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MAJOR ARTICLE

Can the Ceftriaxone Breakpoints Be Increased Without Compromising Patient Outcomes?

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Background. In 2010, the Clinical Laboratory and Standards Institute recommended a 3-fold lowering of ceftriaxone breakpoints to 1 mcg/mL for *Enterobacteriaceae*. Supportive clinical data at the time were from fewer than 50 patients. We compared the clinical outcomes of adults with *Enterobacteriaceae* bloodstream infections treated with ceftriaxone compared with matched patients (with exact matching on ceftriaxone minimum inhibitory concentrations [MICs]) treated with extended-spectrum agents to determine if ceftriaxone breakpoints could be increased without negatively impacting patient outcomes.

Methods. A retrospective cohort study was conducted at 3 large academic medical centers and included patients with *Enterobacteriaceae* bacteremia with ceftriaxone MICs of 2 mcg/mL treated with ceftriaxone or extended-spectrum β-lactams (ie, cefepime, piperacillin/tazobactam, meropenem, or imipenem/cilastatin) between 2008 and 2014; 1:2 nearest neighbor propensity score matching was performed to estimate the odds of recurrent bacteremia and mortality within 30 days.

Results. Propensity score matching yielded 108 patients in the ceftriaxone group and 216 patients in the extended-spectrum β-lactam group, with both groups well-balanced on demographics, preexisting medical conditions, severity of illness, source of bacteremia, and source control interventions. No difference in recurrent bacteremia (odds ratio [OR], 1.16; 95% confidence interval [CI], 0.49–2.73) or mortality (OR, 1.27; 95% CI, 0.56–2.91) between the treatment groups was observed for patients with isolates with ceftriaxone MICs of 2 mcg/mL. Only 6 isolates (1.6%) with ceftriaxone MICs of 2 mcg/mL were extended-spectrum β-lactamase (ESBL)–producing.

Conclusions. Our findings suggest that patient outcomes are similar when receiving ceftriaxone vs extended-spectrum agents for the treatment of *Enterobacteriaceae* bloodstream infections with ceftriaxone MICs of 2 mcg/mL. This warrants consideration of adjusting the ceftriaxone susceptibility breakpoint from 1 to 2 mcg/mL, as a relatively small increase in the antibiotic breakpoint could have the potential to limit the use of large numbers of extended-spectrum antibiotic agents.

Keywords. antibiotic breakpoints; bacteremia; ceftriaxone; ESBL.

As the prevalence of multidrug-resistant bacteria rises and antibiotics in development remain limited, preserving the utility of existing antibiotic agents is imperative [1]. To meet this goal, breakpoints used to define bacteria as susceptible to antibiotics need to be informed by the best available in vitro and clinical data. If the antibiotic breakpoints recommended are unnecessarily high, critically ill patients may receive potentially ineffective agents. On the contrary, if the recommended breakpoints are too low, a greater proportion of bacteria will appear to be not susceptible to tested agents, and patients may receive antibiotic agents with a more extended spectrum of activity than necessary, potentially accelerating the development of antibiotic resistance.

Over the past several years, the Clinical and Laboratory Standards Institute (CLSI) lowered antibiotic breakpoints for a number of commonly used antibiotic agents [2]. CLSI antibiotic breakpoint recommendations are informed by the best available data, which are frequently limited to experimental data (eg, minimum inhibitory concentration [MIC] distributions, pharmacokinetic–pharmacodynamic modeling). Although in vitro data are hypothesis generating and the necessary first step in considering antibiotic breakpoint changes, confirmation through clinical outcomes analysis ensures that recommendations truly optimize patient outcomes.

