The Use of Cefepime for Treating AmpC β-Lactamase–Producing Enterobacteriaceae

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Background. AmpC β-lactamase–producing organisms are associated with significant morbidity and mortality. Induction of resistance to third-generation cephalosporins after exposure to these agents complicates treatment options and carbapenems are considered optimal therapy. The role of cefepime, however, remains unclear. Our objective was to compare clinical outcomes for patients receiving cefepime compared with meropenem for invasive infections caused by organisms expressing AmpC β-lactamases.

Methods. Hospitalized patients with blood, bronchoalveolar lavage, or intra-abdominal fluid cultures growing Enterobacter spp, Serratia spp, or Citrobacter spp were evaluated using the cefotetan–boronic acid disk test and the cefotetan–cloxacillin Etest to identify organisms with AmpC β-lactamase production from February 2010 to January 2011. In patients with organisms hyperproducing AmpC β-lactamases (positive by both methods), clinical outcomes for patients receiving cefepime or meropenem therapy were compared. To minimize the possibility of treatment selection bias, 1:1 nearest neighbor propensity score matching was performed prior to regression analysis.

Results. Of 399 patients meeting eligibility criteria, 96 (24%) had confirmed infections with AmpC β-lactamase–producing organisms. Propensity score matching of patients infected with AmpC β-lactamase–positive organisms treated with cefepime or meropenem yielded 32 well-balanced patient pairs with no difference in 30-day mortality (odds ratio, 0.63; 95% confidence interval [CI], .23–2.11; P = .36) or length of hospital stay after infection (relative risk, 0.96; 95% CI, .79–1.26; P = .56) between the 2 groups.

Conclusions. Cefepime may be a reasonable option for the treatment of invasive infections due to AmpC β-lactamase–producing organisms, particularly when adequate source control is achieved.

Keywords. AmpC β-lactamases; Enterobacter; gram-negative resistance; cefepime; boronic acid.
susceptibility of AmpC β-lactamase–producing organisms to ceftazidime using the current Clinical and Laboratory Standards Institute (CLSI) breakpoint of \( \leq 8 \, \mu g/mL \) \[13\]-\[15\]. Additionally, ceftazidime has a reduced affinity for β-lactamases and also appears to be a poor inducer of AmpC β-lactamases \[16\], \[17\]. However, in vitro studies also suggest that an inoculum effect exists and that ceftazidime may be a less reliable agent for the treatment of high inoculum infections caused by organisms expressing AmpC β-lactamases \[18\], \[19\]. The therapeutic effectiveness of ceftazidime compared with carbapenems has not been previously evaluated. With the growing need to preserve the existing armamentarium of antibiotics, particularly the broadest-spectrum agents currently available, carbapenems, the role of ceftazidime in the treatment of AmpC β-lactamase–producing organisms needs to be further explored. Our objective was to compare clinical outcomes of patients with invasive infections caused by AmpC β-lactamase–producing organisms treated with ceftazidime to those of patients treated with meropenem.

METHODS

Study Population
The Johns Hopkins Hospital is a 1059-bed tertiary care hospital in Baltimore, Maryland. All patients hospitalized at Johns Hopkins Hospital between 1 February 2010 and 31 January 2012 with bloodstream infections, pneumonia (confirmed by bronchoalveolar fluid cultures), or intra-abdominal infections (confirmed by intra-abdominal fluid cultures) growing Enterobacter spp, Serratia marcescens, or Citrobacter spp were eligible for inclusion. The microbiology laboratory prospectively identified patients after relevant cultures demonstrated growth of any of these organisms. Enterobacter spp, S. marcescens, and Citrobacter spp were targeted, as chromosomally-mediated AmpC β-lactamases have been best described for these organisms and we sought to make the most efficient use of available laboratory resources. Cultures were tested by 2 phenotypic methods (ceftotetan–boronic acid disk tests and ceftotetan–cloxacillin Etest strips) for the detection of AmpC β-lactamases as described below. Patients had to receive ceftazidime or meropenem as empiric therapy and for at least an additional 72 hours as definitive therapy to meet eligibility criteria. Additionally, isolates had to be susceptible in vitro to the agent prescribed. Patients who tested negative for AmpC β-lactamase production by at least 1 test were excluded from the clinical outcomes analysis. Because meropenem is the formulary carbapenem at Johns Hopkins Hospital, all patients receiving carbapenem therapy received meropenem. Antibiotic therapy was selected at the discretion of the treating physician, who was not aware of AmpC β-lactamase testing results at the time of antibiotic selection.

