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The Retrospective Cohort of Extended-infusion Piperacillin-Tazobactam (RECEIPT) Study

A Multicenter Study

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Posted: 08/16/2011; Pharmacotherapy. 2011;31(8):767-775.

Abstract and Introduction

Abstract

Study Objective. To compare the effectiveness of extended-infusion piperacillin-tazobactam with that of similar-spectrum, nonextendedinfusion β-lactam antibiotics in the treatment of gram-negative infections.
Design. Multicenter, retrospective medical record review.
Setting. Fourteen hospitals throughout the United States.
Patients. A total of 359 adults treated for gram-negative infections between January 1, 2007, and February 28, 2010, with either 4-hour extended-infusion piperacillin-tazobactam (186 patients) or nonextended-infusion comparator antibiotics (173 patients), which consisted of cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.
Measurements and Main Results. Deidentified data were collected on demographics, renal function, Acute Physiology and Chronic Health Evaluation II score, chronic health conditions, source of infection and type of organism, intensive care unit (ICU) length of stay, total length of stay, type and duration of antimicrobial therapy, and in-hospital mortality. The primary outcome was mortality rate of the patients receiving extended-infusion piperacillin-tazobactam versus those receiving nonextended-infusion comparator antibiotics. Secondary outcomes were hospital length of stay, ICU length of stay, and total duration of antibiotic therapy. Baseline characteristics were similar between groups, except a significantly lower proportion of patients in the extended-infusion group were treated with a concomitant intravenous aminoglycoside (5.9% vs 16.2%, p<0.01), were infected with *Pseudomonas* species (22.6% vs 39.9%, p<0.01), or had positive respiratory cultures (30.7% vs 43.4%, p=0.01). Antibiotic duration, hospital length of stay, and ICU length of stay were similar between groups. In-hospital mortality was significantly decreased in the extended-infusion piperacillin-tazobactam group versus those receiving comparator antibiotics (9.7% vs 17.9%, p=0.02). Multivariate analysis confirmed that extendedinfusion piperacillin-tazobactam prolonged survival by 2.77 days (p<0.01) and reduced the risk of mortality (odds ratio 0.43, p=0.05).
Conclusion. Pharmacodynamic dosing using extended-infusion piperacillintazobactam demonstrated favorable outcomes, including mortality, when compared with nonextended-infusion, similar-spectrum β-lactams in the treatment of patients with documented gram-negative infections. Prospective, randomized trials are needed to further corroborate these findings.

Introduction

Ever-increasing resistance among gramnegative infections and increasing mortality associated with these organisms have led to the reevaluation of the optimal method to administer current antibiotics.[1] Pharmacodynamic dosing of β-lactam antibiotics either by continuous or extended infusion has been well referenced in the literature for years.[2–16] Extending the administration time of piperacillin-tazobactam may maximize the time free drug is available at concentrations in excess of the minimum inhibitory concentration without the notable intravenous catheter access drawbacks of continuous infusions.[2]

In 2007, a retrospective review was conducted of 4-hour extended-infusion piperacillintazobactam versus traditional 30-minute infusion (i.e., nonextended infusion) of piperacillintazobactam in patients with documented *Pseudomonas aeruginosa* infections.[3] Reduced 14- day mortality and hospital length of stay were demonstrated in those patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 17 or higher; however, overall mortality benefit and benefit in patients with APACHE II scores less than 17 were not demonstrated in the study. A multisite, retrospective cohort study attempted to replicate the results of that study in

patients with any documented gram-negative infection.[6] When comparing extended infusion with nonextended infusion of piperacillin-tazobactam, no impact was noted on 30-day mortality or length of stay overall or in any of the subgroups studied.

Limitations from previous studies have led to the need to further characterize the effects of extended infusion on mortality, hospital length of stay, and intensive care unit (ICU) length of stay and to describe the patient population that benefits most from extended-infusion administration. In the first above-mentioned study,[3] the infections were caused by *P. aeruginosa*, and as these organisms are more likely to exhibit higher minimum inhibitory concentrations of antibiotics, these infections would be most likely to benefit from extended-infusion therapy. Unfortunately, these results would not necessarily be generalizable to all gram-negative infections. Only patients with a higher severity of illness score in that study demonstrated a benefit from extended infusion versus nonextended infusion.[3] The multisite cohort study collated data from two institutions, but proved to be underpowered to demonstrate a mortality difference between nonextended- and extended-infusion piperacillin-tazobactam for the primary outcome.[6]

The objective of this study—the Retrospective Cohort of Extended-Infusion Piperacillin- Tazobactam (RECEIPT) study—was to compare the effectiveness of extended-infusion piperacillin- tazobactam with that of similar-spectrum, nonextended-infusion β-lactam antibiotics in the treatment of documented gram-negative infections.