In 2010, the CLSI recommended a 3-fold lowering of ceftriaxone breakpoints (ie, 8 mcg/mL to 1 mcg/mL) against *Enterobacteriaceae* and removed the requisite extended-spectrum β-lactamase (ESBL) phenotypic testing for organisms with ceftriaxone MICs ≥2 mcg/mL[3]. These changes were largely motivated by observations that some ESBL-producing organisms demonstrate elevated yet still susceptible ceftriaxone MICs

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(using the previous breakpoints), and confirmatory ESBL testing proved time-consuming for clinical microbiology laboratories [3]. Before 2010, ceftriaxone-susceptible, -intermediate, and -resistant interpretive criteria were as follows: ≤8, 16–32, and ≥64 mcg/mL. In 2010, they were recategorized, with susceptible, intermediate, and resistant defined as ≤1, 2, and ≥4 mcg/mL.

As was stated in a document outlining the rationale for the ceftriaxone breakpoint changes, "While highly desirable, clinical data from controlled or even uncontrolled trials were few" [3]. At the time the changes were recommended, data from fewer than 50 patients demonstrating poorer clinical outcomes associated with higher ceftriaxone MICs had been published [3, 4]. Moreover, these data lacked consideration of underlying patient and treatment characteristics that may have influenced the relationship between ceftriaxone MICs and clinical outcomes. The aim of this study was to compare the clinical outcomes of adults with *Enterobacteriaceae* bloodstream infections treated with ceftriaxone with matched patients (with exact matching on ceftriaxone MICs) treated with extended-spectrum agents to determine if ceftriaxone breakpoints could be increased without negatively impacting patient outcomes.

METHODS

Setting and Participants

All patients ≥18 years old with *Enterobacteriaceae* bacteremia from January 2008 to December 2014 hospitalized at the Hospital of the University of Pennsylvania, the University of Maryland Medical Center, and The Johns Hopkins Hospital were retrospectively identified. Inclusion was limited to patients with blood cultures demonstrating growth of any of the following *Enterobacteriaceae*: *Escherichia coli*, *Citrobacter* species, *Enterobacter* spp., *Klebsiella* spp., *Proteus mirabili*s, and *Serratia* spp. Only the first episode of bacteremia per patient during the study period was analyzed. The ceftriaxone breakpoint was lowered from 8 to 1 mcg/mL, along with the discontinuation of ESBL confirmatory testing, on July 1, 2012, January 15, 2013, and April 1, 2014, for the Hospital of the University of Pennsylvania, the University of Maryland Medical Center, and The Johns Hopkins Hospital, respectively. Before these time periods, at all 3 sites, *E. coli*, *Klebsiella* spp., and *P. mirabilis* organisms with MICs ≥2 mcg/mL for ceftriaxone or aztreonam underwent further screening for ESBL production. A decrease of >3 MIC doubling dilutions for either ceftriaxone or ceftazidime tested in combination with 4 mcg/mL of clavulanic acid, vs its MIC when tested alone, was used to confirm ESBL status [5].

Exposure and Outcomes

The primary exposure was receipt of ceftriaxone monotherapy. For the first 2 days of therapy (day 1 being the day blood cultures were obtained), an in vitro active extended-spectrum antibiotic agent was permitted (ie, cefepime, piperacillin/tazobactam, meropenem, or imipenem-cilastatin), but the patient had to subsequently be converted to ceftriaxone and continue on this agent for the remainder of the treatment duration. Unexposed patients were those who received in vitro active cefepime, piperacillin/tazobactam, meropenem, or imipenem/cilastatin (hereafter referred to as "extended-spectrum") therapy for the entire treatment duration. Outcomes included subsequent bloodstream infections with the same organism and all-cause mortality, both within 28 days from the day blood cultures were obtained.

Exclusion Criteria

Patients meeting any of the following criteria were excluded: (a) *Enterobacteriaceae* with ceftriaxone MICs >8 mcg/mL, as these isolates are categorized as resistant to ceftriaxone using both the previous and current CLSI breakpoints; (b) duration of therapy beyond 15 days, as therapy beyond this duration may indicate more complex infections (eg, meningitis, endocarditis, osteomyelitis, undrained intra-abdominal abscesses, etc.); (c) receipt of additional agents with gram-negative coverage in combination with ceftriaxone or extended-spectrum therapy (beyond day 2 of antibiotic therapy); and (d) death within 48 hours from the time the first positive blood culture was obtained, as the severity of illness likely signified that death was independent of antibiotic selection.

