

Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae*: MIC Matters

Nan-Yao Lee,^{1,2} Ching-Chi Lee,^{1,2} Wei-Han Huang,⁴ Ko-Chung Tsui,^{5,8} Po-Ren Hsueh,^{6,7,a} and Wen-Chien Ko^{1,2,3,a}

¹Department of Internal Medicine, ²Center for Infection Control, National Cheng Kung University Hospital and Medical College, and ³Department of Medicine, National Cheng Kung University Medical College, Tainan; ⁴Department of Clinical Pathology, Buddhist Tzu-Chi General Hospital, Hualien; ⁵Department of Clinical Pathology Cathay General Hospital, and Departments of ⁶Laboratory Medicine and ⁷Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei; and ⁸Fu-Jen Catholic University School of Medicine, New Taipei City, Taiwan

Background. Extended-spectrum β -lactamase (ESBL)–producing *Enterobacteriaceae* isolates are important clinical pathogens. In addition, the efficacy of cefepime for such infections is controversial.

Methods. We performed a retrospective study of monomicrobial bacteremia caused by ESBL producers at 2 medical centers between May 2002 and August 2007. The patients definitively treated with in vitro active cefepime (cases) were compared with those treated with a carbapenem (controls) in a propensity score–matched analysis to assess therapeutic effectiveness. The 30-day crude mortality is the primary endpoint.

Results. A total of 178 patients were eligible for the study. Patients who received cefepime ($n = 17$) as definitive therapy were more likely to have a clinical failure (odds ratio [OR] 6.2; 95% confidence interval [CI], 1.7–22.5; $P = .002$), microbiological failure (OR 5.5; 95% CI, 1.3–25.6; $P = .04$), and 30-day mortality (OR 7.1; 95% CI, 2.5–20.3; $P < .001$) than those who received carbapenem therapy ($n = 161$). Multivariate regression revealed that a critical illness with a Pitt bacteremia score ≥ 4 points (OR 5.4; 95% CI, 1.4–20.9; $P = .016$), a rapidly fatal underlying disease (OR 4.4; 95% CI, 1.5–12.6; $P = .006$), and definitive cefepime therapy (OR 9.9; 95% CI, 2.8–31.9; $P < .001$) were independently associated with 30-day crude mortality. There were 17 case-control pairs in the propensity scores matched analysis. The survival analysis consistently found that individuals who received cefepime therapy had a lower survival rate (log-rank test, $P = .016$).

Conclusions. Based on the current Clinical and Laboratory Standards Institute susceptible breakpoint of cefepime (minimum inhibitory concentration ≤ 8 $\mu\text{g/mL}$), cefepime definitive therapy is inferior to carbapenem therapy in treating patients with so-called cefepime-susceptible ESBL-producer bacteremia.

The presence of extended-spectrum β -lactamases (ESBLs) in various members of the *Enterobacteriaceae* family, particularly *Klebsiella pneumoniae* and

Escherichia coli, is of great microbiological and clinical importance [1]. Bacteremia caused by ESBL-producing *Enterobacteriaceae* isolates compared with that caused by non-ESBL-producing isolates is associated with a delay in the institution of appropriate antimicrobial therapy [2]. The current standard of therapy for ESBL-producing organisms is a carbapenem [3, 4]. Increasingly empirical use of carbapenems in response to outbreaks of infections caused by ESBL producers has been accompanied by the rapid emergence of carbapenem resistance in nosocomial gram-negative pathogens [5]. Therapeutic options other than carbapenems, such as cefepime, would be attractive [4]. There have been anecdotal experiences of successful

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^aP.-R. H. and W.-C. K. contributed equally to this work.

Correspondence: Wen-Chien Ko, Division of Infectious Disease, Dept of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, 704, Tainan, Taiwan (winston3415@gmail.com).

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treatment of infections caused by ESBL-producing organisms with cefepime [6, 7]. However, cefepime has not been subjected to prospective randomized clinical trials to compare its efficacy and outcome with other active agents for infections caused by ESBL-producing *Enterobacteriaceae*. Because such trials present several practical challenges, the literature to date has been largely limited to observational analyses without comparators [3, 8].