Methods

This was a multicenter, retrospective medical record review conducted between January 1, 2007, and February 28, 2010, among 14 unique hospitals representing each geographic region of the United States. For-profit and nonprofit hospitals were included, as was a blend of community, university, and municipal hospitals. Hospital size ranged from 150–850 beds and included 23–170 ICU beds.

All data shared were deidentified, and institutional review board approval was obtained at sites requiring approval for exempt research.

Inclusion Criteria

Patients were included if they were aged 18 years or older; were hospitalized for at least 72 hours; had a documented gram-negative infection; received treatment with extended-infusion piperacillin-tazobactam or a nonextended infusion of cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam; and received these antibiotics for more than 48 hours. Patients with mixed gram-positive and gram-negative infections, as well as those with fungal coinfections, were included.

Exclusion Criteria

Subjects were excluded if they received more than 24 hours of effective antibiotics before the initiation of extended-infusion piperacillintazobactam or nonextended infusion of comparator antibiotic, if they received concomitant β-lactam antibiotics, if the gram-negative infection identified was proven intermediate or resistant to initial empiric therapy, or if therapy for grampositive or fungal organisms was inappropriate.

Piperacillin-tazobactam Dosing

All sites used a piperacillin-tazobactam dose of 3.375 g intravenously every 8 hours as a 4-hour infusion for the extended-infusion treatment in patients with an estimated creatinine clearance of at least 20 ml/minute. Dosing was not consistent among institutions in patients with an estimated creatinine clearance of less than 20 ml/minute. Intravenous dosing methods for these patients were as follows:

- 4.5 g every 12 hours as a 30-minute infusion
- 3.375 g every 8 hours as a 4-hour infusion
- 3.375 g every 12 hours as a 4-hour infusion (most common)
- 3.375 g every 12 hours as a 30-minute infusion
- 2.25 g every 8 hours as a 30-minute infusion

- 2.25 g every 12 hours as a 4-hour infusion

Data Collection

Patient data, including demographics and comorbid conditions such as diabetes mellitus, acute coronary syndrome, chronic heart failure, hepatic dysfunction, renal dysfunction, malignancy, human immunodeficiency virus disease, chronic obstructive pulmonary disease, organ transplantation, and immunosuppressive therapy, were collected from patients' medical records. The APACHE II scores[17] were calculated from data collected on the day of antibiotic initiation along with the cause and type of infection. Length of stay was defined as the total duration of hospitalization, without respect to ICU admission or antibiotic administration, for survivors. Length of stay in the ICU was defined as the number of whole days spent in the ICU. Duration of antibiotic therapy was defined as the number of consecutive whole days on which study antibiotics were administered. Those patients with no data regarding their survival were assumed to be alive. Concomitant antibiotics were fluoroquinolones, intravenous aminoglycosides, or inhaled aminoglycosides. No data were collected with regard to gram-positive treatments or antifungal therapies.

Outcomes

The primary outcome measured was mortality rate of patients receiving extended-infusion piperacillin-tazobactam versus those receiving nonextended-infusion comparator antibiotics. Mortality assessment in a priori subgroups included ICU admissions, patients receiving nonextended-infusion piperacillin-tazobactam, and patients with APACHE II scores of 17 or higher. Secondary outcomes included hospital length of stay, ICU length of stay, and total duration of antibiotic therapy in the extendedinfusion group versus the group receiving nonextended-infusion comparator antibiotics, and mortality rate between extended-infusion and nonextended-infusion piperacillin-tazobactam.

Statistical Analysis

A sample size calculation was completed based on previous research.[3, 6] Assuming a mortality rate of 8.5% in the comparator group and a 50% relative risk reduction being used to define clinical significance, a sample size of 284 patients was required to provide a power of 80% using an α of 0.05.

Statistical analyses were conducted by using SAS, version 9.2 software (SAS Institute Inc., Cary, NC). Descriptive statistics were evaluated with the $\chi^{[2]}$ test, Fisher exact test, and Wilcoxon rank sum test, as appropriate. Multivariate analysis for time to death was based on the gLIMMIX Procedure (SAS Institute Inc.) by using a negative binomial distribution for the response and using the random-effects model to account for variance among institutions. The multivariate analysis for death as a binary variable also used the gLIMMIX Procedure and the random-effects model.