Data Collection

Demographic, preexisting medical conditions; source of bacteremia and source control measures; and microbiologic, treatment, and outcomes data were manually collected through electronic medical record review from each of the 3 institutions and entered into a secure REDCap database. Infectious diseases–trained physicians determined the likely source of infection and appropriateness of source control measures (ie, removal of infected hardware, drainage of infected fluid collections, or resolution of obstruction for biliary or urinary sources while receiving antibiotic therapy). ICU admission and Pitt bacteremia score on day 1 of bacteremia were used to evaluate illness severity. Antibiotic MIC data were determined using the Vitek 2 automated platform (bioMérieux, Durham, NC) for isolates from the Hospital of the University of Pennsylvania and the University of Maryland Medical Center. The BD Phoenix automated system (BD Diagnostics, Sparks, MD) was used for MIC determination for isolates from The Johns Hopkins Hospital. This study was approved by the institutional review board of each participating institution, with waivers of informed consent.

Statistical Analysis

We performed an initial exploratory analysis to identify which ceftriaxone MICs could reasonably be evaluated. From the initial cohort of 4967 patients, 1553 patients met eligibility criteria (Figure 1). There were only 44 patients with isolates with ceftriaxone MICs ≥4 mcg/mL who remained on ceftriaxone monotherapy after antimicrobial susceptibility testing (AST) results

