

## Cefepime Therapy for Cefepime-Susceptible Extended-Spectrum $\beta$ -Lactamase-Producing *Enterobacteriaceae* Bacteremia

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The role of cefepime for extended-spectrum  $\beta$ -lactamase (ESBL) bacteremia is unclear if susceptible in vitro. In a propensity score-matched study of patients with ESBL bacteremia, risk of death was 2.87 times higher for patients receiving cefepime compared with carbapenems (95% confidence interval [CI], .88–9.41). We compared 14-day mortality of patients with ESBL bacteremia receiving empiric cefepime versus empiric carbapenem therapy in a propensity score-matched cohort. There was a trend towards increased mortality in the cefepime group (hazard ratio, 2.87; 95% CI, .88–9.41), which enhances the existing literature suggesting that cefepime may be suboptimal for invasive ESBL infections.

**Keywords.** bacteremia; carbapenem; cefepime; ESBL; multidrug-resistant organisms.

Current guidance suggests that routine testing for extended-spectrum  $\beta$ -lactamase (ESBL) production is not necessary when using the recommended cephalosporin minimum inhibitory concentration (MIC) interpretive criteria for *Enterobacteriaceae*. This suggests that cefepime may still be an option for infections caused by ESBL-producing organisms, if susceptible in vitro [1, 2]. Cefepime may appear to be active against ESBL-

producing organisms when conducting in vitro susceptibility testing [3–5]. However, a growing body of clinical data is challenging the assumption that cefepime is efficacious against ESBL-producing organisms [6–13]. Existing studies are limited by small sample sizes, 12-hour cefepime redosing intervals, imbalances in patient characteristics between study arms, and multiple other simultaneously administered antibiotics with potential activity against ESBLs—making it difficult to isolate the impact of cefepime for the treatment of ESBL bacteremia. We sought to determine the impact of empiric, in vitro-active cefepime therapy compared with empiric carbapenem therapy on 14-day mortality in a cohort of patients with ESBL bacteremia who all received culture-directed “definitive” therapy with a carbapenem.

### METHODS

Patients  $\geq 12$  years of age (and at least 40 kg) hospitalized at The Johns Hopkins Hospital between November 2006 and March 2015 had to meet the following criteria to be eligible for study inclusion: (1) first episode of clinically significant monomicrobial ESBL bacteremia, (2) bacteremia with *Enterobacteriaceae* susceptible in vitro to cefepime and carbapenems, (3) empiric parenteral therapy with cefepime (for at least 48 hours) or a carbapenem, (4) transition to or maintenance on carbapenem therapy (ertapenem, meropenem, or imipenem-cilastatin) once ESBL status was known. The primary outcome was 14-day mortality. This time period was selected because it was thought to be most reflective of death attributable to suboptimal, empiric anti-infective therapy. Pertinent clinical data were extracted from medical records through chart review. Likely sources of infection and data regarding removal of infected sources were collected. Source control was defined as the removal of relevant devices or drainage of infected fluid collections within 5 days of the onset of bacteremia. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Antibiotic susceptibility testing was determined by the BD Phoenix Automated System (BD Diagnostics). *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* organisms flagged by the Phoenix instrument as ESBL producers were confirmed as such using the ESBL Etest strips (bioMérieux). During the study period, susceptibility results for cefepime were routinely masked, regardless of in vitro susceptibility results, for bacteremia caused by ESBL-producing organisms.

Baseline characteristics were summarized using the Fisher’s exact test for categorical variables and a 2-tailed Wilcoxon rank-sum test for continuous variables. To make comparisons on the primary outcome more accurate, propensity score

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matching was used to adjust for differences in baseline characteristics between the treatment groups. The probability of a patient being treated with cefepime (ie, propensity score) was calculated using a logistic regression model based on the following pretreatment characteristics: age, Pitt bacteremia score, intensive care unit-level care, immunosuppression, pre-existing medical conditions, and source of bacteremia. Sources of bacteremia were grouped into high-risk (central venous catheter, intra-abdominal, pneumonia, and skin and soft tissue) and low-risk (urinary tract and biliary) categories. Nearest neighbor matching (1:3) with replacement and exact matching on source control status was performed to estimate the average treatment effect on the patients treated for cefepime. The overall hazard ratio (HR) was calculated using a semi-parametric Cox proportional hazards regression model, with the proportional hazards assumption checked by testing time interaction terms in a time-transformed Cox proportional hazards model. Analysis was performed in Stata/SE version 12.0 (StataCorp, College Station, TX) and R version 3.1.2.

