Clinical Impact of Revised Cefepime Breakpoint in Patients With Enterobacteriaceae Bacteremia

Kap Sum Foong,1,2 Abigail L. Carlson,1,2 Satish Munigala,1 Carey-Ann D. Burnham,3 and David K. Warren1

1Section of Infectious Diseases, Department of Medicine, University of Illinois, Peoria, Illinois; 2Veterans Affairs St. Louis Health Care System, St. Louis, Missouri; 3Division of Laboratory and Genomic Medicine, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri

The impact of the revised Clinical and Laboratory Standards Institute interpretative criteria for cefepime in Enterobacteriaceae remains unclear. We applied the new breakpoint on 644 previously defined cefepime-susceptible Enterobacteriaceae isolates. We found no differences in mortality or microbiological failure, regardless of isolates being susceptible or cefepime-susceptible dose-dependent by current criteria.

Keywords. bacteremia; cefepime; cefepime-susceptible dose-dependent; CLSI; Enterobacteriaceae; susceptibility.

In 2014, the Clinical and Laboratory Standards Institute (CLSI) revised the interpretive criteria for cefepime susceptibility among Enterobacteriaceae. Under the former criteria, Kirby-Bauer disk diffusion zone diameter for cefepime-susceptible, -intermediate, and -resistant interpretive criteria were as follows: ≥18 mm (minimum inhibitory concentration [MIC], ≤8 μg/mL), 15–17 mm (MIC, 16 μg/mL), and ≤14 mm (MIC, ≥32 μg/mL). In 2014, they were re-categorized as susceptible (≥25 mm; MIC, ≤2 μg/mL), susceptible dose-dependent (SDD; 19–24 mm; MIC, 4–8 μg/mL), and resistant (≤18 mm; MIC, ≥16 μg/mL). The intermediate category was discontinued [1].

Several retrospective studies have since investigated the clinical impact of new cefepime breakpoint in Enterobacteriaceae infections and concluded that Gram-negative infections with higher MICs or cefepime-SDD isolates were associated with increased mortality. However, these studies were limited by including non-Enterobacteriaceae bacteremias, polymicrobial infections, and combination antimicrobial therapy [2–6]. We aim to determine if Enterobacteriaceae bacteremia isolates, previously identified as cefepime-susceptible and now reclassified as cefepime-SDD by the 2014 CLSI criteria, are associated with higher mortality and microbiological failure when compared with isolates that were identified as cefepime-susceptible by both criteria.

METHODS

Study Setting

We performed a retrospective cohort study from January 2005 through December 2013 at a 1250-bed teaching hospital. We included all inpatients aged ≥18 years with a blood culture(s) positive for Enterobacteriaceae who received cefepime within 24 hours before or after the first positive blood culture.

Cohort

Patients were excluded if they met any of the following exclusion criteria: (1) Enterobacteriaceae with a cefepime disk diffusion diameter ≤18 mm; (2) polymicrobial bacteremia (ie, bloodstream infection with >1 organism); (3) cefepime discontinued <72 hours after the initial dose; (4) combination antimicrobial therapy; (5) death <48 hours after the initial cefepime dose; or (6) missing or duplicate data.

Microbiology

Before November 2013, bacterial identification was performed using phenotypic methods, including VITEK 2, API, and other biochemical methods. After November 2013, bacteria identification was performed using matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker BioTyper). The CLSI-defined Kirby Bauer disk diffusion method was used for antimicrobial susceptibility testing at our microbiology laboratory. For the purpose of this study, an extended-spectrum beta-lactamases (ESBL)–producing strain was defined based on a typical phenotypic susceptibility profile (ie, susceptible to cefotetan, resistant to cefazolin, and intermediate or resistant to ceftazidime and/or ceftriaxone). We also identified chromosomal AmpC β-lactamase-producing Enterobacteriaceae [7].