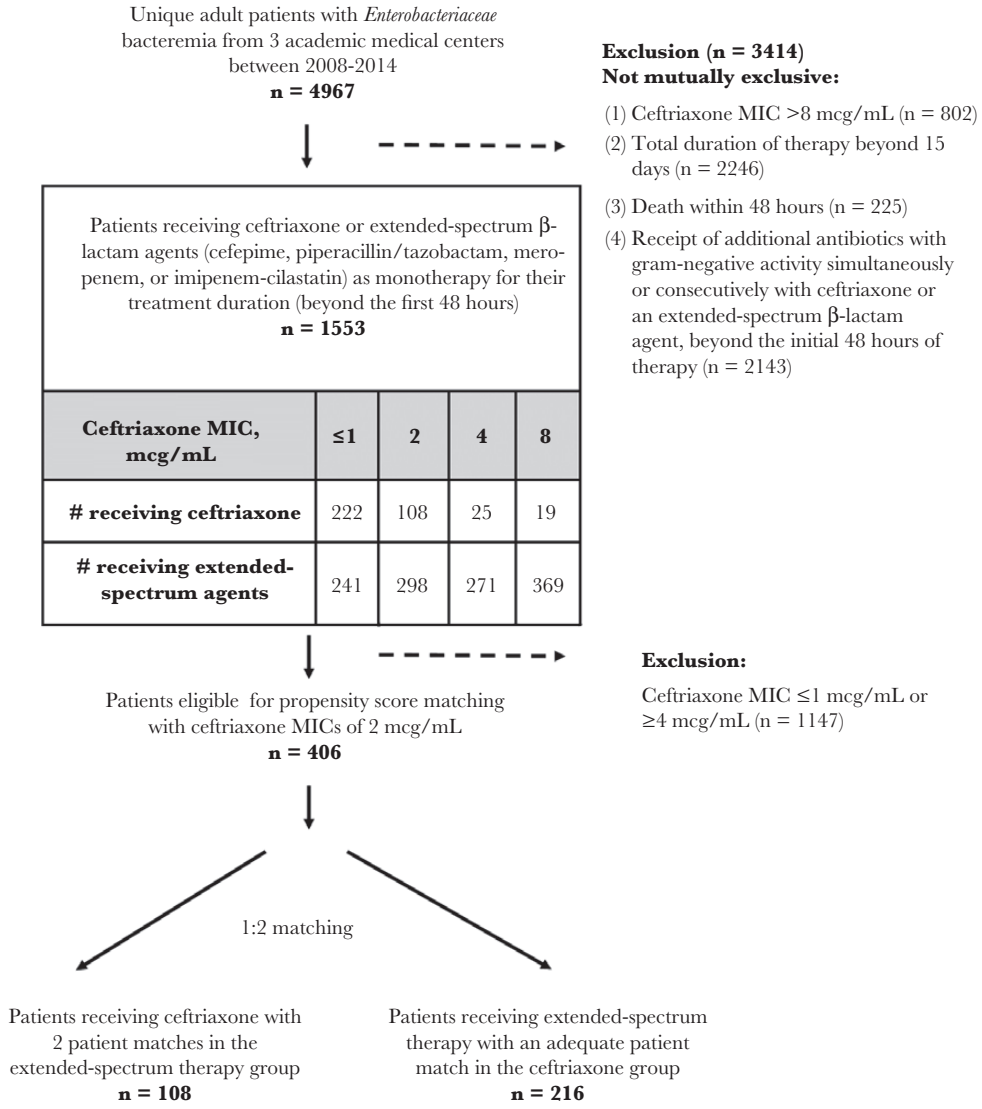

Figure 1. Design of a study of patients with *Enterobacteriaceae* bloodstream infections with ceftriaxone minimum inhibitory concentrations (MICs) of 2 mcg/mL receiving ceftriaxone vs extended-spectrum agents.

were available. This precluded a meaningful analysis of patients with ceftriaxone MICs of ≥4 mcg/mL. All of these patients were in the period before the implementation of ceftriaxone breakpoint changes in their respective institutions.

Propensity score matching of patients with *Enterobacteriaceae* bloodstream infections with ceftriaxone MICs of 2 mcg/mL was undertaken to account for factors that commonly influence antibiotic treatment decisions. Propensity scores were calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of receipt of ceftriaxone therapy, the "exposed" group. Covariates included in generating the propensity score included (a) calendar year of bloodstream infection, (b) age, (c) preexisting conditions (end-stage liver disease, end-stage renal disease requiring dialysis, structural lung disease, congestive heart failure with an ejection fraction of <45%, diabetes), (d) immunocompromised status (HIV, chemotherapy within 6 months, absolute neutrophil count [ANC] <100 cells/mm^3 at the time of blood culture collection, active immunomodulatory therapy, or corticosteroids for ≥14 days), (e) Pitt bacteremia score on day 1 of bacteremia, (f) ICU stay on day 1 of bacteremia, (g) source of bacteremia, and (h) appropriate source control measures. Each patient receiving ceftriaxone was matched to 2 patients receiving extended-spectrum therapy if 2 patients with a propensity score within 0.20 standard deviations of the propensity score of the ceftriaxone patient could be identified. Patients who did not meet caliper criteria were excluded from further analysis. Patients were matched 1:2 without replacement using an optimal (nongreedy) algorithm. Propensity score distributions and standardized biases (with the goal of ≤0.10) before and after

matching were evaluated. Logistic regression was conducted using the matched groups to evaluate (a) the odds of recurrent bloodstream infections with the same organism and (b) all-cause mortality, both within 28 days of the collection date of the first positive culture. Data analysis was performed using Stata, version 13.0 (Stata Corp., College Station, TX).

RESULTS

Propensity score matching yielded a cohort of 324 patients (Figure 1; Table 1). For patients receiving ceftriaxone, the dosages administered were as follows: 1 g every 12 hours (6%), 1 g every 24 hours (64%), 2 g every 12 hours (4%), and 2 g every 24 hours (26%). For patients receiving extended-spectrum agents, the following agents were prescribed: piperacillin/tazobactam (46%), cefepime (39%), meropenem (14%), and imipenem/cilastatin (1%).