Current documentation from the Clinical and Laboratory Standards Institute suggests that when using the new cephalosporin interpretive criteria for *Enterobacteriaceae*, routine testing for ESBLs is no longer necessary. However, the interpretive criteria of cefepime for *Enterobacteriaceae* remain unchanged [9]. The current susceptible breakpoint of cefepime (≤ 8 $\mu\text{g/mL}$) failed to identify all ESBL-producing *E. coli*, *K. pneumoniae*, or *Klebsiella oxytoca* isolates [10, 11]. The clinical role of cefepime therapy for infections caused by so-called cefepime-susceptible ESBL-producing organisms remains unclear. The aim of this study was to compare the clinical outcome of adults who have ESBL-producing *Enterobacteriaceae* bacteremia that was treated with cefepime with that of adults treated with a carbapenem.

METHODS

Study Design and Patients

A retrospective study among adults (age ≥ 18 years) with ESBL-producing *E. coli* and *K. pneumoniae* bacteremia at 2 hospitals, the National Cheng Kung University Hospital (NCKUH) in southern Taiwan and the National Taiwan University Hospital (NTUH) in northern Taiwan, was undertaken between May 2002 and August 2007 [12]. Individuals with ESBL-producing *Escherichia cloacae* bacteremia were identified from a previously described cohort at NCKUH between 2001 and 2008 [13]. If the patients experienced more than 1 bacteremic episode, only the first episode was included. The study was approved by the NCKUH Institutional Review Board. This analysis was reported using the format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [14].

Eligible patients fulfilled all of the following criteria: (1) clinically significant monomicrobial bacteremia demonstrated via the isolation of ESBL producer alone in blood cultures, compatible with sepsis syndrome; and (2) parenteral therapy with cefepime or a carbapenem for more than 48 hours until the end of antimicrobial therapy or death. The empirical therapy cohort (ETC) included patients who received empirical cefepime or carbapenem monotherapy, of which the first dose was administered during the first 24 hours after blood cultures had been drawn. The definitive therapy cohort (DTC) consisted of patients receiving definitive cefepime or

carbapenem monotherapy if the causative isolate was in vitro-susceptible to the prescribed drug according to the current susceptible criteria of CLSI [15]. Antimicrobial therapy administered within 5 days after bacteremia onset was regarded as empirical therapy and administered afterward as definitive therapy.

In view of the differences in baseline characteristics among patients receiving cefepime and carbapenem therapy and based on the final parameter estimates in the multivariate model, a propensity score (an estimated probability of mortality) was assessed for each case. Subsequently, each patient receiving cefepime definitive therapy (the case group) was matched to a patient receiving carbapenem therapy (the control group) with a similar propensity score. A maximal difference of 5% in the likelihood of the mortality was allowed in the matching process. If there was more than 1 match with an identical propensity score, the one with a similar source of bacteremia (the initial secondary matching variable) or the closest date of bacteremia onset (the backup secondary matching variable) would have a higher priority in the matching process.

The clinical choice of antibiotics was at the discretion of the attending physician. Patients received the following intravenous doses or adjusted equivalents in cases of renal insufficiency: ertapenem (1 g every 24 hours), imipenem (0.5 g every 6 hours), meropenem (1 g every 8 hours), or cefepime (1–2 g every 8 hours; 3–6 g/day). In both hospitals, the prescriptions of carbapenems and cefepime were approved by infectious disease specialists and pharmacists for their indications and dosages.

In Vitro Susceptibility Tests and ESBL Detection

ESBL production was detected using the phenotypic confirmatory test recommended by CLSI [9]. For *E. cloacae* isolates, the ESBL phenotype was determined using the Etest ESBL strip (AB Biodisk, Solna, Sweden) and confirmed by polymerase chain reaction and sequence analyses [13]. The minimum inhibitory concentrations (MICs) of carbapenems and cefepime were determined using the agar dilution method, and the interpretation followed the breakpoints recently recommended by CLSI in 2011 [9].

Clinical Evaluation and Outcomes

Clinical information was retrieved from medical charts and collected in a case record form. Bacteremia was defined as the isolation of the organisms in 1 or more separately obtained blood cultures with compatible clinical features. Patients receiving cefepime or carbapenem therapy for more than 48 hours were included for assessment of outcome. The primary outcome was the crude 30-day mortality. Immunosuppression was referred to the receipt of corticosteroid (at least 10 mg or an equivalent dosage daily) for more than 2 weeks or of

antineoplastic chemotherapy or antirejection medication 4 weeks before the onset of bacteremia. The severity of underlying medical illness was stratified as being fatal, ultimately fatal, or nonfatal [16]. The severity of bacteremia was graded on the day of bacteremia onset using the Pitt bacteremia score [17].

