MAJOR ARTICLE

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

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Background. Piperacillin-tazobactam is frequently used to treat *Pseudomonas aeruginosa* infections in critically ill patients. In an effort to improve clinical outcomes, an extended-infusion dosing scheme for piperacillin-tazobactam therapy was devised using a Monte Carlo simulation and was adopted into clinical practice at Albany Medical Center (Albany, New York). This study evaluates the clinical implications of extended infusion of piperacillin-tazobactam therapy for critically ill patients with *P. aeruginosa* infection.

Methods. We performed a cohort study of patients who received piperacillin-tazobactam therapy for a *P. aeruginosa* infection that was susceptible to piperacillin-tazobactam during the period January 2000–June 2004. Prior to February 2002, all patients received intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 h); after this time, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 h every 8 h). Data on demographic characteristics, disease severity, and microbiology were collected, and outcomes were compared between groups.

Results. A total of 194 patients comprised the 2 study groups: 102 patients received extended infusions of piperacillin-tazobactam, and 92 patients received intermittent infusions of piperacillin-tazobactam. No differences in baseline clinical characteristics were noted between the 2 groups. Among patients with Acute Physiological and Chronic Health Evaluation–II scores $\geqslant$17, 14-day mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; $P = .04$), and median duration of hospital stay after collection of samples for culture was significantly shorter for patients who received extended-infusion therapy than for patients who received intermittent-infusion therapy (21 days vs. 38 days; $P = .02$).

Conclusions. These results indicate that extended-infusion piperacillin-tazobactam therapy is a suitable alternative to intermittent-infusion piperacillin-tazobactam therapy, and they strongly suggest that improved outcomes may be realized by administering extended-infusion piperacillin-tazobactam therapy to critically ill patients with *P. aeruginosa* infection.

Pseudomonas aeruginosa is a frequent cause of serious infections among hospitalized patients [1–5]. Despite advances in antibiotic therapy, infections secondary to *P. aeruginosa* are still associated with considerable morbidity and mortality [6–13]. Antibiotic treatment of this pathogen is extremely challenging, because it is endowed with multiple resistance mechanisms, including β-lactamases, efflux pumps, and a rather impermeable outer membrane [2]. These mechanisms often result in higher MICs for *P. aeruginosa* than for other common gram-negative pathogens in the hospital environment [1, 3–5]. Consequently, antimicrobial chemotherapy for *P. aeruginosa* often produces suboptimal results [6–9, 11–15].

We sought to improve the outcomes (i.e., patient survival and duration of hospitalization after the onset of infection) associated with *P. aeruginosa* infection at our institution by exploring the ways to optimize the pharmacodynamics of first-line antipseudomonal β-lactam antibiotics. "Pharmacodynamics" is the term used to describe the relationship between measures of

Received 14 July 2006; accepted 2 October 2006; electronically published 2 January 2007.

Presented in part: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., October 2004 (abstract O-1617).

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Clinical Infectious Diseases 2007; 44:357–63

1058-4838/2007/4403-0008$15.00

drug exposure and antimicrobial activity. Tremendous progress has been made in identifying the pharmacodynamic target (i.e., the measure of drug exposure) associated with maximal microbiological effect [16, 17]. For β-lactams, in vitro and animal studies have demonstrated that the best predictor of bacterial killing is the time during which the non–protein-bound, or free drug, concentration exceeds the MIC of the organism (*f*T>MIC) [16–21]. Free β-lactam concentrations do not have to remain above the MIC for the entire dosing interval. Although the precise *f*T>MIC varies for different drug-bacteria combinations, near-maximal bactericidal effect is typically observed when the free drug concentration exceeds the MIC for 60%–70%, 50%, and 40% of the dosing interval for the cephalosporins, penicillins, and carbapenems, respectively [16–21].