Results

Data were collected on a total of 645 patients, of whom 359 met inclusion criteria. Patients eliminated from the final analysis were excluded for insufficient data (248 patients), lack of documented gram-negative infection (18), pathogen proven resistant to therapy (11), or treatment with multiple β-lactams (9). One hundred eighty-six patients received extendedinfusion piperacillin-tazobactam, and 173 patients received nonextended-infusion comparators. In the comparator group, 84 patients received piperacillin-tazobactam, 36 received meropenem, 26 received cefepime, 23 received imipenem-cilastatin, 3 received ceftazidime, and 1 received doripenem.

Baseline characteristics and concomitant antibiotics administered to the 359 patients meeting the inclusion criteria are shown in Table 1. Characteristics were similar between groups overall, except the extended-infusion group had a significantly lower proportion of patients with concomitant intravenous aminoglycoside use (5.9% vs 16.2%, p<0.01) and a higher rate of chronic heart failure (15.6% vs 8.7%, p=0.05). With the exceptions of *Pseudomonas* species, *Streptococcus* species, and the group of unknown or other organisms, infectious causes were similar between groups (Table 2). A significantly lower proportion of patients in the extended-infusion group had positive respiratory cultures (30.7% vs 43.4%, p=0.01), and the comparator group also had a significantly higher proportion of patients with positive cultures from other sources (Table 3).

Table 1. Baseline Characteristics of the 359 Patients Treated with Extended-Infusion Piperacillin-Tazobactam or Nonextended-Infusion Comparator Antibiotics

Characteristic	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion Comparator Group[a] (n=173)	p Value
Age (yrs), median (interquartile range)	65 (52–77)	62 (51–76)	0.48
No. (%) of Patients			
Male	95 (51.1)	94 (54.3)	0.54
Comorbid conditions			
Diabetes mellitus	69 (37.1)	56 (32.4)	0.35
Acute coronary syndrome	37 (20.0)	25 (14.5)	0.17
Chronic heart failure	29 (15.6)	15 (8.7)	0.05
Chronic renal failure	42 (22.6)	37 (21.4)	0.79
Hepatic failure	8 (4.3)	6 (3.5)	0.68
Chronic obstructive pulmonary disease	22 (11.8)	17 (9.8)	0.54
Transplant	8 (4.3)	11 (6.4)	0.38
Immunosuppressant therapy	16 (8.6)	17 (9.8)	0.69
Malignancy	35 (18.8)	26 (15)	0.34
Concomitant antibiotics			
Fluoroquinolone	68 (36.6)	62 (35.8)	0.89
Intravenous aminoglycoside	11 (5.9)	28 (16.2)	<0.01
Inhaled aminoglycoside	3 (1.6)	5 (2.9)	0.49
Creatinine clearance (ml/min)[b]			0.14
> 87	35 (18.8)	34 (19.7)	
30.9–87	76 (40.9)	62 (35.8)	
< 30.9	40 (21.5)	28 (16.2)	
Missing data	35 (18.8)	49 (28.3)	
APACHE II score			0.07
< 9	50 (26.9)	28 (16.2)	
9–19	56 (30.1)	67 (38.7)	
> 19	27 (14.5)	30 (17.3)	
Missing data	53 (28.5)	48 (27.8)	

APACHE = Acute Physiology and Chronic Health Evaluation.

[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

[b]Estimated by using the Cockcroft-gault equation.

Table 2. Infectious Etiologies

Organism	No. (%) of Patients		p Value
	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion omparator Group[a] (n=173)	
Acinetobacter sp	1 (0.5)	4 (2.3)	0.2
Bacteroides sp	7 (3.8)	4 (2.3)	0.43
Citrobacter sp	10 (5.4)	6 (3.5)	0.38
Escherichia coli	79 (42.5)	59 (34.1)	0.1
Enterobacter sp	24 (12.9)	20 (11.6)	0.7
Klebsiella sp	46 (24.7)	41 (23.7)	0.82
Proteus sp	11 (5.9)	17 (9.8)	0.17
Providencia sp	2 (1.1)	3 (1.7)	0.68
Pseudomonas sp	42 (22.6)	69 (39.9)	<0.01
Serratia sp	8 (4.3)	7 (4.1)	0.9
VSE	14 (7.5)	11 (6.4)	0.66
VRE	6 (3.2)	5 (2.9)	0.85
MSSA	3 (1.6)	6 (3.5)	0.26
MRSA	10 (5.4)	15 (8.7)	0.22
CoNS	11 (5.9)	13 (7.5)	0.54
Streptococcus sp	3 (1.6)	13 (7.5)	0.01
Unknown or other	19 (10.2)	35 (20.2)	0.01