Clinical failure was defined as follows: (1) for at least 5 days, the initial antimicrobial therapy failed to resolve sepsis symptoms or (2) signs or a fatal outcome ensued. The development of bacteremia due to the identical bacterial species with ESBL production during antimicrobial therapy for at least 72 hours was regarded as a microbiological failure.

Statistical Analysis

Data were analyzed using the SPSS software for Windows, version 12.0. Continuous variables were expressed as mean values \pm SDs and compared using the Mann-Whitney *U* test or Student *t* test. Categorical variables were expressed as percentages of total numbers of patients analyzed and compared using the Fisher exact test or χ^2 test, as appropriate. Independent predictors for mortality were identified by means of logistic regression analysis. Variables with a *P* value of .1 or less, as determined using univariate analysis, were included in a multiple conditional logistic regression analysis. A Cox proportional hazard model was used to compare survival in both groups, adjusted for confounding variables. A *P* value less than .05 was considered statistically significant, and all tests were 2-tailed. Crude mortality rates of the 2 study groups were compared using the Kaplan-Meier curve and log-rank test.

RESULTS

A total of 472 patients with bacteremia caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *E. cloacae* were identified.

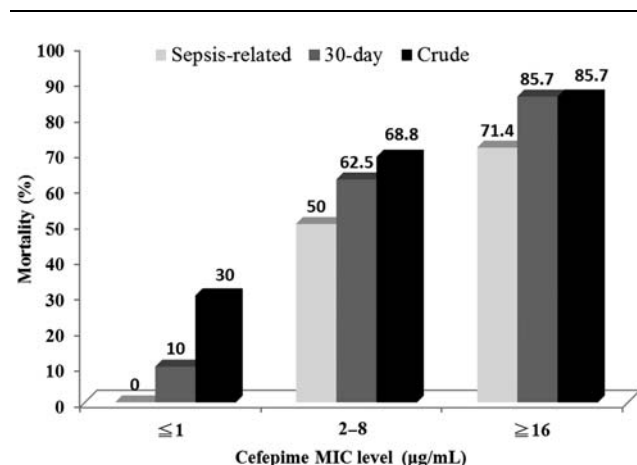


Figure 1. Mortality rates of 3 subgroups of patients who received cefepime therapy (*n*=33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

Among them, 33 cases, including 18 cases with *E. cloacae* bacteremia, 8 with *E. coli* bacteremia, and 7 with *K. pneumoniae* bacteremia, were treated using cefepime for more than 48 hours. Of these cases, pneumonia (8 cases, 24.2%) and catheter-related infection (6 cases, 18.2%) were the major sources of infection, followed by urosepsis (6 cases, 18.2%), skin and soft infections (5 cases, 15.2%), and intraabdominal infections (2 cases, 6.0%). Eight cases had primary bacteremia. Males accounted for 57.5% (19 cases), and 36.4% (12 cases) had polymicrobial bacteremia.

The percentages of ESBL-producing isolates that were susceptible (MIC \leq 8 µg/mL), intermediate (16 µg/mL), or resistance (\geq 32 µg/mL) to cefepime, according to CLSI 2011, were 78.8%, 9.1%, or 12.1%, respectively. Although there was a borderline significant difference in the mortality rates among 3 species (*E. cloacae*, 6/18 [33.3%]; *E. coli*, 6/8 [75.0%]; *K. pneumoniae*, 5/7 [71.4%]; *P* = .07), the proportions of cefepime-susceptible isolates varied significantly among the 3 species (18, 100% of *E. cloacae*; 4, 50.0% of *E. coli*; and 4, 57.1% of *K. pneumoniae*; *P* = .005). The mortality rate among bacteremia due to nonsusceptible *E. coli* or *K. pneumoniae* was 75% (3/4) and 100% (3/3), respectively.

Of 33 patients who received cefepime therapy, 25 (75.8%) experienced clinical failure and 13 (39.4%) died of sepsis. There was a significant increase in sepsis-related mortality because the cefepime MICs increased (*P* = .004, linear-by-linear association). The sepsis-related (*P* = .006), 30-day (*P* = .004), and crude mortality rates (*P* = .045) were lower in the causative isolates, with a MIC \leq 1 µg/mL than those of other MIC categories (Figure 1).