With advances in computer technology and mathematical modeling, it is now possible to apply pharmacodynamic principles to clinical practice; one frequently used technique is a Monte Carlo simulation [16, 22–25, 28]. This technique incorporates the variability in pharmacokinetic parameters among patients (between-patient variability) when predicting antibiotic exposures or drug concentration–time profiles for a large number of patients. More importantly, Monte Carlo simulation can be used to determine the probability that an antibiotic dosing regimen achieves the drug exposure target associated with maximal microbiological effect across the range of MICs observed in the clinic [16, 22–25].

We used a Monte Carlo simulation to identify an alternative way of administrating piperacillin-tazobactam therapy to optimize the therapeutic outcomes (i.e., survival and duration of hospitalization) for our patients with *P. aeruginosa* infection. At our institution, piperacillin-tazobactam was the most frequently administered β-lactam among hospitalized patients with serious infections, particularly among those in the intensive care unit with documented or suspected *P. aeruginosa* infection. Although our hospital antibiogram indicated that the majority of *P. aeruginosa* isolates that were recovered in our institution were susceptible to piperacillin-tazobactam, the results of an internal Monte Carlo simulation study (figure 1) demonstrated that the most commonly used piperacillin-tazobactam dosing strategy (a 30-min infusion of 3.375 g intravenously every 4 or 6 h) did not provide high probabilities of target attainment (50% *f*T>MIC) for the full range of MIC values deemed to be susceptible by the Clinical Laboratory Standards Institute [25–28]. The simulation also indicated that attaining 50% *f*T>MIC for the piperacillin aspect of the combination (figure 1) was best achieved with a 4-h infusion of 3.375 g of piperacillin-tazobactam administered intravenously every 8 h as an alternative to standard intermittent-infusion dosing schemes of 3.375 g administered intravenously for 30 min every 4 or 6 h [26]. Specifically, the Monte Carlo simulation revealed that the probability of achieving a near bactericidal

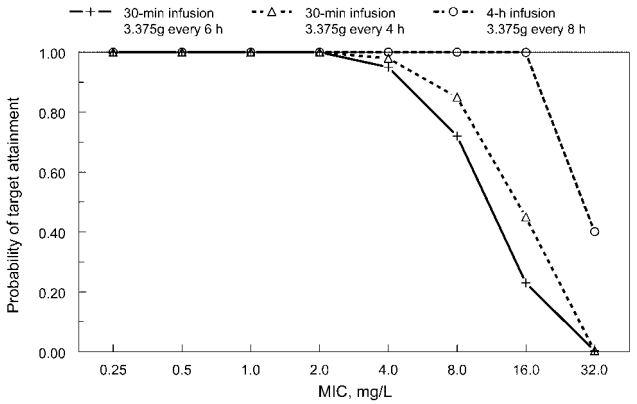

Figure 1. Results of the probability of target attainment analysis for piperacillin-tazobactam therapy. The figure depicts the probability of achieving free piperacillin concentration in excess of the MIC for 50% (near-maximal effect) of the dosing interval (50% *f*T>MIC) for increasing MIC values for a 30-min infusion of piperacillin-tazobactam 3.375 g administered intravenously every 6 h *(A)* and every 4 h *(B)* and a 4-h infusion of piperacillin-tazobactam 3.375 g administered intravenously every 8 h *(C)*. The x-axis reflects increasing MIC values (in mg/L), and the y-axis reflects the probability of target attainment.

effect (50% *f*T>MIC) was significantly higher for the prolonged infusion administration at MIC values >1 mg/L (intermittent dosing every 6 h) and at MIC values >4 mg/L (intermittent dosing every 4 h) [26].

This mathematical simulation was so compelling that the novel extended-infusion protocol was quickly adopted into practice at Albany Medical Center Hospital (Albany, New York) in February 2002 following approval by the hospital's Pharmacy and Therapeutics Committee and Medical Executive Committee. The new protocol instituted a hospital-wide substitution program to allow for automatic conversion of written orders for intermittent infusion of piperacillin-tazobactam to be dosed as extended infusion of piperacillin-tazobactam. This follow-up study evaluates the protocol's clinical outcomes among patients with *P. aeruginosa* infection, to determine if extended infusion of piperacillin-tazobactam delivered results superior to those associated with traditional intermittent dosing.