Pertinent demographic and clinical data were extracted from medical records for all patients meeting eligibility criteria. The primary outcome was 30-day all-cause mortality from the day of first positive culture, and the secondary outcome was length of hospital stay after first positive culture. The Johns Hopkins University School of Medicine Review Board, with a waiver of informed consent, approved the study \[20\] (NA_0046435).

Statistical Analysis
Patients prescribed ceftazidime may differ on some relevant baseline characteristics compared with patients prescribed meropenem; therefore, propensity score methods were used to ensure similarity of the 2 groups. Covariates included in the propensity score were age, previous history of a multidrug-resistant gram-negative organism within the past 12 months, organism isolated, duration of hospitalization from the time of admission to the time the first positive culture was obtained, intensive care unit admission, vasopressor requirement, or mechanical ventilation within 24 hours of the time the first positive culture was obtained, McCabe score, source control (central line removal or drainage of any infected fluid collections), and any immunosuppressive condition.

To match patients with similar propensity scores with exact matching for source control, 1:1 nearest neighbor matching without replacement was used. A matched-pair analysis was conducted using the matched samples. Patients who did not have a match within 0.25 propensity score standard deviations were excluded from the analysis. Pearson \( \chi^2 \) testing (Fisher’s exact test when appropriate) and Wilcoxon rank-sum tests were used to describe prematch data and McNemar test and the paired sample \( t \) test were used to analyze baseline characteristics between patients receiving ceftazidime and meropenem after matching. Covariate balance was evaluated by assessing standardized biases. In addition to antibiotic therapy, variables with standardized biases >0.25 were included in the regression outcome model (doubly robust model) to adjust for any residual bias and to increase precision. Logistic regression and linear regression were used to analyze the outcomes of 30-day mortality and length of hospital stay from first positive culture until discharge (which was normally distributed), respectively. Patients who died in the first 30 days were excluded from the length-of-stay analysis and only included in the mortality analysis. For all statistical tests, 2-sided \( P \) values <.05 were considered statistically significant. Data were analyzed using Stata software, version 12.0 (StataCorp, College Station, Texas) and the MatchIt Program, a component of the R Statistical package.

Definitions
Previous infection or colonization with a multidrug-resistant gram-negative organism was defined as any positive culture growing within the previous 12 months with an organism resistant to at least 1 agent in at least 3 of the following classes: (1) aminoglycosides, (2) antipseudomonal penicillins, (3) antipseudomonal penicillin β-lactamase inhibitors, (4) third-generation cephalosporins,
(5) aztreonam, or (6) carbapenems [21]. Patients were categorized as immunocompromised if they received a previous solid-organ transplant, bone marrow transplant within 12 months, or chemotherapy within the past 6 months; were infected with the human immunodeficiency virus; had a documented congenital immunodeficiency; received any immunomodulatory agents within the past 30 days; or received at least 10 mg of corticosteroids for >14 days.

**Laboratory Methods**

After standard microbiology testing was performed, phenotypic testing to detect AmpC β-lactamasases was conducted. Isolates were stored at −80°C between experiments. Molecular testing is diagnostic for organisms possessing plasmid-mediated AmpC β-lactamasases (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp) as these organisms are not expected to harbor genes for these enzymes when they do not express AmpC β-lactamasases [22]. However, as molecular testing is unable to differentiate between the presence of the genetic material for AmpC β-lactamase production vs actual enzyme expression, its role in detecting induced resistance mediated by chromosomal AmpC β-lactamasases is unclear and phenotypic testing is necessary. Testing with Etest strips and cefotetan–boronic acid disks were performed on all clinical isolates to test for high-level expression of AmpC β-lactamasases. Cefotetan–cloxacillin Etest strips and cefotetan–boronic acid disks take advantage of inhibition of AmpC β-lactamasases by cloxacillin and boronic acid, respectively [23]. Both methods have been reported to have sensitivities and specificities ranging from 88% to 100% compared to molecular testing for plasmid-mediated AmpC β-lactamasases and have the ability to distinguish AmpC β-lactamasases from extended-spectrum β-lactamasas (ESBLs) [24–28]. For the current study, only isolates testing positive by both methods were considered to have AmpC β-lactamase expression.