According to our study criteria, there were 112 patients in the ETC and 178 in the DTC (Figure 2). Of those in the ETC, 21 patients were empirically treated with cefepime and 91 with a carbapenem (28 ertapenem, 13 meropenem, and 50 imipenem). Of 101 patients in the ETC, antimicrobial therapy did not change when the susceptibility results were available. However, the causative isolates from 11 patients were in vitro resistant to cefepime (4 isolates) or ertapenem (7), which were regarded as inappropriate empirical therapy. Of the ETC, the 30-day mortality rate was lower for the causative isolates, with a MIC \leq 1 µg/mL (0/2, 0%) than those with other MIC categories (MIC 2–8 µg/mL: 6/15 [40%]; \geq 16 µg/mL: 4/4 [100%]; *P* = .037). Mortality rates of those empirically, appropriately treated with cefepime were higher than those treated with a carbapenem, 47.1% vs 11.9% (sepsis-related mortality, *P* = .002), 58.8% vs 17.9% (30-day mortality, *P* = .001), or 64.7% vs 39.3% (crude mortality, *P* = .07).

A total of 178 patients were included in the DTC, and the 30-day mortality rate was lower in the isolates with a MIC \leq 1 µg/mL (1/6, 16.7%) than those with a higher MIC (MIC 2–8 µg/mL: 5/11 [45.5%]; \geq 16 µg/mL: 4/4, 100%; *P* = .035).

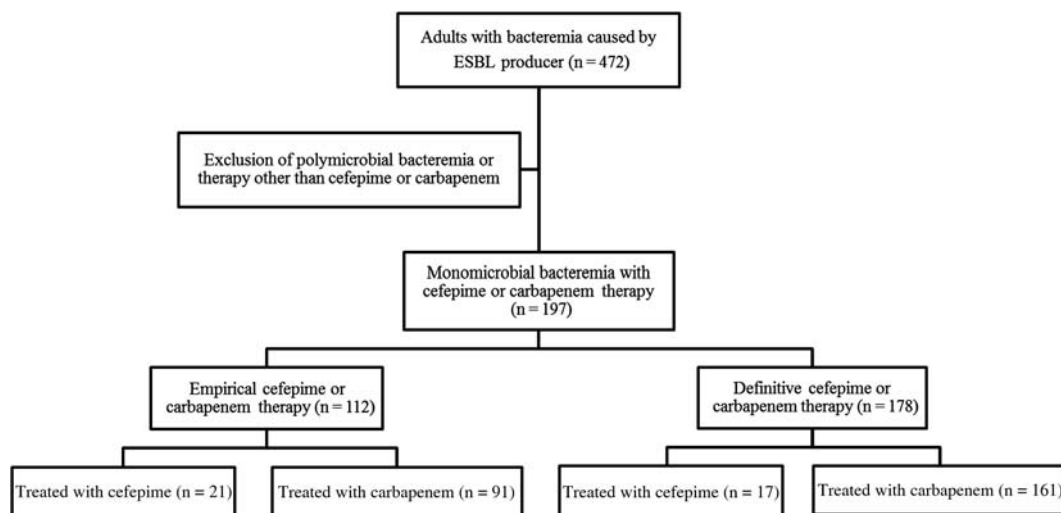


Figure 2. Study inclusion and exclusion criteria applied for patient identification. Abbreviation: ESBL, extended-spectrum β -lactamase.

Seventeen patients treated with cefepime for cefepime-susceptible, ESBL-producer bacteremia were compared with 161 patients treated with a carbapenem (44 ertapenem, 25 meropenem, and 92 imipenem). There were no significant differences in terms of age, sex, comorbidity, source of bacteremia, or disease severity (Table 1). Patients who received cefepime therapy had more clinical failure (odds ratio [OR], 6.2; 95% confidence interval [CI], 1.7–22.5; $P = .002$), microbiological failure (OR, 5.5; 95% CI, 1.3–25.6; $P = .04$), and 30-day mortality (OR, 7.1; 95% CI, 2.5–20.3; $P < .001$) than those who received carbapenem therapy. However, the median hospital stay after bacteremia onset was 31 days (interquartile range [IQR], 27–55) or 30 days (IQR, 17–56), respectively, for the survivors receiving definitive cefepime or carbapenem therapy ($P = .3$).