METHODS

Study design and population. A retrospective cohort study was conducted among all patients who received piperacillin-tazobactam for *P. aeruginosa* infection between January 2000 and June 2004 at Albany Medical Center Hospital. Prior to February 2002, all patients received traditional infusions of piperacillin-tazobactam; in February 2002 and after, all patients (100%) received extended infusions of piperacillin-tazobactam by automatic conversion. Two study groups were compared: patients who received a standard infusion of piperacillin-tazobactam (a 30-min infusion of 3.375 g intravenously every 4

or 6 h) and patients who received the new extended-infusion protocol (a 4-h infusion of 3.375 g intravenously every 8 h). This study received expedited approval from the Albany Medical Center Hospital institutional review board.

Inclusion criteria. Patients with culture results positive for *P. aeruginosa* were included if all the following criteria were met: (1) age ⩾18 years, (2) absolute neutrophil count ⩾1000 cells/mm^3, (3) positive *P. aeruginosa* culture result meeting the Centers for Disease Control and Prevention's criteria for infection [29], (4) piperacillin-tazobactam therapy administered within the first 72 h of the onset of *P. aeruginosa* infection, and (5) receipt of piperacillin-tazobactam for ⩾48 h.

Exclusion criteria. Patients were excluded if they met any of the following criteria: (1) receipt of >1 day of intermittent infusion of piperacillin-tazobactam before conversion to the extended-infusion protocol, (2) receipt of a concurrent β-lactam antibiotic with activity against *P. aeruginosa* within 5 days of initiation of piperacillin-tazobactam therapy (excluding fluoroquinolones and aminoglycosides), (3) isolation of a *P. aeruginosa* isolate that was intermediate or resistant to piperacillin-tazobactam, (4) receipt of dialysis, (5) receipt of a solid-organ or bone marrow transplant, or (6) receipt of a diagnosis of cystic fibrosis.

Data. Data was extracted from patients' medical records by a trained reviewer using a structured data instrument. Data elements included age, sex, race, medical history and comorbidities, health care institution exposure for >72 h within 180 days before hospital admission, duration of hospitalization prior to collection of a *P. aeruginosa*–positive sample (including the total duration of hospitalization and the duration of time in the intensive care unit), location of hospitalization at collection of sample for *P. aeruginosa* culture (intensive care unit vs. non–intensive care unit), mechanical ventilation status at sample collection for culture, number of consecutive days receiving mechanical ventilation prior to collection of sample for culture, source of *P. aeruginosa* infection, severity of illness at collection of sample for culture (as calculated by means of the APACHE II score [30]), microbiologic and treatment data, and comorbid conditions (e.g., diabetes mellitus or HIV infection).

The APACHE II score was defined as the worst physiological score calculated during the initial 24 h after *P. aeruginosa* culture sample collection. The source of *P. aeruginosa* infection was determined by sample culture assessment and the physician's clinical description in the medical record.

Microbiological data included all cultures positive for *P. aeruginosa* and the date and time at which the culture sample was collected. Other organisms present at the same *P. aeruginosa* culture site or causing an infection at a distal site, as well as susceptibilities reported by the microbiology laboratory, were also recorded. Susceptibility testing was performed using the Kirby-Bauer method and was interpreted according to Clinical Laboratory Standards Institute guidelines [27].

Treatment data included information about all antimicrobials administered in response to *P. aeruginosa* infection (i.e., date, time, dose, route, and duration). Antibiotics provided for concurrent infections were also recorded. Concomitant therapy with an aminoglycoside or fluoroquinolone was deemed "combination therapy" if it was provided within 96 h of the *P. aeruginosa*–positive culture result and was administered for ⩾24 h. Culture-to-antibiotic time was measured in hours and represented the difference in time between when the first *P. aeruginosa*–positive sample was sent to the lab for culturing and the documented time of initial antibiotic administration.