Clinical Data

We queried the hospital’s Microbiology Laboratory database to identify all Enterobacteriaceae blood isolates during the study period. Demographic, microbiologic, treatment, and outcome data were extracted from the medical informatics database. Sources of bacteremia were determined using International Classification of Diseases 9th Revision, Clinical Modification (ICD-9 CM), diagnosis codes. The Elixhauser comorbidity index was used to define the severity of underlying health conditions [8] and was dichotomized into <3 and ≥3.
The 2014 CLSI cefepime-SDD interpretative category was created based on a cefepime dosing regimen of 2 g Q8 hours [1]. For this, we categorized cefepime regimens into standard dosing of <6 g/d (eg, 1 g Q8 hours or 2 g Q12 hours) and high dosing of 6 g/d (ie, 2 g Q8 hours). Cefepime was administered through standard infusion over 30–60 minutes at our institution. Data on serum creatinine, creatinine clearance estimated by Cockcroft-Gault formula, and renal replacement therapy were collected to account for renal dosage adjustment [9].

Bacteremia was classified into community- or nosocomial-acquired, defined as the first positive blood culture in <48 hours or ≥48 hours after hospitalization, respectively.

**Outcome**

The primary exposure of interest was cefepime susceptibility re-categorization of previously identified cefepime-susceptible Enterobacteriaceae isolates using the revised CLSI breakpoint, dichotomized into cefepime-susceptible and cefepime-SDD. The primary outcomes included 30-day all-cause mortality and microbiological failure. Microbiological failure was defined as subsequent bacteremia with the same organism after 72 hours of cefepime treatment and within 30 days of the initial positive blood culture. Dates of death were extracted from the hospital medical informatics database and from the Social Security Death Index.

**Statistical Analysis**

Data were analyzed using SAS Software (version 9.3; SAS Institute Inc., Cary, NC). Demographic characteristics and blood culture data were compared based on cefepime susceptibility status. Categorical variables were assessed using the χ² test, Fisher exact test, or univariable logistic regression, where appropriate. Comparisons of continuous variables were done using the Kruskal-Wallis test. To determine the independent predictors associated with mortality and microbiological failure, we performed multivariable logistic regression analyses. All variables with \( P < .20 \) in univariable analyses were considered for entry in the model using backwards stepwise regression, with retention in the final model if \( P < .05 \). Given that cefepime susceptibility was the main independent variable of interest, it was forced into both regression models. This study was approved by the Human Research Protection Office at Washington University in St. Louis.

**RESULTS**

During the study period, 2776 patients with cefepime-susceptible Enterobacteriaceae bacteremia were identified; 664 of these patients met the inclusion criteria. When the new breakpoint was applied, 26 (3.9%) isolates were re-categorized into cefepime-SDD, and 638 (96.1%) isolates remained cefepime-susceptible. *Escherichia coli* (32.5%) was the most commonly isolated Enterobacteriaceae, followed by *Klebsiella pneumoniae* (28.3%), and *Enterobacter cloacae* complex (13.3%). The common sources of bacteremia were genitourinary (33.4%), pulmonary (17.8%), and gastrointestinal infections (15.5%) (Supplementary Table 1).

Overall, the cefepime-susceptible and cefepime-SDD groups were similar with respect to baseline characteristics, source of bacteremia, sepsis, renal functions, mode of infection acquisition, and length of stay (Supplementary Table 1). Patients in the cefepime-SDD arm were more likely to be of nonwhite race, have an Elixhauser comorbidity score of ≥2 (84.6% vs 64.9%; \( P = .038 \)), and have isolation of an ESBL-producing isolate (34.6% vs 3.4%; \( P < .001 \)), AmpC β-lactamase-producing isolate (50.0% vs 27.7%; \( P = .014 \)), and *Enterobacter cloacae* complex (42.4% vs 12.1%; \( P < .001 \)).

The mortality rate was 11.5% (\( n = 3/26 \)) and 10.2% (\( n = 65/638 \)) in the cefepime-SDD and cefepime-susceptible groups, respectively. An Elixhauser comorbidity index of ≥3 (adjusted odd ratio [aOR], 2.36; 95% confidence interval [CI], 1.19–4.69) and sepsis (aOR, 2.44; 95% CI, 1.40–4.24) were independently associated with 30-day all-cause mortality (Table 1).