In the multivariate analysis, definitive cefepime therapy (OR, 9.9; 95% CI, 2.8–31.9; $P < .001$), the presence of critical illness (a Pitt bacteremia score ≥ 4 points; OR, 5.4; 95% CI, 1.4–20.9; $P = .016$), and rapidly fatal underlying disease (OR, 4.4; 95% CI, 1.5–12.6; $P = .006$) were independently associated with 30-day mortality, after adjustment of other confounding variables (Table 2).

Seventeen patients who received definitive cefepime therapy could be matched on the basis of the propensity score. All patients were matched with less than 1% difference in their propensity score. After adjustment for confounding factors, including gender, hospital-onset bacteremia, urosepsis, rapidly fatal underlying disease, and a Pitt bacteremia score ≥ 4 points, cefepime treatment remained associated with a higher mortality (adjusted OR, 6.8; 95% CI, 1.5–31.2; $P = .01$; Cox regression model). The Kaplan-Meier survival analysis also revealed that the individuals who received cefepime therapy had

a lower survival rate than those who received carbapenem therapy (log-rank test, $P = .016$; Figure 3). In the survivors, definitive cefepime therapy was not associated with a longer hospital stay (31 days vs 29 days; $P = .9$).

DISCUSSION

In the present study, suboptimal clinical and microbiological outcomes were seen in patients who received cefepime therapy for bacteremia caused by ESBL-producing organisms that were apparently susceptible, according to current CLSI criteria [9]. A multivariable analysis showed that cefepime therapy was independently associated with a poor outcome. Moreover, there was an increasing risk of clinical failure and sepsis-related mortality as the cefepime MIC of the causative isolates increased. Revision of the susceptible breakpoint of cefepime to 1 $\mu\text{g/mL}$ would provide a wider margin of safety. This was indicated in our subgroup analysis, which showed a favorable outcome in patients with bacteremia caused by ESBL-producing organisms with a cefepime MIC $\leq 1 \mu\text{g/mL}$ who were treated with cefepime.

Bhat et al warned that the current CLSI cefepime breakpoint, that is, MIC $\leq 8 \mu\text{g/mL}$, might fail to predict a favorable outcome in patients with bacteremia caused by gram-negative organisms [18]. Although some organisms may have relatively high cefepime MICs in β -lactamase-producing organisms, the MICs are still in the susceptible range (“hidden resistance”) [18, 19]. Because the *Enterobacteriaceae* isolates are becoming increasingly resistant, a less stringent interpretation of the relationships among MICs, ESBL producers and clinical outcome, may provide therapeutic alternatives in difficult situations [20]. It has been acknowledged that the cephalosporin breakpoints

Table 1. Characteristics of Patients with Bacteremia Caused by Extended-Spectrum β -Lactamase–Producing Organisms Treated With Cefepime or a Carbapenem

Characteristic	Cefepime Group, n = 17	Carbapenem Group, n = 161	Matched Carbapenem Group, n = 17	P Value ^a	P Value ^b
Age, median (IQR), years	70 (54–82)	70 (54–78)	73 (45–85)	.9	.9
Gender, male	12 (70.6)	87 (54.0)	8 (47.1)	.2	.3
Route of acquisition				.004	1.0
Hospital onset	17 (100.0)	110 (68.3)	17 (100.0)		
Community onset	0 (0)	51 (31.7)	0 (0)		
Length of hospital before bacteremia, median (IQR), days	30 (7–53)	12 (0–40)	22 (10–63)	.07	.7
Comorbidity					
Diabetes mellitus	9 (52.9)	95 (41.6)	10 (58.8)	.4	1.0
Chronic kidney disease	5 (29.4)	58 (36.0)	6 (35.3)	.8	1.0
Malignancy	3 (17.6)	60 (37.3)	5 (29.4)	.2	.7
Immunosuppression	2 (11.8)	43 (26.7)	5 (29.4)	.3	.4
Liver cirrhosis	4 (23.5)	23 (14.3)	4 (23.5)	.3	1.0
None	2 (11.8)	23 (14.3)	0 (0)	1.0	.5
Severity of underlying disease (McCabe classification)				.7	1.0
Rapidly fatal	1 (5.9)	19 (11.8)	1 (5.9)		
None or nonrapidly fatal	16 (94.1)	142 (88.2)	16 (94.1)		
Pitt bacteremia score, ≥ 4 points	12 (70.6)	107 (66.5)	12 (70.6)	1.0	1.0
Severe sepsis	12 (70.6)	96 (59.6)	12 (70.6)	.4	1.0
Source of bacteremia					
Vascular catheter-related infection	5 (29.4)	32 (19.9)	7 (41.2)	.4	.7
Primary bacteremia	4 (23.5)	21 (13.0)	3 (17.6)	.3	1.0
Intraabdominal infection	3 (17.6)	25 (15.5)	2 (11.8)	.7	1.0
Pneumonia	2 (11.8)	41 (25.5)	2 (11.8)	.4	1.0
Skin and soft-tissue infection	2 (11.8)	9 (5.6)	2 (11.8)	.3	1.0
Urosepsis	1 (5.9)	38 (23.6)	2 (11.8)	.1	1.0
Length of hospital stay of survivor after bacteremia, median (IQR), days	31 (27–55)	30 (17–56)	29 (12–54)	.3	.9
Sepsis-related mortality	9 (52.9)	18 (11.2)	1 (5.9)	<.001	.007
30-day mortality	10 (58.8)	27 (16.8)	2 (11.8)	<.001	.01
Crude mortality	11 (64.7)	59 (36.6)	9 (52.9)	.04	.7