In brief, testing with Etest strips (bioMérieux, Durham, North Carolina) was conducted in real time as follows. A standardized inoculum of organism was swabbed onto a blood agar plate (BBL Trypticase Soy Agar plate with 5% sheep blood) and incubated for 24 hours in a 34°C–37°C ambient-air incubator. After vortexing and turbidity analysis, a single AmpC Etest strip, impregnated with a gradient of cefotetan 0.5–32 µg/mL on one end and cefotetan 0.5–32 µg/mL plus cloxacillin on the other end, was placed on the Mueller-Hinton agar plate with the inoculum. After a 24-hour period of incubation at 34°C–37°C, plates were assessed for antibiotic susceptibility per the manufacturer’s instructions [29].

All isolates were then tested using the cefotetan–boronic acid disk method. Disks containing 30 µg cefotetan and 120 mg of phenylboronic acid were placed on Mueller-Hinton agar that was inoculated with each isolate and incubated overnight at 34°C–37°C. A difference of the inhibition zones of cefotetan and boronic acid compared with cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was considered confirmation of cefotetan alone of ≥5 mm was confirmed by molecular testing. One of the authors (R.G.) conducted experiments with Etest strips and another author (A.A.R.) performed cefotetan–boronic acid testing. At the time of the testing, both investigators were blinded to antibiotic susceptibility results and the results of the other phenotypic test. For quality control, *K. pneumoniae* ATCC strain 700603 (negative control) and *K. pneumoniae* ATCC strain BAA-1144 (positive control) reference organisms were used for the Etest method and *E. coli* ATCC strain 25922 (negative control) and *Enterobacter cloacae* ATCC strain BAA-1143 (positive control) were used for the boronic acid test.

**RESULTS**

**Description of the Cohort**

Of the 399 patients evaluated with positive cultures for *Enterobacter* spp, *Citrobacter* spp, or *Serratia* spp, 96 (24%) had clinical isolates with AmpC β-lactamase–producing organisms positive by both Etest and boronic acid methods. Discrepancies were noted for 31 clinical isolates; these patients were excluded from the analysis (Figure 1). Of all isolates tested, 38%, 15%, and 1% of *Enterobacter* spp, *Serratia* spp, and *Citrobacter* spp, respectively, were positive for expression of AmpC β-lactamase production by both phenotypic methods (Table 1). There were no organisms producing AmpC β-lactamasases susceptible to ceftriaxone using the revised CLSI breakpoint (≤1 µg/mL). Ninety-six percent of AmpC β-lactamase–producing organisms were susceptible to cefepime (Figure 2). Of all AmpC β-lactamase producers, 97%, 22%, and 19% were susceptible to meropenem, piperacillin-tazobactam, and aztreonam, respectively.

**Baseline Characteristics**

There were 78 patients meeting eligibility criteria for the mortality analysis; 46 were prescribed cefepime and 32 were prescribed meropenem. All included patients were infected with organisms susceptible to their respective treatment agent and received appropriate drug dosing, as outlined in the Johns Hopkins Antibiotic Guidelines (1–2 g every 8 hours for both agents, adjusted for renal insufficiency) [30]. Notable differences in baseline characteristics existed between the 2 groups; patients receiving meropenem were more likely to have a greater number of preexisting medical conditions, to have a history of colonization or infection with a multidrug-resistant gram-negative organism, and to have compromised immune systems (Table 2). Propensity score matching yielded 32 matched pairs. Although balance improved for most covariates, the absolute standardized differences remained >0.25 for history of a multidrug-resistant gram-negative organism. In the matched patient pairs, all 24 bacteremic patients with central lines had central line removal during antibiotic therapy, and there were...
2 patients in each arm with undrained intra-abdominal fluid collections.

**Clinical Outcomes**

In the propensity score–matched cohort, there were 10 deaths (31.2%) and 11 deaths (34.3%) within 30 days for patients receiving cefepime and meropenem, respectively \((P = .99)\). In univariable analysis, the odds of mortality for patients receiving cefepime compared with meropenem were 0.60 \((95\% \text{ confidence interval } [CI], .23–2.31; P = .36)\) in the matched sample (Table 3). Not surprisingly, markers of severity of illness including intensive care unit admission, McCabe score in categories 2 or 3 compared to category 1, mechanical ventilation, and vasopressor requirement were independently associated with or had a trend towards a higher odds of 30-day mortality. Evaluating the matched pairs, there was no difference in 30-day mortality between patients prescribed cefepime or meropenem after adjusting for prior multidrug-resistant gram-negative organisms, as this covariate had a standardized bias >0.25 in the post-match cohort \((\text{odds ratio}, 0.63; 95\% \text{ CI}, .23–2.11; P = .36)\).