Two (7.7%) of 26 patients in the cefepime-SDD group had microbiological failure, compared with 19 (3.0%) of 638 in the cefepime-susceptible arm. There were no significant independent predictors associated with microbiological failure (Table 1).

**DISCUSSION**

We found that the revised CLSI reporting of *Enterobacteriaceae* changed 3.9% of the previously identified cefepime-susceptible isolates to cefepime-SDD. This rate was similar to the previously published range of 1%–3% [10–12]. Our analyses suggest no difference in 30-day all-cause mortality and microbiological failure between cefepime-SDD and cefepime-susceptible *Enterobacteriaceae* bacteremia after incorporating 2014 CLSI breakpoint on previously collected cefepime-susceptible *Enterobacteriaceae* isolates.

Recent observational studies have suggested that the revised CLSI breakpoint for cefepime are associated with increased mortality and microbiological failure in Gram-negative infections with higher MICs or cefepime-SDD isolates [2–6]. However, these studies were confounded by non-*Enterobacteriaceae* infections (eg, *Pseudomonas aeruginosa* and *Acinetobacter* species), polymicrobial infections, and combination antimicrobial therapy for treatment of Gram-negative infection [2, 4, 6]. To overcome the limitations of previous studies, we used more rigorous inclusion criteria. After taking into account confounders, our findings suggest that the new 2014 CLSI breakpoint was not associated with worse clinical outcomes.

CLSI guidelines assert that, with lower cephalosporin breakpoints, ESBL-producing organisms that would have been categorized as susceptible using former breakpoint would now be considered resistant [13]. Therefore, routine ESBL detection in *Enterobacteriaceae* is no longer recommended for
### Table 1. Univariable and Multivariable Logistic Regression Predicting 30-Day All-Cause Mortality and Microbiological Failure Among 644 Patients With *Enterobacteriaceae* Bacteremia