Outcomes. The following clinical outcomes were assessed: (1) patient vital status 14 days after *P. aeruginosa*–positive culture sample collection (14-day mortality) and (2) duration of hospital length of stay (LOS) after collection of *P. aeruginosa*–positive culture sample collection until discharge or death. Patients who died within 14 days of collection after *P. aeruginosa*–positive culture samples were excluded from the LOS analysis.

Data analysis plan. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using Student's *t* test or Mann-Whitney *U* test. Multivariable analyses were performed to determine the independent association of treatment with the outcome of interest while adjusting for confounding variables (variables found to be significantly different among treatment groups).

Classification and Regression Tree (CART) analysis was used to identify the patients who were at the lowest and greatest risk for 14-day mortality [31]. The variables included at CART model setup were age, sex, diabetes mellitus and HIV infection status, history of health care exposure, LOS prior to culture sample collection, residence in the intensive care unit at culture sample collection, consecutive days in the intensive care unit prior to culture sample collection, receipt of mechanical ventilation at culture sample collection, consecutive days receiving mechanical ventilation prior to culture sample collection, APACHE II score at culture sample collection, concomitant use of an aminoglycoside and/or fluoroquinolone, and infection source. Optimal tree selection was performed on the basis of pruning and 10-fold cross-validation. The relationship between piperacillin-tazobactam dosing and outcome was examined in CART-derived populations who were at lowest and greatest risk for 14-day mortality. For all analyses, $P < .05$ was considered to be statistically significant for 2-tailed tests. All calculations were performed using Systat for Windows, version 11.0 (Systat), and CART software (Salford Systems).

RESULTS

Baseline clinical characteristics of the study population are presented in table 1. Of the 194 patients who satisfied the inclusion

Table 1. Demographic and clinical characteristics of the study population.

Characteristic	Value (n = 194)
Age, mean years ± SD	63.2 ± 17.2
Male sex	119 (61.3)
White	173 (89.2)
Diabetes mellitus	56 (28.9)
HIV infection	3 (1.5)
History of health care exposure	72 (37.1)
Duration of hospital stay prior to culture sample collection, median days (range)	6 (0–89)
In ICU at onset of infection	126 (64.9)
Consecutive days in ICU prior to onset of infection, median days (range)	3 (0–59)
Receiving mechanical ventilation at culture sample collection	108 (55.7)
Consecutive days receiving mechanical ventilation prior to culture sample collection, median days (range)	1 (0–59)
APACHE II score at onset of infection, mean days ± SD	15.7 ± 7.2
Concomitant treatment with an aminoglycoside	47 (24.2)
Concomitant treatment with a fluoroquinolone	16 (8.2)

NOTE. Values are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

criteria, 92 patients received the traditional intermittent infusion and 102 patients received the extended infusion. Only 4 (4.3%) of the patients who received the intermittent infusion received 3.375 g intravenously every 4 h; the overwhelming majority received infusions every 6 h. The mean duration of piperacillin-tazobactam therapy was 8.4 days (SD, ± 4.4 days). The 14-day mortality rate was 11.9% (23 patients died); among the patients who survived at least 14 days after culture sample collection, the median LOS after culture sample collection was 20 days (range, 3–159 days).

No significant differences in baseline characteristics were noted between the groups after bivariate analysis was performed (table 2). The mean duration of piperacillin-tazobactam therapy was identical for the 2 groups (8.4 days), and an equivalent number of patients received an aminoglycoside or a fluoroquinolone. The primary culture sample sources were similar between groups, and the respiratory tract was the predominant source of infection in both groups. The only notable difference in culture sample source was a higher rate of skin and soft-tissue infections among the patients who received intermittent infusion. The 14-day mortality rate among patients with skin and soft-tissue infections was 5.9%, compared with 13.1% of patients with non-skin soft-tissue infections ($P = .2$). Among patients who survived at least 14 days after culture sample collection, the median LOS after culture collection was shorter for patients who had skin and soft-tissue infections (16 days vs. 20 days), but the difference was not significant ($P = .1$).