Data are given as numbers (percentages), unless otherwise specified.

Abbreviation: IQR, interquartile range.

^a Crude analysis (cefepime group vs carbapenem group).

^b Propensity score matched analysis (cefepime group vs matched carbapenem group).

used in most European countries and in the United States failed to detect all ESBLs in clinical *Enterobacteriaceae* isolates [20]. Recent studies and compilations of clinical data suggest that clinical outcome will be better correlated with the MIC values than with the presence or absence of an ESBL enzyme [1, 20–23] and that the MIC value is the important factor in predicting clinical outcome [20, 23]. Most of our patients with clinical failure under cefepime therapy were infected by the isolates with higher cefepime MICs; however, their outcomes will be more favorable if the MICs of the etiological isolates were ≤ 1 $\mu\text{g/mL}$.

It is not surprising that the screening and identification of ESBLs often delay the susceptibility report by 1 or more days and that many laboratories find it difficult to keep up with the changing and complicated recommendations. Our findings support the need for a shift in emphasis from a resistance-based mechanistic system to an MIC-based therapeutic outcome approach when ESBL producers have become endemic [20]. The unfavorable outcome may be related to inadequate antimicrobial efficacy in vivo [24]. It is well documented that clinical success with cefepime therapy correlates with the percentage of time that serum antibiotic

Table 2. Multivariate Logistic Regression Analysis of Associations Between Different Variables and 30-Day Mortality in the Definitive Therapy Cohort

Variable	Survivors (n = 141)	Nonsurvivors (n = 37)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Age, years (mean \pm SD)	65.1 \pm 17.1	69.7 \pm 16.915
Male	78 (55.1)	21 (56.8)	1.06 (.51–2.2)	1.0
Hospital-onset bacteremia	96 (68.1)	31 (83.8)	2.42 (.94–6.22)	.07	1.46 (.47–4.48)	.51
Urosepsis	38 (27.0)	1 (2.7)	0.08 (.01–.57)	.001	0.18 (.02–1.43)	.1
Pitt bacteremia score \geq 4 points	85 (60.3)	34 (91.9)	7.47 (2.19–25.49)	<.001	5.36 (1.37–20.91)	.016
Rapidly fatal underlying disease	9 (6.4)	11 (29.7)	6.21 (2.34–16.47)	<.001	4.42 (1.54–12.64)	.006
Definitive therapy with cefepime	7 (5.0)	10 (27.0)	7.09 (2.48–20.27)	<.001	9.93 (2.77–31.91)	<.001

Data are given as number (percentage) unless otherwise specified. Ellipses indicate not available.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

concentration exceeds the MIC ($\%T > \text{MIC}$) for the infecting organism [25, 26]. Ambrose et al have suggested that the 2-g dose of cefepime every 12 hours has a high probability of achieving pharmacokinetic/pharmacodynamic (PK/PD) targets that have been previously correlated with clinical success [25]. However, clinical outcomes are contradictory for infections caused by the isolates, with MICs ranging from 2 mg/L to 8 mg/L [20, 26]. The analysis by Roos et al showed that the probability of target attainment among gram-negative organisms for which the cefepime MIC is 8 $\mu\text{g/mL}$ is less than 30% when 1 g–2 g of cefepime is administered every 12 hours [27]. Otherwise, patients infected with ESBL-producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii* had a much lower $\%T > \text{MIC}$ than patients infected with fully susceptible organisms [26]. This finding supports the concept that it is inappropriate to interpret a cefepime MIC of

