culture with a Gram-negative organism who received ceftazidime (Fig. 2). Of this group, 390 patients received intermittent infusion, and 202 patients received extended infusion. There was no difference in the baseline characteristics between patients who received extended-infusion ceftazidime compared to intermittent-infusion ceftazidime (58% versus 63% male, P = 0.24; 58 ± 15 years versus 58 ± 16 years, P = 0.89; 43% versus 40% ICU admission, P = 0.55). Patients who received extended infusion had a similar length of stay (26.3 ± 23.0 days versus 23.1 ± 21.7 days; P = 0.07) and similar hospital costs ($99,744 ± $112,657 versus $83,328 ± $87,826; P = 0.22) compared to patients with received intermittent infusion. No statistical difference in mortality was observed (17% versus 20%; P = 0.31).
Of the 87 patients with a positive blood or respiratory culture with *P. aeruginosa* who received cefepime, 54 patients received intermittent infusion and 33 patients received extended infusion. No significant differences in baseline characteristics were noted between the groups. The mean duration of cefepime therapy was similar between the two groups, and an equivalent number of patients received an aminoglycoside, a fluoroquinolone, or colistin. The primary infection sources were similar between groups with the respiratory tract as the predominant source in both groups (Table 1).

The overall mortality was significantly lower in the group that received extended infusion (20% versus 3%; \( P = 0.03 \)) (Table 2).

The median length of stay was similar for patients who received extended infusion compared to patients who received intermittent infusion (14.5 days versus 11 days; \( P = 0.36 \)). For patients admitted to the ICU, the median length of stay was significantly less for patients who received extended-infusion (18.5 days versus 8 days; \( P = 0.04 \)). Patients received mechanical ventilation 4 days less with extended infusion (14.5 versus 10.5; \( P = 0.42 \)).

The median hospital costs were $23,183 less in patients who received extended infusion ($51,231 versus $28,048; \( P = 0.13 \)). Mean hospital costs during antibiotic therapy were similar for patients who received extended-infusion ($15,322 versus $13,736; \( P = 0.78 \)).

Variables associated with hospital mortality on univariate exact logistic regression analysis included cefepime infusion type (OR = 0.12; 95% CI = 0.003 to 0.94), the number of patients with a positive culture while in the ICU (OR = 8.19; 95% CI = 1.58 to 41.78), and the number of patients with a positive culture while in the ICU (OR = 8.19; 95% CI = 1.58 to 41.78).

### TABLE 1 Comparison of demographic characteristics of patients with *P. aeruginosa* bacteremia and/or pneumonia who received cefepime intermittent- or extended-infusion treatment

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Intermittent (( n = 54 ))</th>
<th>Extended (( n = 33 ))</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 (47–73)</td>
<td>65 (48–74)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male patients</td>
<td>33 (61)</td>
<td>18 (55)</td>
<td>0.51</td>
</tr>
<tr>
<td>Charlson score</td>
<td>3 (2–5)</td>
<td>2 (2–4)</td>
<td>0.12</td>
</tr>
<tr>
<td>APACHE II score at onset of infection</td>
<td>15.5 (13–25)</td>
<td>15 (13–22)</td>
<td>0.47</td>
</tr>
<tr>
<td>ID consult</td>
<td>36 (67)</td>
<td>22 (67)</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration of stay (days)</td>
<td>4 (1–13)</td>
<td>3 (2–8)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of culture</th>
<th>Blood</th>
<th>Respiratory</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 (28)</td>
<td>6 (18)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>37 (69)</td>
<td>27 (82)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>2 (4)</td>
<td>0</td>
<td>0.52</td>
</tr>
</tbody>
</table>

| In ICU at onset of infection | 32 (59)                     | 23 (70)                 | 0.49 |
| Inpatient duration of therapy (days) | 5 (3–9)                     | 6 (4–8)                 | 0.61 |
| Concomitant therapy         | Aminoglycoside              | Fluoroquinolone         | Colistin |
|                            | 27 (55)                     | 3 (6)                   | 1 (2)  |
|                            | 18 (33)                     | 1 (2)                   | 0      |
| Concomitant infection       | 27 (50)                     | 11 (33)                 | 0.18   |