## RESULTS

Sixty-three patients with ESBL bacteremia received empiric cefepime therapy before transitioning to carbapenem therapy, and 139 patients received carbapenem therapy for the entire treatment duration. Of the 63 patients receiving cefepime therapy, 17 (27%) had ESBL isolates with cefepime MICs  $\leq$  8 mcg/mL, and only these patients were included in the cefepime group (Table 1). Four (24%), 9 (52%), and 4 (24%) of the 17 patients in our cohort receiving cefepime had ESBL isolates with cefepime MICs of 1 mcg/mL, 4 mcg/mL, and 8 mcg/mL, respectively.

Cefepime was dosed as follows (or an adjusted equivalent dose in cases of renal insufficiency): 2 grams every 8 hours and 1 gram every 8 hours for 12 (71%) and 5 (29%) patients, respectively. Carbapenem therapy was administered as follows: ertapenem (1 g every 24 hours), imipenem-cilastatin (0.5 g every 6 hours), and meropenem (1 g every 8 hours), with appropriate dosage adjustment in the setting of impaired renal function. No patients received extended-infusion therapy or combination antibiotic therapy with an aminoglycoside or fluoroquinolone in either treatment group.

In the propensity-matched cohort, including 17 patients receiving empiric cefepime therapy followed by carbapenem therapy and 51 patients receiving carbapenem therapy for the entire treatment duration, adequate balance was achieved based on the standardized differences obtained for all variables. In the matched cohort, 7 patients in the cefepime group (41%) and 10 patients in the carbapenem group (20%) died within 14 days of the first day of bacteremia. Two of the patients receiving cefepime who did not survive until day 14 was infected with an organism with a cefepime MIC of 1 mcg/mL, and the other 5 patients had organisms with cefepime MICs of 4 mcg/mL. In

**Table 1. Baseline Characteristics of a Cohort of 68 Propensity Score-Matched Patients With ESBL-Producing Bacteremia Receiving Cefepime or Carbapenem Therapy Empirically, With in Vitro Activity of the ESBL Isolates to These Agents**

	Cefepime (n = 17)	Carbapenem (n = 51)	P Value
Age (mean, SD)	61 (44.5)	51 (25.5)	.74
Male (n, %)	10 (58.9)	30 (58.8)	1.00
Organism			
<i>Escherichia coli</i> (%)	5 (29.4)	17 (33.3)	1.00
<i>Klebsiella</i> spp (%)	12 (72.7)	30 (58.9)	.57
<i>Proteus mirabilis</i> (%)	0 (0.0)	2 (3.9)	—
Pitt bacteremia score (mean, SD)	3 (3)	3 (3)	.42
Intensive care unit level care (n, %)	6 (35.3)	14 (27.5)	.55
Source of bacteremia (n, %)			
Central venous catheter	6 (35.3)	24 (47.1)	.41
Urinary tract	6 (35.3)	15 (29.4)	.76
Biliary	0 (0.0)	6 (11.8)	—
Intra-abdominal	2 (11.8)	7 (13.7)	1.00
Pneumonia	3 (17.6)	7 (13.7)	.70
Skin and soft tissue	0 (0.0)	2 (3.9)	—
Pre-existing medical conditions (n, %)			
End-stage liver disease	4 (23.5)	8 (15.7)	.48
End-stage renal disease	2 (11.8)	3 (5.9)	.26
Structural lung disease	4 (23.5)	9 (17.6)	.72
Diabetes mellitus	6 (35.3)	14 (27.5)	.55
Congestive heart failure	3 (17.6)	6 (11.8)	.68
Immunocompromised <sup>a</sup> (n, %)	6 (35.3)	22 (43.1)	.78
Source control achieved <sup>b</sup> (n, %)	13 (76.5)	42 (82.4)	.73

Abbreviations: ESBL, extended-spectrum  $\beta$ -lactamase; SD, standard deviation.

<sup>a</sup> Patients were characterized as immunocompromised if they met any of the following criteria: (1) corticosteroid therapy equivalent to prednisone  $\geq$  2 mg/kg or  $\geq$  20 mg daily for at least 14 days, (2) biologic agents in the preceding 30 days, (3) solid organ transplant, (4) hematopoietic stem cell transplant in the preceding 1 year, (5) cancer chemotherapy within 6 months, (6) congenital immunodeficiency, or (7) human immunodeficiency virus with CD4  $\leq$  200 cells/mL.