≤ 8 mg/L as an indication of susceptibility for gram-negative organisms. Our study and several anecdotal reports revealed that patients would have therapeutic failure if cefepime were to be used for infections caused by ESBL-producing organisms [19, 21, 28]. The recommended dose of cefepime has the greatest likelihood of achieving PD targets against isolates of fully susceptible *Enterobacteriaceae* (ie, MIC ≤ 1 $\mu\text{g/mL}$) [25, 26], as found in our study. Furthermore, cefepime could be prescribed in prolonged or continuous infusion regimens with a greater probability of achieving the desired PK/PD targets [29].

There were no randomized controlled trials to evaluate the treatment effects of various comparator antibiotics for bacteremia caused by ESBL-producing organisms. However, if diagnostic microbiology laboratories cannot aggressively test for ESBL production, these cases of hidden resistance will go undetected by the microbiologists and clinicians, with a potential for negative consequences [18]. Currently, it is too early to consider cefepime a safe option for treating ESBL-producer infections, particularly those caused by isolates with MICs between 2 $\mu\text{g/mL}$ and 8 $\mu\text{g/mL}$. Moreover, the discordance between the CLSI and EUCAST (European Committee on Antimicrobial Susceptibility Testing, <http://www.eucast.org>) guidelines may cause confusion among microbiologists and infectious disease specialists. With our clinical data, the role of cefepime in the treatment of ESBL-producer infections seems to be in compliance with the EUCAST guidelines, but only for infections caused by the isolates with a low MIC (≤ 1 $\mu\text{g/mL}$).

Our study did have several limitations. First, 3 gram-negative bacilli were unequally distributed, with a predominance of *E. cloacae* isolates. This is probably related to the clinical practice of not performing ESBL detection for bacteremic cefotaxime-resistant *E. cloacae* isolates, for which cefepime therapy often was initiated. It is unethical to conduct randomized controlled trials of cefepime therapy for infections

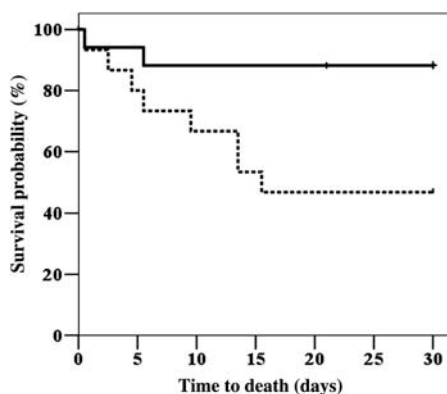


Figure 3. Kaplan-Meier survival analysis curves for patients with bacteremia caused by extended-spectrum β -lactamase-producing organisms; bacteremia treated using a carbapenem (solid line) vs cefepime (broken line; log-rank test, $P = .016$).

caused by ESBL-producing *E. coli* or *K. pneumoniae* [30]. However, the case and control groups were comparable in terms of baseline demographic characteristics and severity of illness. The difference in primary outcome between the case and control groups was statistically significant and consistent after adjusting confounding factors. Second, the outcome data on individuals with ESBL-producer bacteremia were combined for analysis. It is generally assumed that *E. coli*, *K. pneumoniae*, or *E. cloacae* behave similarly because such a combination was commonly adopted in the literature [21, 31]. Third, because only clinical data regarding the hospitalization period were available, we could only analyze the in-hospital outcome. It remains undetermined whether there is any difference in long-term outcome between the 2 study groups. Fourth, to date there is no study that suggests increasing invasiveness or lethality inherited in clinical isolates with a specific ESBL. Therefore, in our ESBL-producing isolates, molecular characterization of β -lactamases, though not done, may be of limited clinical significance.

In summary, a suboptimal clinical outcome ensues when parenteral cefepime is given for bacteremia caused by ESBL-producing organisms that are susceptible to cefepime on the basis of the current susceptible breakpoint of CLSI. Cefepime therapy may be limited for bacteremia caused by ESBL-producing *Enterobacteriaceae* isolates with a cefepime MIC ≤ 1 μ g/mL.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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