3-1-2023

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MAJOR ARTICLE

High-dose Cefepime vs Carbapenems for Bacteremia Caused by Enterobacterales With Moderate to High Risk of Clinically Significant AmpC β-lactamase Production

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Background. Limited data suggest that serious infections caused by Enterobacterales with a moderate to high risk of clinically significant AmpC production can be successfully treated with cefepime if the cefepime minimum inhibitory concentration (MIC) is ≤2 μg/mL. However, isolates with a cefepime-susceptible dose-dependent (SDD) MIC of 4–8 μg/mL should receive a carbapenem due to target attainment and extended-spectrum β-lactamase (ESBL) concerns.

Methods. This was a retrospective cohort study of hospitalized patients with *E. cloacae*, *K. aerogenes,* or *C. freundii* bacteremia from January 2015 to March 2022 receiving high-dose cefepime or a carbapenem. Cox regression models were used with incorporation of inverse probability of treatment weighting and time-varying covariates.

Results. Of the 315 patients included, 169 received cefepime and 146 received a carbapenem (ertapenem n = 90, meropenem n = 56). Cefepime was not associated with an increased risk of 30-day mortality compared with carbapenem therapy (adjusted hazard ratio [aHR], 1.45; 95% CI, 0.79–2.14), which was consistent for patients with cefepime SDD isolates (aHR, 1.19; 95% CI, 0.52–1.77). Multivariable weighted Cox models identified Pitt bacteremia score >4 (aHR, 1.41; 95% CI, 1.04–1.92), deep infection (aHR, 2.27; 95% CI, 1.21–4.32), and ceftriaxone-resistant AmpC-E (aHR, 1.32; 95% CI, 1.03–1.59) to be independent predictors associated with increased mortality risk, while receipt of prolonged-infusion β-lactam was protective (aHR, 0.67; 95% CI, 0.40–0.89).

Conclusions. Among patients with bacteremia caused by Enterobacterales with moderate to high risk of clinically significant AmpC production, these data demonstrate similar risk of 30-day mortality for high-dose cefepime or a carbapenem as definitive β-lactam therapy.

Keywords. ampC β-lactamase-producing Enterobacterales; antimicrobial stewardship; bacteremia; carbapenem; cefepime; propensity score; time-varying analysis.

Gram-negative infections pose serious therapeutic problems due to rising antimicrobial resistance, which caused >2.8 million infections and 35 000 deaths annually in the United States from 2012 to 2017 [1]. Several Enterobacterales spp. contain chromosomally encoded and inducible *ampC* genes, with *E. cloacae*, *K. aerogenes*, and *C. freundii* demonstrating a moderate to high risk for clinically significant inducible AmpC production (AmpC-E) [2]. Exposure of these bacteria to certain β-lactam antibiotics, even if they demonstrate initial in vitro susceptibility, can induce *ampC* gene expression, which may lead to clinical failure [3].

Due to growing concern regarding increased selection of carbapenem-resistant organisms, noncarbapenem treatment strategies have been explored [4]. Cefepime, a weak *ampC* inducer, withstands hydrolysis via formation of a stable acyl enzyme complex [5]. Retrospective studies have shown that cefepime has efficacy similar to that of carbapenems for the treatment of *Enterobacter* spp. bacteremia [6, 7]. However, limited data highlighting treatment-emergent cefepime resistance and concerns about diminished cefepime efficacy for the treatment of cefepime-susceptible dose-dependent (SDD) AmpC-E isolates (cefepime minimum inhibitory concentration [MIC] 4–8 μg/mL) lend hesitancy to its use [8, 9].

Concerns of diminished cefepime efficacy for the treatment of SDD AmpC-E arose, in part, from failure of cefepime to meet

Received 11 January 2023; editorial decision 16 January 2023; accepted 23 January 2023; published online 25 January 2023

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https://doi.org/10.1093/ofid/ofad034

necessary pharmacodynamic targets secondary to inadequate dosing and/or interval schedules [10–12]. Reese and colleagues demonstrated this by showing that cefepime 2 g every 12 hours failed to achieve target attainment of 50% free drug concentration greater than the MIC ($fT > MIC$) with cefepime MICs of 8 and 16 μg/mL [13]. Based on similar pharmacodynamic/pharmacokinetic (PK/PD) data as well as limited clinical experience with Enterobacterales infections, the Clinical Laboratory and Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) revised cephalosporin susceptibility breakpoints, increased the recommended total daily dose of cefepime for Enterobacterales SDD isolates, and removed the requirement for ESBL phenotype detection [14–16]. Following guideline updates, an observational study demonstrated better outcomes with carbapenems compared with cefepime in patients with *E. cloacae* bacteremia; however, there were limited data on the use of high-dose cefepime [17].

Considering the limited available data, the Infectious Diseases Society of America (IDSA) Guidance on the Treatment of Antimicrobial-Resistant Gram-negative Infections suggests that infections caused by AmpC-E can be successfully treated with cefepime, with the caveat that cefepime SDD AmpC-E isolates have a higher likelihood of being extended-spectrum β-lactamase (ESBL) producers and, thus, should preferentially be treated with a carbapenem as cefepime is considered suboptimal [18]. Still, due to sparse data from heterogeneous PK/PD and retrospective observational studies, in addition to the lack of routine ESBL screening for Enterobacterales spp. other than *E. coli* and *K. pneumoniae*, questions remain pertaining to the treatment of AmpC-E bacteremia [6, 19–23]. As such, the purpose of this study was to evaluate outcomes in patients with AmpC-E bacteremia receiving high-dose cefepime or a carbapenem as definitive β-lactam therapy.