The results of the CART analysis are presented in figure 2. The CART analysis, which was used to identify patients at lowest and greatest risk for 14-day mortality, resulted in a tree that contained 2 terminal nodes. An APACHE II score ⩾17 was the most important predictor of 14-day mortality: 14-day mortality was 21.5% among patients who had an APACHE II score ⩾17 versus 5.2% among patients who had an APACHE II score <17 ($P < .01$). Among patients who survived at least 14 days after culture sample collection, the median LOS was significantly longer in the APACHE II score ⩾17 group than in the APACHE-II score <17 group (27.5 days vs. 18 days; $P = .02$).

Comparison of outcomes associated with extended infusion and intermittent infusion of piperacillin-tazobactam in the CART-derived populations are presented in figure 2. When stratified by APACHE II score, the clinical benefit of extended infusion was statistically significant among patients with an APACHE II score ⩾17; both 14-day mortality ($P = .04$) and median LOS ($P = .02$) were lower for the patients who received extended infusion than for patients who received intermittent infusion. No differences in 14-day mortality and hospital LOS were noted for patients with an APACHE II score <17. Overall, 14-day mortality was lower in the group that received extended infusion than in the group that received intermittent infusion (8.8% vs. 15.2%), but the difference did not achieve statistical significance ($P = .17$). Overall median LOS after culture sample collection was also lower in the extended infusion group, compared with the intermittent infusion group (18 days vs. 22.5 days) but the difference was of borderline significance ($P = .09$).

DISCUSSION

With the hope of improving clinical outcomes for patients with *P. aeruginosa* infection, the extended-infusion piperacillin-tazobactam dosing scheme was quickly adopted into clinical practice at Albany Medical Center Hospital to optimize the drug's pharmacodynamic profile against the range of *P. aeruginosa* MICs considered to be susceptible by the Clinical Laboratory Standards Institute (i.e., ⩽64 mg/L). Administering a β-lactam agent as an infusion for longer than the conventional 30–60 min duration has 2 main effects. First, it produces a lower peak concentration of the drug; because the bacterial kill rate for these agents is not concentration dependent, this does not present a major disadvantage [15–19]. 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 practice should yield a higher probability of attaining a good clinical outcome.

Prolonged infusion offers several advantages over continuous infusion (an alternative β-lactam dose optimization method-

Table 2. Comparison of demographic and clinical characteristics and source of infection for patients who received an extended infusion of piperacillin-tazobactam and patients who received an intermittent infusion of piperacillin-tazobactam.

Demographic or clinical characteristic	Extended infusion (n = 102)	Intermittent infusion (n = 92)	P
Age, mean years ± SD	62.8 ± 18.3	63.9 ± 16.1	.6
Male sex	65 (63.7)	54 (58.7)	.5
Diabetes mellitus	28 (27.5)	28 (30.4)	.6
HIV infection	1 (1.0)	2 (2.2)	.5
History of health care exposure	35 (34.3)	37 (40.2)	.4
Duration of stay prior to culture sample collection, median days (range)	7 (0–89)	6 (0–52)	.5
In ICU at onset of infection	63 (61.8)	63 (68.5)	.3
Consecutive days in ICU prior to onset of infection, median days (range)	3.5 (0–30)	2 (0–52)	.9
Receiving mechanical ventilation at culture sample collection	56 (54.9)	52 (56.5)	.8
Consecutive days receiving mechanical ventilation prior to culture sample collection, median days (range)	1 (0–59)	1 (0–48)	.8
APACHE II score at onset of infection, mean ± SD	15.3 (6.7)	16.2 (7.6)	.3
Duration of therapy, mean days ± SD	8.4 (4.4)	8.4 (4.5)	.9
Concomitant treatment with an aminoglycoside	21 (22.8)	26 (25.5)	.6
Concomitant treatment with a fluoroquinolone	5 (5.9)	10 (10.9)	.2
Primary source of culture sample			
Respiratory tract	55 (53.9)	48 (52.2)	.8
Urinary tract	21 (20.6)	12 (13.0)	.2
Skin or soft tissue	11 (10.8)	23 (25.0)	.009
Intravenous catheter	3 (2.9)	0 (0)	.1
Abdomen	4 (3.9)	1 (1.1)	.2
Other	8 (7.8)	8 (8.7)	.8