VSE = vancomycin-sensitive *Enterococcus* sp; VRE = vancomycin-resistant *Enterococcus* sp; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative *Staphylococcus* sp.

[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

Table 3. Infectious Sources

Source	No. (%) of Patients		p Value
	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion Comparator Group[a] (n=173)	
Urinary tract	76 (40.9)	63 (36.4)	0.39
Respiratory tract	57 (30.7)	75 (43.4)	0.01

Intravenous catheter or bloodstream	41 (22)	47 (27.2)	0.26
Skin or skin structure	36 (19.4)	35 (20.2)	0.84
Other	13 (7.0)	28 (16.2)	0.01

[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

For the primary outcome, in-hospital mortality was significantly decreased in the extended-infusion piperacillin-tazobactam group versus the comparator antibiotic group (9.7% vs 17.9%, p=0.02; Table 4). Although the proportion of *Pseudomonas* species was significantly different between groups at baseline, the difference in mortality attributable to these bacteria was not significant between groups (extended-infusion group 42.1% vs comparator group 35.5%, p=0.64). Table 4 further displays the secondary outcomes: hospital length of stay, length of ICU stay, and antibiotic duration, each excluding patients who died during the study. Although none of the secondary outcomes were significantly different between groups, the duration of antibiotic therapy tended to be longer in the extended-infusion group (9.1 vs 8 days, p=0.06).

Table 4. Outcomes

Outcome	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion Comparator Group[a] (n=173)	p Value
Mortality, no. (%)	18 (9.7)	31 (17.9)	0.02
	No. (%) of Survivors		
	(n=168)	(n=142)	
Hospital LOS (days)			0.21
< 9	38 (22.6)	43 (30.3)	
9–22	90 (53.6)	63 (44.4)	
> 22	40 (23.8)	36 (25.4)	
ICU LOS (days)			0.14
< 4	24 (14.3)	27 (19)	
4–18	41 (24.4)	45 (31.7)	
> 18	21 (12.5)	19 (13.4)	
None	82 (48.8)	51 (35.9)	
Antibiotic duration (days)			0.06
< 5	49 (29.2)	65 (45.8)	
5–11	96 (57.1)	71 (50.0)	
> 11	41 (24.4)	37 (26.1)	

LOS = length of stay; ICU = intensive care unit.
[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

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Outcome	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion Comparator Group[a] (n=173)	p Value
Mortality, no. (%)	18 (9.7)	31 (17.9)	0.02
	No. (%) of Survivors		
	(n=168)	(n=142)	
Hospital LOS (days)			0.21
< 9	38 (22.6)	43 (30.3)	
9–22	90 (53.6)	63 (44.4)	
> 22	40 (23.8)	36 (25.4)	
ICU LOS (days)			0.14

< 4	24 (14.3)	27 (19)	
4–18	41 (24.4)	45 (31.7)	
> 18	21 (12.5)	19 (13.4)	
None	82 (48.8)	51 (35.9)	
Antibiotic duration (days)			0.06
< 5	49 (29.2)	65 (45.8)	
5–11	96 (57.1)	71 (50.0)	
> 11	41 (24.4)	37 (26.1)	

LOS = length of stay; ICU = intensive care unit.
[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

Figure 1 shows the primary outcome along with the a priori subgroups. Compared with the nonextended-infusion piperacillin-tazobactam group, extended-infusion piperacillin-tazobactam demonstrated a significant decrease in in-hospital mortality (9.7% vs 20.2%, p=0.03). When extended-infusion piperacillin-tazobactam was compared with nonextended infusions of β-lactams other than piperacillin-tazobactam, the results were not significantly different (9.7% vs 15.7%, p=0.17). Among those admitted to the ICU, extended-infusion treatment retained numeric superiority in mortality rate versus all β-lactam comparators (14.9% vs 22.5%, p=0.14). Mortality probability curves for extendedinfusion versus nonextended-infusion piperacillintazobactam and the group of other β-lactams are shown in Figure 2.