**Table 1. Proportion of Microorganisms Testing Positive by Both the Cefotetan–Cloxacillin Etest and Cefotetan–Boronic Acid Disk Test for AmpC \(\beta\)-Lactamase Production**

<table>
<thead>
<tr>
<th>Organisms ((n = 399))</th>
<th>AmpC (\beta)-Lactamase Positive, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacter</em> spp ((n = 213))</td>
<td>82 (38%)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em> ((n = 131))</td>
<td>51</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em> ((n = 77))</td>
<td>31</td>
</tr>
<tr>
<td><em>Enterobacter asburiae</em> ((n = 3))</td>
<td>0</td>
</tr>
<tr>
<td><em>Enterobacter hormaechei</em> ((n = 2))</td>
<td>0</td>
</tr>
<tr>
<td><em>Serratia marcescens</em> ((n = 86))</td>
<td>13 (15%)</td>
</tr>
<tr>
<td><em>Citrobacter</em> spp ((n = 100))</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em> ((n = 70))</td>
<td>1</td>
</tr>
<tr>
<td><em>Citrobacter koseri</em> ((n = 30))</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 1.** Design of a study comparing clinical outcomes of patients with AmpC \(\beta\)-lactamase–producing organisms who received cefepime therapy vs meropenem therapy. Several patients met >1 exclusion criteria.

**Figure 2.** Distribution of cefepime minimum inhibitory concentrations of 96 AmpC \(\beta\)-lactamase–producing organisms and 272 organisms not producing AmpC \(\beta\)-lactamase from blood, bronchoalveolar lavage fluid, and intra-abdominal fluid isolates. Black bars represent organisms expressing AmpC \(\beta\)-lactamases based on positive testing by both the cefotetan–cloxacillin Etest and cefotetan–boronic acid disk testing, and gray bars represent organisms not expressing AmpC \(\beta\)-lactamases based on negative results by both methods. Thirty-one patients with discrepant results by Etest and boronic acid were excluded.
Excluding patients who died within 30 days from when the first positive culture was obtained, the median duration of hospital stay from the time of first positive culture to discharge was 12.6 days for patients receiving cefepime and 14.6 days for patients receiving meropenem in the matched cohort (P = .63). In the doubly robust model, the length of stay from the time of infection for patients who received cefepime was not statistically different from patients prescribed meropenem (relative risk, 0.96; 95% CI, .79–1.26; P = .56).

Sixteen patients in the cohort (25%) had a positive culture from any source within 30 days of the initial positive culture growing the same species. None of the patients treated with meropenem had a meropenem-resistant organism on subsequent culture. One patient treated with cefepime for an E. cloacae pneumonia (cefepime minimum inhibitory concentration [MIC] = 2 µg/mL) had a corneal culture 6 days after initiating cefepime therapy growing E. cloacae with a cefepime MIC of 16 µg/mL.

**DISCUSSION**

Our results suggest that cefepime may be a therapeutic option for invasive infections caused by AmpC β-lactamase–producing organisms. A number of investigators have demonstrated higher mortality, longer hospital lengths of stay, and higher hospital costs for patients infected with AmpC β-lactamase–producing organisms compared with susceptible isolates of the same organisms; thus, optimal treatment of these pathogens is essential [2–5, 7, 31]. We evaluated 32 propensity-score matched pairs of patients receiving cefepime compared with meropenem for invasive infections with confirmed AmpC β-lactamase–producing organisms, and found no significant difference in mortality or length of hospital stay between the 2 groups. Although previous studies have indicated that third-generation cephalosporins appear to be suboptimal choices for treating infections caused by pathogens producing AmpC β-lactamases, the role of cefepime has been unsettled and many experts recommend resorting to carbapenem therapy, which appear to have both excellent in vitro and in vivo activity against these organisms [1, 3, 5, 6, 9, 10, 32]. However, widespread use of carbapenems would likely exacerbate our current multidrug-resistant gram-negative organism crisis [33].