| 30-Day All-Cause Mortality | Microbiological Failure |
|----------------------------|-------------------------|
| **Age, median (IQR), y**   | **Yes (n = 68)**        | **No (n = 596)**       | **P** | **aOR (95% CI)** |
| 62 (56–72)                 | 59 (49–69)              |                      | .013  | ...              |
| **Gender**                 |                         |                      | .116  | ...              |
| Male, No. (%)              | 44 (64.7)               | 326 (54.7)           | ...   | ...              |
| Female, No. (%)            | 24 (35.3)               | 270 (45.3)           | ...   | ...              |
| **Race**                   |                         |                      | ...   | ...              |
| White, No. (%)             | 42 (61.6)               | 372 (62.4)           | Reference | 12 (57.1)     | 402 (62.5) | Reference | ...   |
| Black, No. (%)             | 18 (26.5)               | 179 (30.0)           | 696   | 7 (33.4)     | 190 (29.6) | .664     | ...   |
| Other, No. (%)             | 8 (11.7)                | 45 (7.6)             | ...   | 2 (9.5)      | 51 (7.9)   | .726     | ...   |
| **Elixhauser comorbidity index ≥3, No. (%)** | 57 (83.8)               | 379 (63.6)           | <.001 | 2.36 (1.19–4.69) | 11 (52.4)     | 425 (66.1) | .193   | ...   |
| **Sepsis, No. (%)**        | 47 (69.1)               | 260 (43.6)           | <.001 | 2.44 (1.40–4.24) | 10 (47.6)     | 297 (46.2) | .897   | ...   |
| **Cefepime disk diffusion diameter ≥25 mm (susceptible), No. (%)** | 65 (95.6)               | 573 (96.1)           | ...   | 19 (90.5)    | 619 (96.3) | ...     | ...   |
| 19–24 mm (SDD), No. (%)    | 3 (4.4)                 | 23 (3.9)             | 0.88 (0.25–3.07) | 2 (9.5) | 24 (3.7) | 3.00 (0.66–13.75) | ...   |
| **Causative *Enterobacteriaceae*** |                         |                      | ...   | ...              |
| *Escherichia coli, No. (%)* | 22 (32.3)               | 194 (32.5)           | .974  | ...              |
| *Klebsiella pneumoniae, No. (%)* | 22 (32.3)               | 166 (27.8)           | .435  | ...              |
| *Enterobacter cloacae complex, No. (%)* | 3 (4.4)                 | 85 (14.3)            | .022  | ...              |
| *Serratia marcescens, No. (%)* | 8 (11.8)                | 50 (8.4)             | .350  | ...              |
| *Proteus mirabilis, No. (%)* | 6 (8.8)                 | 24 (4.0)             | .071  | ...              |
| *Enterobacter aerogenes, No. (%)* | 4 (5.9)                 | 20 (3.4)             | .295  | ...              |
| *Klebsiella oxytoca, No. (%)* | 1 (1.5)                 | 22 (3.7)             | .498  | ...              |
| *Citrobacter freundii complex, No. (%)* | 1 (1.5)                 | 7 (1.2)              | .581  | ...              |
| *Salmonella species, No. (%)* | 1 (1.5)                 | 4 (0.7)              | .418  | ...              |
| Others, b No. (%)          | 0                      | 24 (4.0)             | .160  | ...              |
| **ESBL producer, No. (%)**  | 0                      | 31 (5.2)             | .063  | ...              |
| **AmpC β-lactamase-producing organism, No. (%)** | 16 (23.5)               | 174 (29.2)           | .396  | 10 (47.6)     | 180 (28.0) | .082   | ...   |
| **Source of bacteremia**   |                         |                      | ...   | ...              |
| *Genitourinary, No. (%)*   | 19 (27.9)               | 203 (34.1)           | .344  | ...              |
| *Pulmonary, No. (%)*       | 17 (25.0)               | 101 (16.9)           | .100  | ...              |
| *Gastrointestinal, No. (%)* | 11 (16.2)               | 92 (15.4)            | .873  | ...              |
| *Skin and soft tissue, No. (%)* | 3 (4.4)                 | 36 (6.0)             | .788  | ...              |
| *Bone and joint, No. (%)*  | 1 (1.5)                 | 21 (3.5)             | .717  | ...              |
| *Staphylococcus aureus*, No. (%)* | 4 (5.9)                 | 81 (13.6)            | .084  | ...              |
| *Primary bacteremia alone, No. (%)* | 10 (14.7)               | 82 (13.8)            | .830  | ...              |
| *Other, b No. (%)*         | 5 (7.4)                 | 48 (8.1)             | .840  | ...              |
| **Cefepime dosage**        |                         | ...                  | .173  | ...              |
| >60 mL/min, No. (%)        | 31 (45.6)               | 358 (60.1)           | ...   | ...              |
| <=60 mL/min, No. (%)       | 31 (45.6)               | 358 (60.1)           | ...   | ...              |
In our cohort, 4.7% of the cefepime-SDD and cefepime-susceptible Enterobacteriaceae isolates phenotypically exhibited ESBL production. Emerging clinical data have reported higher mortality and inferiority of cefepime to carbapenems in treating ESBL-producing Enterobacteriaceae infection [3, 5, 14]. ESBL production was not predictive of mortality and microbiological failure in our multivariable analyses. However, ESBL screening and cefepime treatment for invasive ESBL-producing Enterobacteriaceae infection remain controversial [13, 14].

Pharmacokinetic–pharmacodynamic modeling concluded that a 65% $f_{T > MIC}$ for Enterobacteriaceae isolates with MICs of 4–8 µg/mL was reached at 70%–90% probability with cefepime 2 g Q8 hours [15]. This prompted a CLSI recommendation of high-dose cefepime for cefepime-SDD Enterobacteriaceae [1]. We found that only 42.3% of the cefepime-SDD arm received high-dose cefepime. There were no differences in mortality or microbiological failure between high- vs standard-dose cefepime in patients with cefepime-SDD Enterobacteriaceae bacteremia. Because this is a retrospective study, the 2014 CLSI recommendation of using high-dose cefepime would not have been applied to these previously collected Enterobacteriaceae isolates for 2005–2013. Thus, we were unable to fully evaluate whether high-dose cefepime would have led to a more favorable outcome for patients with cefepime-SDD Enterobacteriaceae bacteremia. Future studies are needed to answer this clinical question.