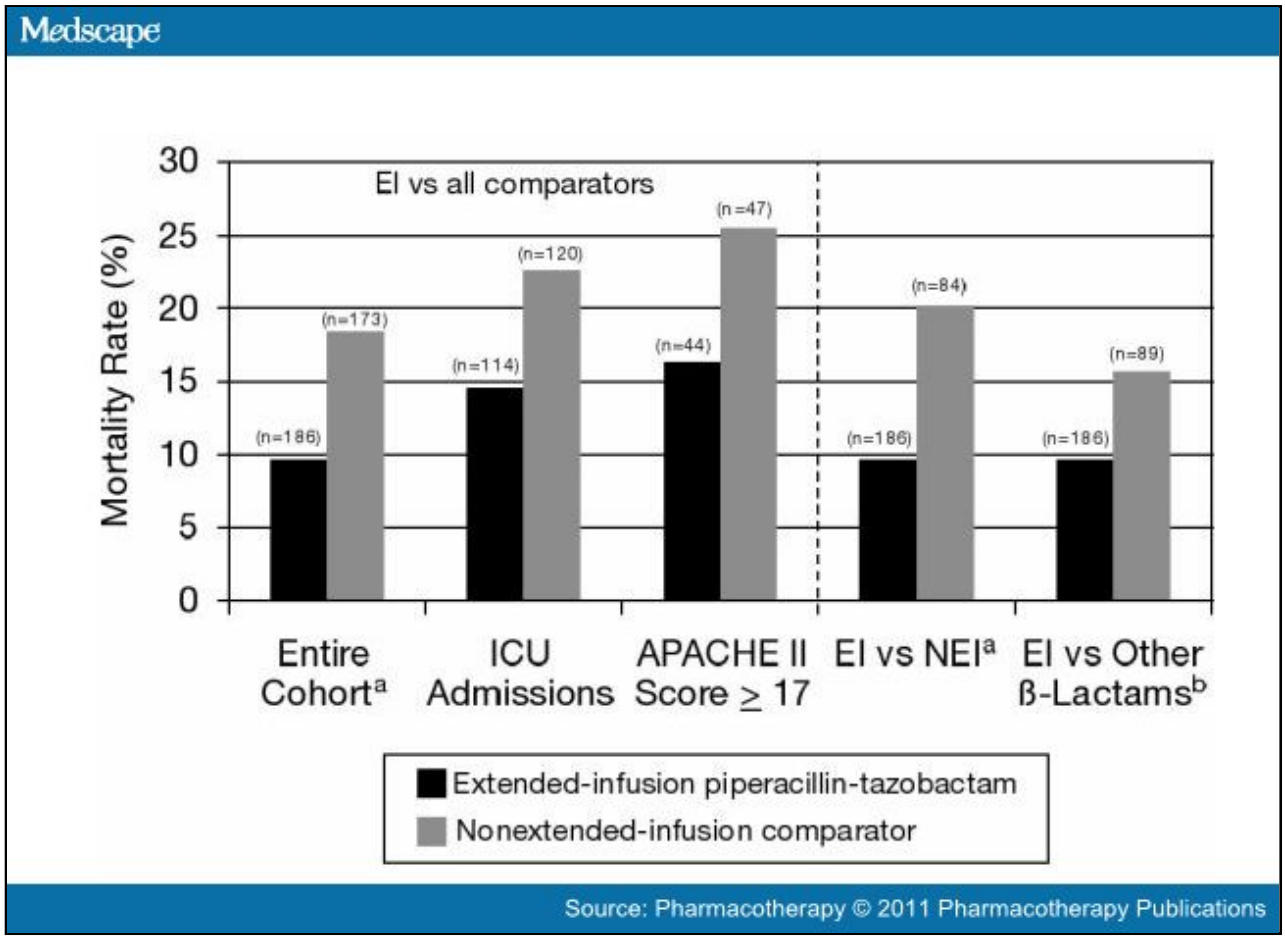

Figure 1. Comparison of mortality rates in the a priori subgroups. ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation; EI = extendedinfusion piperacillin-tazobactam; NEI = nonextendedinfusion piperacillin-tazobactam. ap<0.05 for EI vs comparator. bNonextended-infusion cefepime, ceftazidime, imipenem-cilastatin, meropenem, or doripenem.