NOTE. Values are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

ology), as well. Although continuous infusion is a rational method to optimize *f*T>MIC, it is not always realistic, for multiple reasons. For example, an intravenous line or a lumen of an intravenous catheter must be dedicated to infusion of the antibiotic; this is not always practical, especially for patients who have limited intravenous access or patients who require multiple daily infusions (who often have other concerns, such as compatibility and access site issues). Extended infusion of piperacillin-tazobactam circumvented many of the aforementioned issues observed in the continuous infusion approach, because it allows 4 h between each 8 h dosing interval when other agents could be administered through the same intravenous line. Thus, the patient does not need a dedicated intravenous line for the administration of a continuous β-lactam infusion. Furthermore, extended infusion achieves the targeted *f*T>MIC at a total daily dose that is less than the total daily dose in standard β-lactam dosing methods.

This follow-up, retrospective analysis assessed the clinical viability of the extended infusion protocol that was adopted into practice solely on the basis of the strength of Monte Carlo simulation data. Because piperacillin-tazobactam is often used empirically in critically ill patients, we felt that it was important to examine the impact of extended infusion among the most vulnerable patients. Patients at greatest risk for deleterious outcomes were identified by CART (figure 2) [31]. With CART, the entire population was divided into 2 groups: those who had a high likelihood of achieving the outcome of interest and those who did not. When these populations were identified, the influence of piperacillin-tazobactam therapy was examined within the resultant risk-stratified populations. We also limited the study to patients who had documented *P. aeruginosa* infection, for several reasons. First, patients with *P. aeruginosa* infection who met the inclusion and exclusion criteria represented a relatively homogeneous patient population; this minimized potential biases and increased the ability to detect differences between treatment groups. Second, patients with *P. aeruginosa* infection are more dependent on antimicrobial therapy than other populations, because they tend to be critically ill and to have an impaired innate immune system [11, 14]. Third, *P. aeruginosa* isolates typically have a higher range of MICs to piperacillin-tazobactam than do other organisms; as such, the benefits of optimizing *f*T>MIC would be better elucidated in this patient population [4, 5, 14, 15].

Our results indicated that extended infusion of piperacillin-tazobactam is a suitable alternative to intermittent dosing and strongly suggested that improved outcomes can be achieved by