Cefepime, with its dipolar charge, has the advantage of penetrating bacterial outer membranes more rapidly than third-generation cephalosporins, readily reaching its target and avoiding β-lactamase inactivation [34]. Additionally, it has a reduced affinity for β-lactamases and appears to be a poor inducer of

### Table 2. Baseline Characteristics of Patients Infected With AmpC β-Lactamase–Producing Organisms Treated With Cefepime Compared to Meropenem

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Overall Cohort (n = 78)</th>
<th>Propensity-Matched Cohort (n = 64)</th>
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<tbody>
<tr>
<td></td>
<td>Cefepime (n = 46)</td>
<td>Meropenem (n = 32)</td>
</tr>
<tr>
<td></td>
<td>Age, y, mean (SD)</td>
<td>51.2 (25.9)</td>
</tr>
<tr>
<td></td>
<td>Duration of hospitalization before positive culture, d, mean (SD)</td>
<td>12.8 (17.0)</td>
</tr>
<tr>
<td></td>
<td>Previous MDRGNa</td>
<td>10.4%</td>
</tr>
<tr>
<td></td>
<td>McCabe score, categories 2–3</td>
<td>42.8%</td>
</tr>
<tr>
<td></td>
<td>Intensive care unit stay</td>
<td>42.7%</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation</td>
<td>29.2%</td>
</tr>
<tr>
<td></td>
<td>Vasopressors</td>
<td>22.9%</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised</td>
<td>29.2%</td>
</tr>
<tr>
<td></td>
<td>Bacteremia</td>
<td>47.9%</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>58.3%</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal infection</td>
<td>43.8%</td>
</tr>
<tr>
<td></td>
<td>Enterobacter spp infection</td>
<td>85.4%</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td>Liver disease</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>Lung disease</td>
<td>8.3%</td>
</tr>
<tr>
<td></td>
<td>Renal disease</td>
<td>56.3%</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>35.4%</td>
</tr>
<tr>
<td></td>
<td>Neurological disease</td>
<td>27.1%</td>
</tr>
</tbody>
</table>

Abbreviations: MDRGN, multidrug-resistant gram-negative organism; SD, standard deviation.

* Previous colonization or infection with an MDRGN within the past 12 months.
AmpC β-lactamases [16, 17]. In vitro susceptibility results of ceftazidime in our cohort mirror those of other groups with close to 100% susceptibility for organisms intermediate or resistant to third-generation cephalosporins [13–15].

Soon after the introduction of ceftazidime, there was report of the emergence of resistance to ceftazidime during treatment of a liver abscess growing Enterobacter aerogenes [19]. A subsequent in vitro study demonstrated excellent ceftazidime susceptibility for a conventional inoculum but a dramatic increase in ceftazidime MICs when a 100-fold higher inoculum was used. The authors suggested caution when prescribing ceftazidime for high-inoculum infections with potential AmpC β-lactamase producers as organisms may test susceptible in vitro but may be ineffective in vivo [18]. However, uncertainty remained as to whether the in vitro phenomenon of an inoculum effect translated to clinical failure with ceftazidime. In murine infections with Enterobacter and Citrobacter spp, emergence of resistance was rare in ceftazidime-treated animals but occurred in substantial proportions of animals treated with third-generation cephalosporins [35, 36]. In a study of 16 patients with Enterobacter spp with reduced susceptibility to third-generation cephalosporins, no emergence of resistance to ceftazidime was observed [37]. Similarly, in cohorts of 477 patients and 20 patients with susceptible Enterobacteriaceae, antecedent ceftazidime use was not associated with the emergence of resistance [8, 38]. A recent study demonstrated approximately 90% success rate when ceftazidime was used to treat 17 E. cloacae AmpC β-lactamase-producing bloodstream infections [39].

The most common cause of AmpC β-lactamase overexpression in clinical isolates is a mutation in a cytoplasmic enzyme leading to AmpC hyperproduction [40]. In many Enterobacteriaceae, AmpC β-lactamase expression is low but may be induced in response to β-lactam exposure, particularly third-generation cephalosporins, a phenomenon best described for Enterobacter spp [5]. In our cohort, 38% of Enterobacter isolates produced AmpC β-lactamases. Studies from 1991 and 2001 reported 19% emergence of Enterobacter spp resistance to third-generation cephalosporins during therapy [7, 8]. Although the higher prevalence seen in our study suggests that resistance to third-generation cephalosporins may be increasing, the lowering of the CLSI breakpoint for third-generation cephalosporins against Enterobacteriaceae in 2010 may be a contributing factor [41].

Our results suggest that AmpC β-lactamase production is less of a concern for Serratia spp and Citrobacter spp, at 15% and 1%, respectively [42, 43]. A study evaluating 76 patients with infections caused by S. marcescens or C. freundii identified emergence of resistance to third-generation cephalosporins in 3% of patients infected with C. freundii; no resistance was observed in isolates of S. marcescens [38]. Other studies identified emergence of third-generation cephalosporin resistance for Citrobacter spp and S. marcescens to be 0% and 7%, respectively [42, 43].