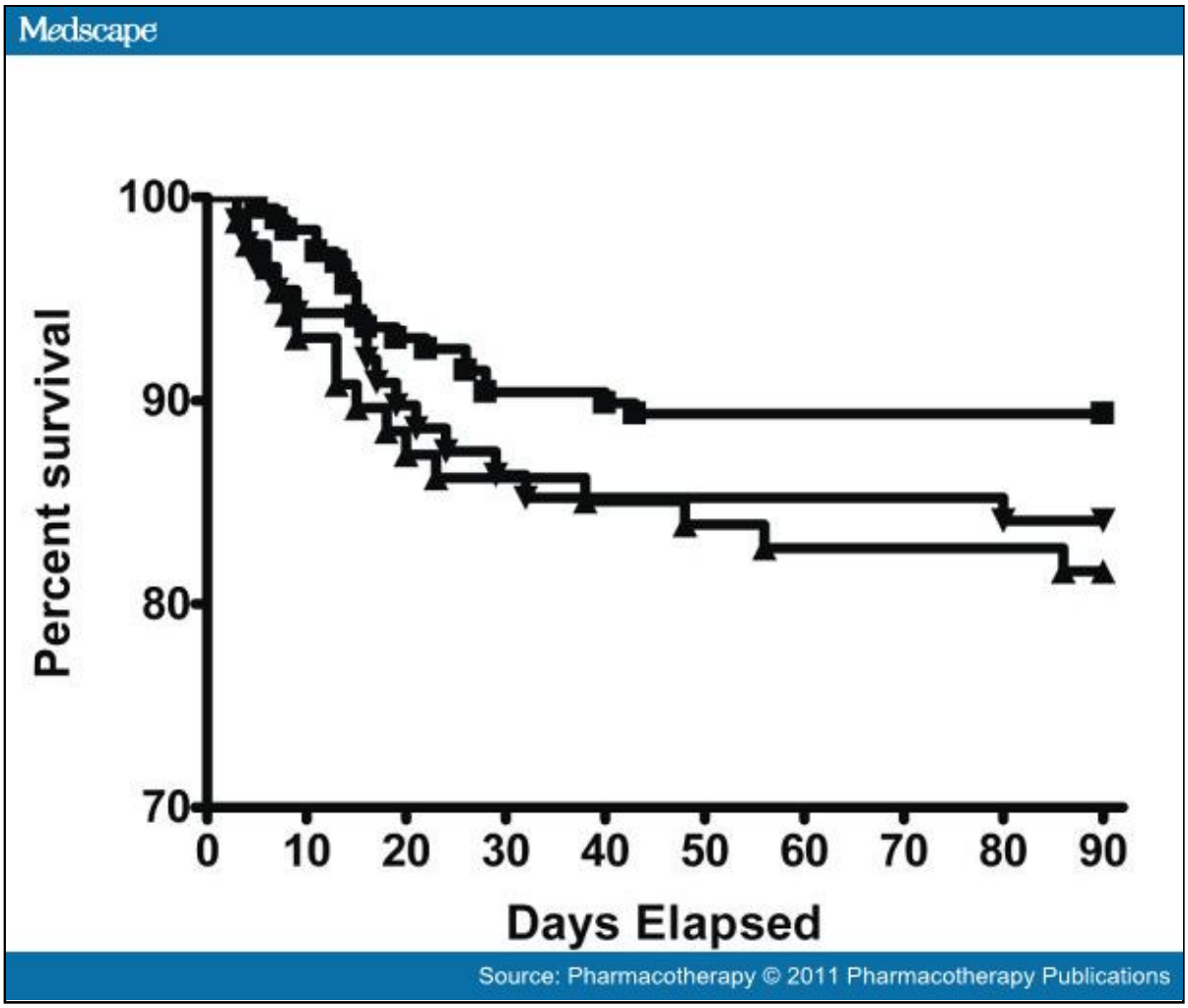

Figure 2. Kaplan-Meier curves for probability of mortality. ■ = extended-infusion piperacillin-tazobactam; ▼ = nonextended infusions of β-lactams other than piperacillin-tazobactam; ▲ = nonextended-infusion piperacillin-tazobactam.