<sup>b</sup> Source control was defined as the removal of relevant hardware or drainage of infected fluid collections within 5 days of the onset of bacteremia.

the matched cohort, there was a trend towards increased mortality in the cefepime group (HR, 2.87; 95% confidence interval [CI], .88–9.41). In addition, higher Pitt bacteremia scores were associated with an increased risk of death within 14 days (HR, 1.90; 95% CI, 1.36–2.66).

## DISCUSSION

Our study enhances the existing literature, which suggests that cefepime is a suboptimal agent for the treatment of invasive ESBL infections. In particular, we found that cefepime is associated with approximately 2.9 times the risk of death within 14 days compared with carbapenems when prescribed empirically for the treatment of ESBL bacteremia. This is concerning because all included patients who received cefepime had in vitro data suggesting that their clinical isolates were susceptible to cefepime, using the current Clinical and Laboratory Standards Institute (CLSI) cefepime breakpoint. Lowering the cefepime breakpoint to harmonize with The European Committee on

Antimicrobial Susceptibility Testing cefepime breakpoint of 1 mcg/mL may not resolve this issue [1, 2]. In our cohort, 24% of isolates had cefepime MICs of  $\leq 1$  mcg/mL. In addition, lowering the breakpoints would increase the number of patients prescribed carbapenems with non-ESBL producing infections. Given the rising prevalence of carbapenemase-producing organisms, there needs to be a balance between implementing effective empirical therapy and preventing the emergence of carbapenem resistance. The use of rapid diagnostic tests for the early detection of ESBLs with appropriate point-of-care education by antibiotic stewardship teams or region-specific risk-based strategies to determine patients most at risk for harboring ESBLs can assist with the selection of appropriate empiric therapy, while limiting the emergence of resistance that comes with the widespread use of carbapenems when prescribed more broadly.

Of the 63 patients who received cefepime therapy, cefepime had in vitro activity against 27% of isolate, using the current CLSI susceptibility criteria of  $\leq 8$  mcg/mL. Cefepime activity against ESBL-producing organisms is variable in the literature, ranging from 18% to 72% [3–5]. However, there is concern that despite observed in vitro activity, cefepime may remain inadequate for the treatment of ESBL-producing infections, in part because of an “inoculum effect” in which the MICs of cefepime increase in the presence of a high bacterial burden of ESBL-producing organisms [9, 14–16]. Because the CLSI breakpoint for cefepime has not decreased and because ESBL testing is no longer recommended, ESBL-producing pathogens will occasionally be reported as “susceptible” to cefepime. Thus, clinicians might be prompted to use cefepime to treat bacteremia due to ESBL-producing pathogens, even though the efficacy of cefepime in these settings is questionable.

Available clinical data has reinforced this concern; however, most patients in the published data received cefepime administered at 12-hour intervals [6, 7, 9–13]. Previous modeling studies have indicated that 2 grams every 12 hours is likely to result in probability of target attainment in approximately 20% of patients compared with doses given every 8 hours, which is likely to result in target attainment approximately 75% of the time (using a cefepime MIC of 8 mcg/mL), prompting the CLSI to implement a susceptible dose-dependent category encouraging doses every 8 hour for organisms with MICs of 4 or 8 mcg/mL [17]. To overcome this limitation of previous studies, we only included patients who received cefepime at 8-hour intervals.

Because this is a single-center study, the proportion of patients receiving cefepime with in vitro activity against ESBLs in our cohort may not be generalizable to other institutions. In addition, we only evaluated patients receiving intermittently dosed cefepime therapy. Reports from institutions using extended-infusion strategy approaches for ESBL bacteremia would be useful to determine whether we can use cefepime for select patients with ESBL bacteremia. Furthermore, we did not repeat automated cefepime susceptibility results using an alternative method, and we

cannot exclude the possibility that discrepancies may have been observed if repeat testing was performed. As with all observational studies, we cannot rule out residual confounding by unmeasured variables related to disease severity.

## CONCLUSIONS

The present study is in agreement with a number of studies in suggesting the inferiority of cefepime to carbapenems for the treatment of invasive ESBL infections; therefore, recruitment into a randomized trial may pose ethical dilemmas because providers might be hesitant to randomize patients to receive potentially suboptimal therapy. As gram-negative resistance continues to escalate, we hope that the recommendation for clinical microbiology laboratories to conduct ESBL screening of *Enterobacteriaceae* is reconsidered both to ensure patients with ESBL infections receive optimal therapy and to avoid the unnecessary overuse of carbapenems due to false concerns that some isolates may be ESBL-producing. This is likely to be less of a burden on clinical microbiology laboratories currently than in the past due to enhanced automated susceptibility platforms with the ability to conduct ESBL testing and as the field of rapid diagnostics continues to advance.

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