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BRIEF REPORT

Clinical Impact of Revised Cefepime Breakpoint in Patients With *Enterobacteriaceae* Bacteremia

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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

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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 χ^2 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 ≥3 (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

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			
	Yes (n = 68)	No (n = 596)	*P*[a]	aOR (95% CI)	Yes (n = 21)	No (n = 643)	*P*[a]	aOR (95% CI)
Age, median (IQR), y	62 (56–72)	59 (49–69)	.013	…	55 (51–58)	60 (50–69)	.111	…
Gender	…	…	.116	…	…	…	.894	…
Male, No. (%)	44 (64.7)	326 (54.7)	…	…	12 (57.1)	358 (55.7)	…	…
Female, No. (%)	24 (35.3)	270 (45.3)	…	…	9 (42.9)	285 (44.3)	…	…
Race	…	…	…	…	…	…	…	…
White, No. (%)	42 (61.8)	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)	.276	…	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	…	…	.742	…	…	…	.197	…
≥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	…	3 (14.3)	213 (33.1)	.096	…
Klebsiella pneumoniae, No. (%)	22 (32.3)	166 (27.8)	.435	…	7 (33.3)	181 (28.2)	.604	…
Enterobacter cloacae complex, No. (%)	3 (4.4)	85 (14.3)	.022	…	2 (9.5)	86 (13.4)	1.00	…
Serratia marcescens, No. (%)	8 (11.8)	50 (8.4)	.350	…	4 (19.1)	54 (8.4)	.102	…
Proteus mirabilis, No. (%)	6 (8.8)	24 (4.0)	.071	…	1 (4.8)	29 (4.5)	1.00	…
Enterobacter aerogenes, No. (%)	4 (5.9)	20 (3.4)	.295	…	2 (9.5)	22 (3.4)	.173	…
Klebsiella oxytoca, No. (%)	1 (1.5)	22 (3.7)	.498	…	0	23 (3.6)	1.00	…
Citrobacter freundii complex, No. (%)	1 (1.5)	7 (1.2)	.581	…	2 (9.5)	6 (0.9)	.024	…
Salmonella species, No. (%)	1 (1.5)	4 (0.7)	.418	…	0	5 (0.8)	1.00	…
Others,[b] No. (%)	0	24 (4.0)	.160	…	0	24 (3.7)	1.00	…
ESBL producer, No. (%)	0	31 (5.2)	.063	…	1 (4.8)	30 (4.7)	1.00	…
AmpC β-lactamase-producing organism, No. (%)	16 (23.5)	174 (29.2)	.396	…	10 (47.6)	180 (28.0)	.082	…
Source of bacteremia[c]	…	…	…	…	…	…	…	…
Genitourinary, No. (%)	19 (27.9)	203 (34.1)	.344	…	4 (19.0)	218 (33.9)	.239	…
Pulmonary, No. (%)	17 (25.0)	101 (16.9)	.100	…	1 (4.8)	117 (18.2)	.149	…
Gastrointestinal, No. (%)	11 (16.2)	92 (15.4)	.873	…	4 (19.0)	99 (15.4)	.552	…
Skin and soft tissue, No. (%)	3 (4.4)	36 (6.0)	.788	…	0	39 (6.1)	.628	…
Bone and joint, No. (%)	1 (1.5)	21 (3.5)	.717	…	1 (4.8)	21 (3.3)	.513	…
SSI, device-associated, No. (%)	4 (5.9)	81 (13.6)	.084	…	1 (4.8)	84 (13.1)	.502	….
Primary bacteremia alone, No. (%)	10 (14.7)	82 (13.8)	.830	…	3 (14.3)	89 (13.8)	1.00	…
Others,[d] No. (%)	5 (7.4)	48 (8.1)	.840	…	1 (4.8)	52 (8.1)	1.00	…
Cefepime dosage	…	…	.173	…	…	…	.394	…
Standard dose (<6 g/d), No. (%)	41 (60.3)	408 (68.5)	…	…	16 (76.2)	433 (67.3)	…	…
High dose (6 g/d), No. (%)	27 (39.7)	188 (31.5)	…	…	5 (23.8)	210 (32.7)	…	…
Renal function, CrCl	…	…	.010	…	…	…	.539	…
>60 mL/min, No. (%)	31 (45.6)	358 (60.1)	…	…	11 (52.4)	378 (58.8)	…	…

Table 1. Continued

	30-Day All-Cause Mortality				Microbiological Failure			
	Yes (n = 68)	No (n = 596)	*P*[a]	aOR (95% CI)	Yes (n = 21)	No (n = 643)	*P*[a]	aOR (95% CI)
30–60 mL/min, No. (%)	15 (22.0)	118 (19.8)	…	…	7 (33.3)	126 (19.6)	…	…
<30 mL/min, No. (%)	11 (16.2)	70 (11.7)	…	…	1 (4.8)	80 (12.4)	…	…
Renal replacement therapy,[e] No. (%)	11 (16.2)	50 (8.4)	…	…	2 (9.5)	59 (9.2)	…	…
Mode of infection acquisition	…	…	.109	…	…	…	.366	…
Community-acquired, No. (%)	42 (61.8)	307 (51.5)	…	…	9 (42.9)	340 (52.9)	…	…
Nosocomial-acquired, No. (%)	26 (38.2)	289 (48.5)	…	…	12 (57.1)	303 (47.1)	…	…

Abbreviations: aOR, adjusted odd ratio; CI, confident interval; CrCl, creatinine clearance; ESBL, extended-spectrum beta-lactamases; IQR, interquartile range; SDD, susceptible dose-dependent; SSI, surgical site infection.

[a]Comparison of 30-day all-cause mortality and microbiological failure. *P* value was calculated using chi-square, Fisher exact, univariable logistic regression, or Kruskal-Wallis test, as appropriate. Variables were not normally distributed; thus, nonparametric tests were used.

[b]Included *Cedecea* species (1), *Citrobacter koseri* (4), *Citrobacter youngae* (1), *Cronobacter sakazakii* complex (1), *Enterobacter cancerogenus* (1), *Enterobacter* species (1), *Hafnia alvei* (1), *Klebsiella* species (1), *Kluyvera* species (1), *Leclercia* species (1), *Pantoea agglomerans* (1), *Pantoea* species (6), *Proteus vulgaris* (1), *Providencia stuartii* (1), and *Serratia liquefaciens* (2).

[c]Some patients had more than 1 infectious source.

[d]Included meningitis, intracranial abscess, endocarditis, parapharyngeal abscess, and retropharyngeal abscess.

[e]Included intermittent hemodialysis, peritoneal dialysis, and continuous venovenous hemodialysis.

be considered resistant [13]. Therefore, routine ESBL detection in *Enterobacteriaceae* is no longer recommended for clinical purposes [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% $fT > MIC$ 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 copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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