\( ^a \) Data are presented as "number (%)" or "median (interquartile range)" as appropriate. \( n \), Number of patients.  
\( ^b \) \( P \) values determined by the Fisher exact test or the Wilcoxon rank-sum test as appropriate.
TABLE 2 Comparison of clinical and economic outcomes for patients with *P. aeruginosa* bacteremia and/or pneumonia who received cefepime intermittent- or extended-infusion treatment

<table>
<thead>
<tr>
<th>Clinical or economic outcome</th>
<th>Infusion treatment&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Intermittent (n = 54)</td>
<td>11 (20)</td>
<td>1 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>LOS</td>
<td>Extended (n = 33)</td>
<td>14.5 (6–30)</td>
<td>11 (7–20)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hospital</td>
<td>ICU</td>
<td>12 (6–21)</td>
<td>10 (6–16)</td>
<td>0.45</td>
</tr>
<tr>
<td>Infection related</td>
<td>18.5 (5.5–32.5)</td>
<td>8 (4–20)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Duration (days) of mechanical ventilation</td>
<td>14.5 (5–30)</td>
<td>10.5 (8–18)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Cost (US$)</td>
<td>Total hospital costs</td>
<td>51,231 (17,558–107,031)</td>
<td>28,048 (13,866–68,991)</td>
<td>0.13</td>
</tr>
<tr>
<td>Infection-related hospital costs</td>
<td>15,322 (8,343–27,337)</td>
<td>13,736 (10,800–23,312)</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as “number (%).”<sup>b</sup> P values determined by the Fisher exact test or the Wilcoxon rank-sum test as appropriate.

82.25), and APACHE II score (OR = 1.12; 95% CI = 1.04 to 1.22). The multivariable model is shown in Table 3. Extended infusion was the reference group for the infusion type variable. The odds of in-hospital death among patients who received intermittent infusion were 16.7 times higher than those who received extended infusion, after adjusting for APACHE II score and ICU admission at the time of positive culture collection (95% CI = 1.57 to 949.35). The odds of in-hospital death were 8.9 times higher among patients who were in the ICU at the time of positive culture (95% CI = 1.45 to 100.85) and were 1.13 times higher for each unit increase in APACHE II score, after adjusting for confounding variables.

**DISCUSSION**

In this study of patients who received extended-infusion cefepime treatment for *P. aeruginosa* pneumonia and/or bacteremia, we observed a significant decrease in mortality and ICU length of stay. We also observed a trend toward decreased hospital length of stay and hospital costs among patients who received extended infusion. Antimicrobial stewardship programs are challenged with the treatment of *P. aeruginosa* infections especially in the setting of increasing antimicrobial resistance. Stewardship principles include selecting the most appropriate agent, dose, and frequency and have been shown to influence clinical outcomes in patients with nosocomial infections (2–4). *P. aeruginosa* is the leading cause of Gram-negative nosocomial pneumonia and the second most common cause of nosocomial bacteremia (12, 13). *P. aeruginosa* is challenging to treat due to multiple resistance mechanisms often resulting in higher MICs in combination with the lack of new antibiotics with antipseudomonal activity (14). For these reasons, antimicrobial stewardship must optimize available antibiotics in an effort to achieve positive outcomes in *P. aeruginosa* infections.

Historically, β-lactams have been administered via intermittent infusion, resulting in high peak concentrations that do not enhance bactericidal activity, and during the dosing interval, concentrations may fall below the susceptible MIC (15–17). Like other β-lactams, cefepime displays time-dependent bactericidal activity whereby efficacy is optimized when 60% T > MIC (17). At our institution, cefepime is frequently used in the treatment of suspected or confirmed *P. aeruginosa* infections. Although the percent susceptibility indicates that 91 and 76% of *P. aeruginosa* isolates are susceptible to cefepime in our institution and ICU, respectively, the results of the Monte Carlo simulation demonstrated that only 2 g every 8 h provided a ≥90% probability of target attainment for the full range of MIC values at our institution. Our antimicrobial stewardship program (ASP) believed it was imperative to combine hospital-specific MIC data and pharmacodynamic modeling to determine the regimen that would result in optimal outcomes for our patients. It is important to note that the percent susceptibility remained consistent during the study time period.