This study is limited by a retrospective cohort in a single institution, and hence our findings may not be generalizable to other populations. Despite a large cohort, only 26 cases of cefepime-SDD Enterobacteriaceae were identified due to its infrequency. This limited our statistical power. Although our database was built to maximize comprehensiveness, ICD-9 CM codes may not accurately reflect the true infectious diagnosis and may result in misclassification bias. Additionally, we were unable to identify source control that may have contributed to variations in clinical outcomes. Lastly, the presence of ESBL production was determined phenotypically in our study. However, this would also be particularly relevant in real-world practice, as accessibility to molecular assay may be limited.

In conclusion, we found no differences in mortality or microbiological failure among cases of Enterobacteriaceae bacteremia treated with cefepime, regardless of isolates being either cefepime-susceptible or cefepime-SDD by current CLSI standards.

**Supplementary Data**

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copystriped and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.
Acknowledgments

Financial support. Research reported in this publication was supported in part by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number UL1 TR002345. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 24th ed. CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
2. Alves MD, Ribeiro VB, Tessari JP, et al. Effect of cefepime dose on mortality of patients with Gram-negative bacterial bloodstream infections: a prospective cohort study. J Antimicrob Chemother 2014; 69:1681–7.
3. Lee NY, Lee CC, Li CW, et al. Cefepime therapy for monomicrobial Enterobacter cloacae bacteremia: unfavorable outcomes in patients infected by cefepime-susceptible dose-dependent isolates. Antimicrob Agents Chemother 2015; 59:7558–63.
4. Rhodes NJ, Liu J, McLaughlin MM, et al. Evaluation of clinical outcomes in patients with Gram-negative bloodstream infections according to cefepime MIC. Diagn Microbiol Infect Dis 2015; 82:165–71.
5. Wang R, Congrove SE, Tschudin-Sutter S, et al. Cefepime therapy for cefepime-susceptible extended-spectrum β-lactamase-producing Enterobacteriaceae bacteremia. Open Forum Infect Dis 2016; 3:ofw132.
6. Altshuler J, Guervil DJ, Ericsson CD, et al. Clinical outcomes in patients with gram-negative infections treated with optimized dosing cefepime over various minimum inhibitory concentrations. J Pharm Pract 2018; 31:34–9.
7. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev 2009; 22:161–82.
8. Johnston JA, Wagner DP, Timmons S, et al. Impact of different measures of comorbid disease on predicted mortality of intensive care unit patients. Med Care 2002; 40:929–40.
9. Hospira. Maxipime (Cefepime) [prescribing information]. Lake Forest, IL: Hospira; 2017.
10. Wagner JL, Kenney RM, Tibbetts RJ, Davis SL. Secular trends associated with Enterobacteriaceae with a cefepime susceptible-dose-dependent MIC. Antimicrob Agents Chemother 2015; 59:1822–3.
11. Hamada Y, Sutherland CA, Nicolau DP. Impact of revised cefepime CLSI breakpoints on Escherichia coli and Klebsiella pneumoniae susceptibility and potential impact if applied to Pseudomonas aeruginosa. J Clin Microbiol 2015; 53:1712–4.
12. Rivera CG, Narayanan PP, Patel R, Estes LL. Impact of cefepime susceptible-dose-dependent MIC for Enterobacteriaceae on reporting and prescribing. Antimicrob Agents Chemother 2016; 60:3854–5.
13. Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother 2012; 67:1569–77.
14. Lee NY, Lee CC, Huang WH, et al. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum β-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis 2013; 56:488–95.
15. Roos JF, Bulitta J, Lipman J, Kirkpatrick CM. Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. J Antimicrob Chemother 2006; 58:967–93.