Abbreviated results of the four multivariate analyses are displayed in Table 5. In the primary analysis where death was determined as a binary outcome, treatment with extended-infusion piperacillin-tazobactam and history of organ transplantation were found to have a statistically significant impact on mortality. In addition, treatment in the ICU for 4–18 days had a significantly higher risk of mortality than an ICU stay of 1–3 days (odds ratio 4.5, p=0.03). The risk of mortality was significantly lower for extended-infusion piperacillin-tazobactam versus nonextended-infusion piperacillin-tazobactam (odds ratio 0.22, p=0.02). When the outcome of death as a function of time was compared, patients in the extended-infusion piperacillintazobactam group survived 2.77 days longer than those in the comparator group (p<0.01).

Table 5. Multivariate Analysis for Extended-Infusion Piperacillin-Tazobactam

Variable	Odds Ratio (95% CI)	p Value
Mortality		
EI vs comparator antibiotics[a]	0.43 (0.18–1.01)	0.053
EI vs NEI piperacillin-tazobactam	0.22 (0.07–0.76)	0.02
EI vs other NEI β-lactams	0.25 (0.04–1.64)	0.15
Time to death (days)		

EI vs comparator antibiotics[a]	2.77 (0.85–4.7)	<0.01

CI = confidence interval; EI = extended-infusion piperacillin-tazobactam; NEI = nonextendedinfusion.
[a]Comparator antibiotics consisted of both NEI piperacillin and other NEI β-lactams (cefepime, ceftazidime, imipenem-cilastatin, meropenem, and doripenem).

Discussion

With the widespread use of piperacillintazobactam as empiric gram-negative coverage and the increasing prevalence of organisms exhibiting elevated minimum inhibitory concentrations of piperacillin-tazobactam, either preservation or optimization of dosing of piperacillin-tazobactam should occur. Extending the infusion time of piperacillin-tazobactam to 4 hours maximizes the pharmacodynamic activity without the intravenous catheter access issues that accompany continuous infusions.[2, 3] The results of this study suggest a mortality benefit when using extended-infusion piperacillintazobactam in place of alternative agents with nonextended-infusion dosing. As demonstrated in Figure 2, there was a survival benefit with extended-infusion piperacillin-tazobactam throughout the first 90 days.

Although the results of the multivariate analysis comparing extended-infusion piperacillin- tazobactam with the comparator group are statistically "marginal," it should be noted that the effect size between the two groups is considerable. In the raw analysis, the reduction in mortality in the extended-infusion piperacillintazobactam group was 8.2%, which results in a number needed to treat of essentially 12 patients to prevent 1 death. Compared with nonextendedinfusion piperacillin-tazobactam, extendedinfusion piperacillin-tazobactam reduced mortality by 78% in the multivariate analysis, and a number needed to treat of 9.5 patients was calculated from the raw analysis. The overall mortality outcome of our study supports the results of the previously mentioned study in patients with P. aeruginosa infections.[3] The mean ± SD APACHE II scores were similar in our study (14.1 ± 7.2) and the other study (15.7 ± 7.2),[3] and the mortality rates for extended- versus nonextended-infusion piperacillin-tazobactam were also comparable (8.8% vs 15.2% in the other study3 and 9.7% vs 20.2% in our study).

The gLIMMIX Procedure used for the multivariate analysis of these data is a relatively new type of statistical process. This procedure is able to simultaneously model both the input variables and the outcome variable to allow for more precise estimation of disparity between groups. In our study, the random-effects model was chosen to model the relationship between each institution, and the negative binomial distribution was chosen to model time to death. Although Poisson regressions have been popular for some time, it has been recognized that this model often inappropriately fits data where the mean and variance are not relatively similar to one another. In this case, a negative binomial model is used to correlate time to death as the mean is 3 days but the variance is over 50 days. The gLIMMIX Procedure incorporates both the negative binomial distribution and the randomeffects model into one succinct multivariate analysis.

A recent article explored the implications of extended-infusion piperacillin-tazobactam at a teaching hospital in Chicago.[18] Within 6 days of implementation, all extended-infusion doses were being administered at the appropriate rate, and none were omitted because of physical incompatibilities. The authors noted a sharp decrease in the number of piperacillin-tazobactam doses/1000 patient-days (mean decrease 116 doses, $p<0.001$) and a 24% reduction in pharmacy expenditures on piperacillin-tazobactam.18 Unfortunately, our study failed to substantiate the length of stay outcome of the previously mentioned trial (median of 21 days in patients with APACHE II scores ≥ 17 who received extended-infusion piperacillin-tazobactam compared with 38 days in patients who received nonextended-infusion piperacillin-tazobactam, $p=0.02$).[3] This result does not eliminate the cost savings potential of extended-infusion piperacillintazobactam which, as demonstrated by the Chicago trial,[18] was attributed to piperacillintazobactam acquisition costs, which can be substantially reduced with the 4-hour extendedinfusion implementation.