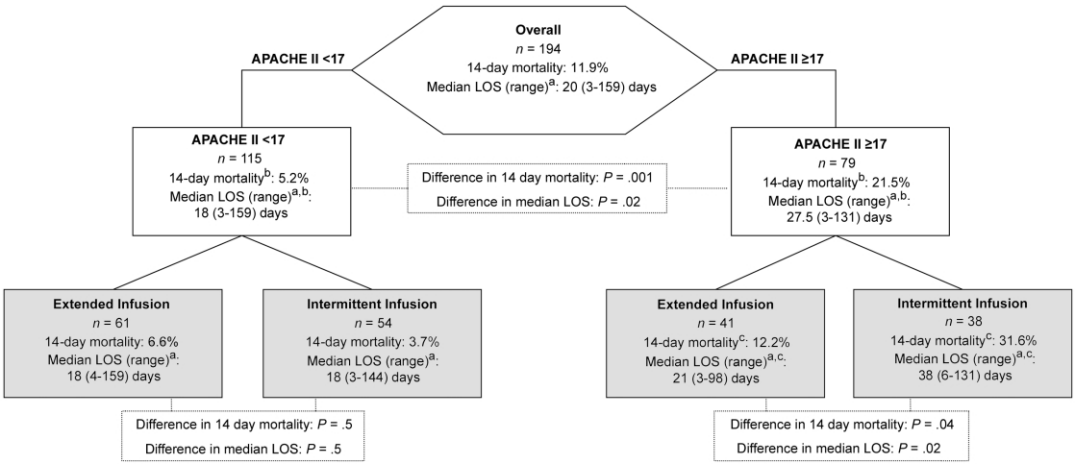

Figure 2. Comparison of outcomes of patients with APACHE II scores ⩾17 and patients with APACHE II scores <17 (the Classification and Regression Tree [CART]–derived breakpoint) who received either an extended infusion of piperacillin-tazobactam or an intermittent infusion of piperacillin-tazobactam. LOS, length of stay. [a]Excludes patients that died within 14 days of collection of *P. aeruginosa*–positive culture sample. [b]Comparison between patients with an APACHE II score <17 and patients with an APACHE II score ⩽17 was $P < .05$. [c]Comparison between the extended group and the intermittent infusion group was $P < .05$.

prolonging the infusion duration in critically ill patients (figure 2). In patients who were identified as having the greatest risk for 14-day mortality (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 extended infusion, compared with patients who received intermittent infusion. No differences between extended infusion and intermittent infusion of piperacillin-tazobactam were observed with respect to outcome in patients at lowest risk for death (APACHE II score <17). Not surprisingly, the vastly different outcomes of patients at the APACHE II score breakpoint canceled each other out when the 2 groups were pooled. 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 demonstrate that improved outcomes can be achieved by optimizing antibiotic pharmacodynamics 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. The extended-infusion piperacillin-tazobactam program continues at Albany Medical Center Hospital on the basis of observed results and the substantial cost savings that are associated with this method. During the year 2001, the year before conversion, piperacillin-tazobactam purchases at our facility totaled ~$275,000; reducing the total daily dose by 25%–50% (by 1–3 doses per day) represented a savings of $68,750–$135,750 in annual direct drug acquisition costs.

There are several limitations to our study that should be noted. First, this was a single center analysis that examined the impact of piperacillin-tazobactam dosing on patients who had culture-positive *P. aeruginosa* infection. Second, it is well documented that the optimal way to compare antibiotic dosing regimens is through a randomized clinical trial. However, such a randomized trial would be costly and difficult to execute for a variety of reasons (e.g., enrolling patients with the target pathogen or studying a critically ill patient population). Although this was a single-center, retrospective cohort study, it examined outcomes before and after the implementation of an automatic dosing substitution program. When the extended infusion method was adopted into clinical practice, all patients received an extended infusion of piperacillin-tazobactam. Thus, prescribing bias was not introduced into the study. It is also important to note that the study comparison groups were of close proximity, thus mitigating any temporal biases introduced by improvements in clinical care standards. Furthermore, the strict inclusion and exclusion criteria resulted in 2 groups that were extremely well balanced at baseline. Finally, the study outcomes were limited to objective end points because of the difficulty in assessing clinical response in the retrospective study design.

In conclusion, to our knowledge, this is the first study to evaluate the clinical outcomes of an extended-infusion β-lactam dosing scheme. The results indicate that extended infusion of piperacillin-tazobactam is a good alternative to intermittent infusion of this agent and strongly suggest that the clinical benefit is particularly striking among critically ill patients with an APACHE II score ⩾17. Further pre- and postprotocol studies at other institutions and future prospective studies would validate our findings and may potentially encourage broader implementation of extended infusion, if it is warranted.

Acknowledgments

T.P.L. is independent of any commercial funder, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study greatly benefited from the gracious critical review of Raymond P. Smith. We would also like to thank Eli N. Perencevich, Jon P. Furuno, and Jessina C. McGregor for their assistance with data analysis, and the Albany Medical Center Research Nurses, for collecting the data. The manuscript was edited by Allison Krug.

Financial support. Society of Infectious Diseases Pharmacists.

Potential conflicts of interest. All authors: no conflicts.

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