The organism distribution was as follows in the matched cohort: *Escherichia coli* (40%, 130), *Klebsiella* spp. (37%, 120), *Enterobacter* spp. (13%, 42), *Serratia marcescens* (4%, 13), Proteus mirabilis (4%, 13), and *Citrobacter* spp. (2%, 6). A total of 2669 *E. coli*, *Klebsiella* spp., or *P. mira*bilis bloodstream isolates were recovered during the period when ESBL confirmatory testing occurred at each of the participating institutions. Of these, 369 (14%) were confirmed ESBL producers, with the ceftriaxone MIC distribution as follows: 1 mcg/mL (<1%, 1), 2 mcg/mL (2%, 6), 4 mcg/mL (3%, 11), 8 mcg/mL (16%, 59), 16 mcg/mL (12%, 44), 32 mcg/mL (3%, 11), 64 mcg/mL (59%, 218), and 128 mcg/mL (5%, 19). For the 6 patients with ceftriaxone MICs of 2 mcg/mL who were identified as ESBL producers, 2 were prescribed ceftriaxone and 4 were prescribed extended-spectrum agents. Although included in the propensity score–matched cohort, the small numbers of isolates with

Table 1. Covariate Balance Between Patients With *Enterobacteriaceae* Bloodstream Infections With Ceftriaxone MICs of 2 mcg/mL Receiving Ceftriaxone vs Extended-Spectrum Agents (Cefepime, Piperacillin/Tazobactam, Meropenem, Imipenem/Cilastatin) Before and After Propensity Score Matching

	Before Matching			After Matching		
	Ceftriaxone (n = 108)	Extended-Spectrum Agent (n = 298)	*P* Value	Ceftriaxone (n = 108)	Extended-Spectrum Agent (n = 216)	*P* Value
Age, median (IQR)	57 (43–68)	59 (48–68)	.41	57 (43–68)	59 (45–68)	.81
Male, n (%)	53 (49)	202 (68)	.001	53 (49)	99 (46)	.64
Race/ethnicity, n (%)						
Hispanic	5 (5)	12 (4)	.78	5 (5)	13 (6)	.80
White	41 (38)	161 (54)	<.01	41 (38)	89 (41)	.63
Black	44 (41)	95 (32)	.10	44 (41)	82 (38)	.63
Asian	5 (5)	9 (3)	.54	5 (5)	11 (5)	>.99
ICU on day 1, n (%)	31 (29)	128 (43)	.01	31 (29)	71 (33)	.53
Pitt bacteremia score on day 1, median (IQR)	2 (1–3)	2 (1–4)	.07	2 (1–3)	2 (1–3)	.45
Source of bacteremia, n (%)						
Pneumonia	6 (6)	30 (10)	.17	6 (6)	13 (6)	>.99
Skin and soft tissue	4 (4)	24 (8)	.18	4 (4)	15 (7)	.32
Urinary tract	57 (53)	69 (23)	<.01	57 (53)	102 (47)	.35
Biliary	10 (9)	33 (11)	.71	10 (9)	22 (10)	.85
Intra-abdominal	13 (12)	77 (26)	.003	13 (12)	32 (15)	.61
Catheter-associated	16 (15)	60 (20)	.25	16 (15)	28 (13)	.73
Osteoarticular	1 (1)	6 (2)	.68	1 (1)	4 (2)	.67
Preexisting medical conditions, n (%)						
End-stage liver disease	5 (5)	33 (11)	.05	5 (5)	15 (7)	.47
End-stage renal disease	9 (8)	27 (9)	1.00	9 (8)	17 (8)	>.99
Structural lung disease[a]	10 (9)	21 (7)	.53	10 (9)	13 (6)	.36
Congestive heart failure	14 (13)	48 (16)	.53	14 (13)	28 (13)	>.99
Diabetes	6 (6)	30 (10)	.17	6 (6)	24 (11)	.15
Immunocompromised, n (%)						
HIV	5 (5)	9 (3)	.54	5 (5)	6 (3)	.52
Chemotherapy within 6 mo	23 (21)	86 (29)	.16	23 (21)	52 (24)	.68
Immunomodulatory therapy ≤30 d or ≥14 d corticosteroids	5 (5)	21 (7)	>.99	5 (5)	15 (7)	.47
Solid organ transplant	15 (14)	42 (14)	>.99	15 (14)	30 (14)	>.99
Bone marrow transplant within 12 mo	3 (3)	15 (5)	.42	3 (3)	11 (5)	.40
Absolute neutrophil count 0–200 cells/mL	1 (1)	24 (8)	.005	1 (1)	11 (5)	.07

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration.