Studies have demonstrated unfavorable results with traditional dosing regimens and the ability to achieve pharmacodynamic targets. One such study integrated population pharmacokinetics and microbiologic surveillance to generate an empirical cefepime dosing strategy against *P. aeruginosa*. Authors of the study concluded that a standard regimen of 2 g every 12 h infused over 30 min achieved the pharmacodynamic target 4 to 38% of the time. In comparison, a nonstandard regimen of 2 g every 8 h infused over 6 h resulted in pharmacodynamic target achievement 18 to 63% of the time (19).

With the aim of improving clinical outcomes for patients with Gram-negative infections, our antimicrobial stewardship program implemented extended infusion of piperacillin-tazobactam, cefepime, and doripenem. In this study, we report our experience with cefepime extended-infusion treatment for patients with *P. aeruginosa* infections. We observed a significant decrease in mortality favoring the extended-infusion group. A similar result was observed by Lodise et al. with extended-infusion piperacillin-tazobactam in patients with *P. aeruginosa* infections. Among the patients with an APACHE II score of ≥17, the 14-day mortality rate was significantly lower among patients who received extended-
infusion therapy than among patients who received intermittent-infusion therapy (12.2% versus 31.6%, respectively; P = 0.04) (26). A second study also demonstrated favorable outcomes, including mortality, when comparing extended-infusion piperacillin-tazobactam to non-extended-infusion, similar-spectrum β-lactams in the treatment of patients with documented Gram-negative infections (27).

We observed a significant decrease in ICU length of stay after implementation of extended infusion. In a prospective, observational study of adult patients with ventilator-associated pneumonia, Nicasio et al. demonstrated that cefepime 2 g every 8 h infused over 3 h would provide the highest probability of target attainment using pharmacodynamic modeling. This study demonstrated a significant decrease in infection-related length of stay (11.7 ± 8.1 days versus 26.1 ± 18.5 days; P < 0.001) (28).

In addition to improved clinical outcomes, a difference in hospital costs favoring extended infusion was observed, although not statistically different. This may be supported by the difference in ICU and hospital lengths of stay. Hospital costs accrued during the days of antimicrobial therapy were not significantly different.

There are several limitations to our study. First, the study represented a small sample size and was a single-center, nonrandomized quasi-experimental design. Our study population included two different time periods that could potentially introduce bias. Our antimicrobial stewardship program determined it was imperative to provide a timely and comprehensive analysis before and after the implementation of an alternative dosing strategy. When extended infusion was implemented, all patients were automatically converted to extended infusion, limiting prescribing bias. The exact time of cefepime administration was not determined, which could impact our observed mortality difference. We excluded patients with intermediate or resistant isolates which may have increased the observed difference. A recent study demonstrated that patients with cefepime MICs of ≥8 µg/ml had an approximately 2-fold increase in 28-day mortality over that of patients with MICs of <8 µg/ml (54.8 and 24.1%, respectively; P = 0.001) (29). MicroScan reports susceptibility to cefepime as an MIC of ≤8 µg/ml; therefore, the exact MICs are not known. One study evaluated the population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. The authors demonstrated that the likelihoods of 2 g every 8 h (3-h infusion) achieving free drug concentrations above the MIC for 50% of the dosing interval were 91.8, 78.1, and 50.3% for MICs of 8, 16, and 32 µg/ml, respectively (30). Given that one advantage of extended infusion is the potential to successfully treat an outbreak with an organism at or above the susceptible breakpoint, potential future directions of our study are to evaluate the clinical outcomes in patients with intermediate or resistant P. aeruginosa isolates and the completion of exact MIC testing on all P. aeruginosa blood and respiratory isolates.

Conclusions. In an era of escalating antimicrobial resistance and lack of new antibiotic discovery, antimicrobial stewardship programs must combine knowledge of individual resistance data and pharmacodynamic modeling to achieve maximal bactericidal exposure for patients with P. aeruginosa infections. This study demonstrates the importance of applying pharmacodynamic modeling to determine the optimal antibiotic regimen in the treatment of P. aeruginosa infections. The days of “one size fits all” for antimicrobials are gone. Cefepime extended infusion provides increased clinical and economical benefits in our setting, and it is likely that a similar benefit would be experienced in other, similar health care settings.

ACKNOWLEDGMENTS

We thank David P. Nicolau for his pharmacodynamic analysis and review of the manuscript, Kurt B. Stevenson for his review of the manuscript, and Mark Lusberg for his review of the statistics.

REFERENCES