As phenotypic testing for detection of AmpC β-lactamases was limited in the past, resistance to third-generation cephalosporins was used as a proxy for induced resistance mediated by AmpC β-lactamases in the aforementioned studies. The CLSI advises that resistance to third-generation cephalosporins can emerge and encourages monitoring susceptibility results in subsequent isolates of organisms potentially harboring this mechanism of resistance, but there are no recommendations for routine AmpC β-lactamase testing [44]. Although techniques...
to identify AmpC β-lactamase–producing organisms are increasingly available, it is unclear if there is a benefit for clinical microbiology laboratories to identify these mechanisms of resistance on a routine basis. First, if an organism tests negative to AmpC β-lactamase production, it does not exclude the possibility of resistance emerging upon exposure to therapy. Second, it appears prudent for clinicians to avoid third-generation cephalosporins for septic patients with Enterobacter spp infections even in the absence of confirmation of AmpC β-lactamase production because of the relatively high prevalence of third-generation cephalosporin resistance in these organisms. Perhaps if susceptibility reports for Enterobacter spp obtained from invasive sites conceal third-generation cephalosporin results, clinicians will avoid prescribing potentially suboptimal agents for serious infections. Our study suggests that as with carbapenems, AmpC β-lactamase–producing organisms tend to retain susceptibility to cefepime and these are reasonable options for invasive infections expressing this resistance mechanism, when cefepime is administered every 8 hours.

There are some potential limitations to this study. First, the sample size was small, making a type II error a concern. However, both statistical approaches—the unadjusted analyses of the matched cohort and the doubly robust model—revealed similar point estimates, underlining the consistency of our findings. With traditional multivariable regression techniques, models become unstable when the sample size is small and the number of covariates included in the model is large relative to the number of outcome events. Matching on propensity scores, however, allows adjustment of many covariates without overloading subsequent regression models for the association between the exposure of interest and a rare outcome [45]. Second, our results were from a single center and prevalence of hyperproduction of inducible chromosomal AmpC β-lactamases likely varies across institutions, making it difficult to generalize our patients’ prevalence of derepressed AmpC β-lactamases to those in other institutions. However, our results are in accord with previous data recognizing Enterobacter spp as the organisms most concerning for inducible chromosomally mediated AmpC β-lactamases [7, 8]. Third, as the vast majority of patients in our matched cohort (>93%) had adequate source control, we are unable to make inferences about patients who did not have central line removal or drainage of fluid collections. The likelihood of selection for resistant derepressed mutants and subsequent clinical failure may vary if source control is not achieved.

Our results may be limited in that we do not have knowledge of ESBL status of the isolates tested. Some AmpC β-lactamase–producing organisms coharbor ESBLs. This appears particularly true for plasmid-mediated AmpC β-lactamase–producing organisms such as E coli, Klebsiella spp, and Salmonella spp, in which coexistence of these resistance mechanisms has been described at approximately 5% [22]. Because organisms such as Enterobacter spp, Citrobacter spp, and S marcescens have been shown to have a low prevalence of ESBL production [1], we do not routinely test them for ESBL production in our microbiology laboratory. To our knowledge, there are no clinical laboratories in the United States routinely testing Enterobacter spp, Citrobacter spp, or Serratia spp with elevated MICs to third-generation cephalosporins for ESBL production. As the anticipated ESBL production for these organisms in our cohort would be low, baseline characteristics were similar in the matched cohort making ESBL distribution likely equal between both treatment groups (if at all present), and physicians treating patients in this study would not have knowledge of the ESBL status of the current infectious pathogen to influence antibiotic selection, coexpression of ESBLs are unlikely to have changed our results.

In summary, our results suggest that cefepime may be an exception to the recommendation to avoid all cephalosporin therapy for invasive infections caused by AmpC β-lactamase–producing organisms or even organisms with the potential for induction. Because of our study’s small sample size, our findings need to be repeated in a larger, prospective, multicenter study. Although the development of resistance and subsequent treatment failure upon exposure to cefepime therapy may be negligible compared to resistance to third-generation cephalosporins, as infections by these organisms can result in significant morbidity and mortality, prudence while on cefepime therapy may still be necessary, particularly if source control is not achieved (eg, central lines retained, fluid collection not drained).

Notes

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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.

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