[a]Chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis, tracheostomy dependency.

ceftriaxone MICs of 2 mcg/mL that were ESBL-producing limited further subgroup analysis of these patients.

Outcomes

In the propensity score–matched cohort, there were 9 (9%) and 16 (8%) bloodstream infection relapses within 28 days in patients who survived until day 28 in the ceftriaxone and the extended-spectrum therapy groups, respectively. Ceftriaxone was not associated with an increased odds of bloodstream infection relapses compared with broad-spectrum therapy (odds ratio [OR], 1.16; 95% confidence interval [CI], 0.49–2.73; $P = .73$).

Ninety-five percent of patients had repeat blood cultures obtained. The median duration of bacteremia (interquartile range [IQR]) in the ceftriaxone and extended-spectrum groups was no different, at 1.2 (1.0–1.6) and 1.1 (1.0–1.8) days, respectively. Similarly, there were 10 (9%) and 16 (7%) deaths within 28 days in the ceftriaxone and broad-spectrum therapy groups, respectively. Ceftriaxone was not associated with an increased odds of 28-day mortality compared with broad-spectrum therapy (OR, 1.27; 95% CI, 0.56–2.91; $P = .56$).

DISCUSSION

We found that there was no difference in recurrent bloodstream infections or 28-day mortality for patients with *Enterobacteriaceae* bloodstream infections with ceftriaxone MICs of 2 mcg/mL receiving ceftriaxone compared with extended-spectrum antibiotic therapy. Current CLSI guidelines recommend a ceftriaxone susceptibility breakpoint of 1 mcg/mL, but our data suggest that increasing this breakpoint to 2 mcg/mL may be a reasonable consideration as a 1-fold change in the current breakpoint does not appear to compromise clinical outcomes but could reduce the prescription of extended-spectrum antibiotic agents.

Reduction of the ceftriaxone breakpoint from 8 to 1 mcg/mL in 2010 was motivated by concerns that ESBL-producing *Enterobacteriaceae* isolates with ceftriaxone MICs in the range of 2–8 mcg/mL (in the absence of routine ESBL testing) would not be identified and that patients who received ceftriaxone in the setting of undetected ESBL production would suffer adverse outcomes [6, 7]. However, available data suggest that ESBL-producing isolates have a low likelihood of having ceftriaxone MICs of ≤2 mcg/mL [8–10]. In 1 study including 3431 ESBL-producing *Enterobacteriaceae* collected from 6 continents, the MIC_{50} and MIC_{90} for third-generation cephalosporins were both >128 mcg/mL [8]. In another cohort including 49 US ESBL-producing isolates, only 3 isolates (6%) had ceftriaxone MICs of 2 mcg/mL [10]. In a third study including 270 ESBL-producing isolates from a US academic center, 5 isolates (2%) had ceftriaxone MICs of 2 mcg/mL [9]. Similarly, in our cohort, only 6 (1.6%) confirmed ESBL-producing isolates had ceftriaxone MICs of 2 mcg/mL. Taken together, available data indicate that while ESBL producers are likely to have ceftriaxone MICs in the nonsusceptible range, not all *Enterobacteriaceae* with ceftriaxone MICs in the nonsusceptible range are ESBL producers and only a small minority have ceftriaxone MICs of 2 mcg/mL. Furthermore, as a number of automated AST panels have the capability of accurately identifying ESBL production with little to no additional hands-on time, ESBL detection has become less labor-intensive than in the past, increasing the likelihood of detecting the infrequent ESBL-producing organism, with ceftriaxone MICs of 2 mcg/mL [11–13].