Limitations

Results from our study are subject to certain limitations that should be discussed. The most notable is the

retrospective study design, which lends itself to several biases. Prescriber bias may be the largest bias present in this study, which may account for the significant difference seen in extended-infusion piperacillin-tazobactam versus nonextended-infusion comparator use in the Pseudomonas species infections noted in Table 2. Prescriber bias likely plays a part in the disparity in extended-infusion piperacillin-tazobactam versus nonextended-infusion comparator use for respiratory tract infections and the concomitant prescribing of aminoglycosides in the nonextended-infusion comparator group.

Table 2. Infectious Etiologies

Organism	No. (%) of Patients		p Value
	Extended-Infusion Piperacillin-Tazobactam Group (n=186)	Nonextended-Infusion omparator Group[a] (n=173)	
Acinetobacter sp	1 (0.5)	4 (2.3)	0.2
Bacteroides sp	7 (3.8)	4 (2.3)	0.43
Citrobacter sp	10 (5.4)	6 (3.5)	0.38
Escherichia coli	79 (42.5)	59 (34.1)	0.1
Enterobacter sp	24 (12.9)	20 (11.6)	0.7
Klebsiella sp	46 (24.7)	41 (23.7)	0.82
Proteus sp	11 (5.9)	17 (9.8)	0.17
Providencia sp	2 (1.1)	3 (1.7)	0.68
Pseudomonas sp	42 (22.6)	69 (39.9)	<0.01
Serratia sp	8 (4.3)	7 (4.1)	0.9
VSE	14 (7.5)	11 (6.4)	0.66
VRE	6 (3.2)	5 (2.9)	0.85
MSSA	3 (1.6)	6 (3.5)	0.26
MRSA	10 (5.4)	15 (8.7)	0.22
CoNS	11 (5.9)	13 (7.5)	0.54
Streptococcus sp	3 (1.6)	13 (7.5)	0.01
Unknown or other	19 (10.2)	35 (20.2)	0.01

VSE = vancomycin-sensitive *Enterococcus* sp; VRE = vancomycin-resistant *Enterococcus* sp; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative *Staphylococcus* sp.

[a]Comparator antibiotics were cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam.

The multisite design of this study introduces the possibility of a site bias. If the institution with the largest data contribution is removed from the data analysis, no significant changes would appear in the data trends; however, statistical significance would be lost for the primary outcome. One can infer that this institution contributes to the

power of the result but does not overtly influence the result. In addition, the use of the random-effects model accounts for treatment in different facilities as an independent variable in the multivariate analyses.

Another limitation of this study is the use of multiple reviewers to retrieve data from patients' medical records. Each reviewer used their own institution's time frame to collect patient data, and each had their own interpretation of the exclusion criteria presented by the primary author, introducing selection bias to the results. Finally, a substantial limitation is the inability to establish causality for the outcomes of these patients.

Conclusion

In the RECEIPT study, extended-infusion piperacillin-tazobactam demonstrated a decreased rate of in-hospital mortality versus comparative β-lactam antibiotics given as traditional, nonextended infusions in treating documented gramnegative infections. Multivariate analysis confirmed that extended-infusion piperacillintazobactam prolonged survival by 2.77 days ($p<0.01$) and reduced the risk of mortality (odds ratio 0.43, $p=0.05$). Hospital length of stay, ICU length of stay, and antibiotic treatment duration were not significantly impacted by the implementation of extended-infusion piperacillintazobactam. Prospective, randomized trials are needed to further corroborate these findings.

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Presented in part at the great Lakes Pharmacy Residency Conference, West Lafayette, Indiana, April 29, 2010, and at the Ohio College of Clinical Pharmacy Spring meeting, Beachwood, Ohio, May 21, 2010.

Acknowledgments
The RECEIPT study group would like to acknowledge Yevgeniya gokun, M.S., for her contributions to the statistical analysis of this project. The primary author would like to acknowledge the advisory roles of Martin Ohlinger, Pharm.D., BCPS, Steven Martin, Pharm.D., BCPS, FCCM, and Thomas M. File, Jr., M.D., M.Sc., MACP, FIDSA, FCCP.

Pharmacotherapy. 2011;31(8):767-775.