CLSI recommendations for antibiotic breakpoints generally assume package-insert dosages and intervals. Advancements in pharmacokinetic–pharmacodynamic modeling have shown that dosing and administration strategies (ie, higher doses, more frequent intervals, extended infusion, etc.) may allow successful target attainment goals for elevated antibiotic MICs. In January 2014, the CLSI adjusted the cefepime MIC susceptibility criteria in accordance with the dosing and interval of cefepime selected, based on supporting experimental and clinical data [2, 14]. In contrast, for ceftriaxone, "where possible, the lowest US FDA-approved dosage regimen (1 g IV every 24 hours) covering indications other than urinary tract infections was considered in setting the susceptibility breakpoint" [3]. In our cohort, most patients received ceftriaxone administered at 1 g every 24 hours, and limited numbers of patients with ceftriaxone MICs of 4 and 8 mcg/m received ceftriaxone for their entire treatment duration. Thus, we were unable to evaluate whether higher daily dosages of ceftriaxone or more frequent intervals would have led to favorable clinical outcomes for patients infected with *Enterobacteriaceae* with ceftriaxone MICs higher than 2 mcg/mL. Studies are needed from institutions that routinely use higher doses and more frequent intervals of ceftriaxone to determine if susceptible dose-dependent breakpoints should be a consideration for ceftriaxone MICs greater than 2 mcg/mL, and in the absence of ESBL production.

There are limitations to consider when interpreting our results. Although broth microdilution methods are generally accepted as the reference method for MIC determination [15], all 3 participating institutions in the current study—similar to most US clinical microbiology laboratories—used automated systems to determine AST results. Results from automated systems can be imprecise due to variability in test systems. Additionally, there is a generally accepted standard of error in reporting AST results of plus or minus 1 dilution [15]. Despite this, most clinicians interpret antibiotic MICs based on the reported results and do not account for the standard error in their clinical decision-making (ie, a ceftriaxone MIC of 1 mcg/mL is treated as susceptible and not as potentially 2 mcg/mL and "intermediate"). We sought to replicate real-world MIC interpretation and have no reason to believe that there was systemic misclassification of ceftriaxone MICs at any of the

participating hospitals. Furthermore, we were unable to determine whether the presence of ESBL production or the ceftriaxone MIC is more influential in the outcomes of patients infected with *Enterobacteriaceae* with ceftriaxone MICs of 2 mcg/mL who were ESBL-producing, given the small number of isolates meeting both criteria. This would be particularly relevant in regions with large proportions of ESBL-producing isolates with relatively low ceftriaxone MICs. Unfortunately, as this was a retrospective study, the possibility of missing data is a concern. We cannot exclude the possibility that patients returned to other facilities with bloodstream infections or passed away at other facilities. During the study period, the electronic health systems available in each facility did not enable access to medical records for patients hospitalized at outside facilities. We do not, however, have reason to believe that critical missing data would be more likely to occur in 1 study group vs the other.

Additionally, despite our use of propensity scores to account for differences in baseline characteristics between the treatment groups and the reassuring covariate balance within the matched pairs, unmeasured residual confounding may have still occurred. The ideal design for this study would have been a cluster randomized controlled study. However, this would prove challenging as most institutions have adopted the 2010 CLSI breakpoint recommendations and it would be difficult (and perhaps unethical) to randomize patients with *Enterobacteriaceae* bacteremia with ceftriaxone MICs of >1 mcg/mL to ceftriaxone therapy after susceptibility results are known. The 3 institutions participating in the present study currently use the 2010 CLSI recommended ceftriaxone breakpoints, but as the study period encompassed a few years before each of the institutions adapted the breakpoint changes, we were able to capture patients receiving ceftriaxone therapy at ceftriaxone MICs beyond the current susceptible range.

In conclusion, our findings suggest that patient outcomes are similar between those receiving ceftriaxone and those receiving extended-spectrum agents for the treatment of *Enterobacteriaceae* bloodstream infections with ceftriaxone MICs of 2 mcg/mL. We believe that adjusting the ceftriaxone susceptibility breakpoint from 1 to 2 mcg/mL warrants consideration. With the general rise in antibiotic MICs globally, a relatively small increase in an antibiotic breakpoint could have the potential to limit the use of large numbers of extended-spectrum antibiotic agents.

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