METHODS

This retrospective cohort study evaluated hospitalized adult patients with *E. cloacae*, *K. aerogenes*, or *C. freundii* bacteremia between January 2015 and March 2022 at 2 urban academic medical centers in Detroit, Michigan, receiving either high-dose cefepime or a carbapenem (meropenem or ertapenem) as definitive therapy. High-dose cefepime was defined as 2 g every 8 hours, while meropenem and ertapenem were dosed 1–2 g every 8 hours and 1 g every 24 hours, respectively. Renally adjusted equivalents and prolonged infusions were administered as appropriate. An additional inclusion criterion was receipt of ≥48 hours of cefepime or carbapenem therapy within 48 hours of index blood culture collection. Patients were excluded if they transferred in from an outside facility with AmpC-E blood culture, were prisoners, pregnant or breastfeeding, had cancer with an Eastern Cooperative Oncology Group (ECOG) score of 3 or 4 [24], had a concomitant infection with in vitro resistance to both cefepime and carbapenem therapy, or if they died or transferred to hospice or an outside facility within 72 hours of index blood culture collection. Although not recommended as definitive therapy by current treatment guidance [18], patients receiving ≤1 dose of ceftriaxone as active empiric therapy were included in the study as it is used in this manner at both study sites, as appropriate.

The primary outcome was mortality within 30 days of index blood culture collection. Microbiological failure (positive blood culture with index organism at ≥48 hours post–initiation of in vitro active agent with documented source control), microbiological relapse (growth of index organism in blood culture following negative blood culture), hospital and intensive care unit (ICU) length of stay (LOS), and 30-day infection-related readmission were also evaluated.

Patient demographics and baseline characteristics were extracted from the electronic health record (EHR) and entered into Research Electronic Data Capture (REDCap) [25]. Comorbidity burden was estimated by the Charlson comorbidity index, and measures of organ function and illness severity were assessed as described by the highest Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Pitt bacteremia score within 48 hours before or on the day of index culture collection [26]. A second Pitt bacteremia score was collected at 48 ± 24 hours of definitive antibiotic therapy initiation to assess clinical response to definitive therapy. All isolates were identified by clinical microbiology laboratories located within the 2 study centers. Susceptibility testing was performed via the Phoenix (BD) or Vitek-2 system (bioMerieux). Regarding hospital guidelines/protocols in place to limit or direct therapeutic selection for AmpC-E blood isolates, 1 of the 2 sites included in their EHR report of microbiological and antimicrobial susceptibility test results that third-generation cephalosporins are not preferred due to the risk of treatment-emergent resistance.

Based on limited subpopulation analyses evaluating high-dose cefepime and carbapenem therapy for infections caused by AmpC-E, conservative estimates of 15% and 60% mortality were anticipated for the cefepime cohort as a whole and those receiving cefepime for cefepime SDD isolates, respectively. Therefore, a total sample size of at least 224 patients, with 60/224 (26.8%) of those patients having cefepime SDD isolates, was determined a priori to achieve 85% power at the 95% confidence level. Nominal variables were compared using the Pearson chi-square test or Fisher exact test. Ordinal and continuous variables were analyzed using the Mann-Whitney *U* test and Student *t* test for nonparametric and parametric data, respectively.

To address nonrandomized allocation of β-lactam therapy, propensity scores were calculated by multivariable logistic

regression to estimate the binary outcome of each patient's probability of receiving cefepime or a carbapenem as definitive therapy. The following covariates were included in the generation of the propensity score due to their statistical difference between groups of $P \leq .1$: admitted from home, referral from clinic, APACHE II score, first active empiric therapy (cefepime, ertapenem, or meropenem), and surgical source control procedure. Using the propensity scores, inverse probability of treatment weighting (IPTW) was applied to create a study pseudo population, balanced for potential covariate bias. Patients receiving cefepime were weighted by the inverse probability of being treated with cefepime while patients receiving a carbapenem were weighted by the inverse probability of being treated with a carbapenem, equivalent to 1 minus the patient's propensity score [27, 28]. Covariate balance by propensity score was assessed with the Kolmogorov-Smirnov (KS) goodness-of-fit statistic and standardized mean differences (SMDs), as appropriate. The prediction ability of the propensity score model was assessed with an area under the receiver operating characteristic (AU-ROC) curve. The primary end point, 30-day mortality, was analyzed for each the unadjusted and IPTW pseudo population using a Cox proportional hazards model with time-varying covariates. The time-varying Cox proportional hazards model accounts for immortal time bias and allows for an assessment of risk associated with variations in the time elapsed from index culture collection to initiation of active empiric and definitive β-lactam therapy between groups. All variables associated with 30-day mortality in univariate analysis with a P value ≤.1, present in ≥10% of all cases, and not already included in the propensity score model were considered for inclusion in the multivariable Cox regression. All tests were 2-tailed, with a P value of ≤.05 considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). This study was reviewed and approved by the Wayne State University and Henry Ford Health System institutional review boards and the Detroit Medical Center's research committee.

RESULTS

In total, 656 patients with positive AmpC-E blood receiving antibiotic treatment were screened for study inclusion, with 315 fulfilling inclusion criteria (cefepime n = 169, carbapenem n = 146) (Figure 1). The median (interquartile range [IQR]) age was 63 (53–74.5) years, 55.2% were male, and 59% were admitted to the ICU at least once during the hospital admission (Table 1). Treatment characteristics are outlined in Table 2. In unadjusted and weighted Cox regression analysis with IPTW and time-varying covariates, cefepime was not associated with an increased risk of 30-day mortality compared with a carbapenem (18.9% vs 17.1%, respectively; adjusted hazard ratio [aHR], 1.45; 95% CI, 0.79–2.14) (Table 3). This finding was consistent for patients with cefepime SDD isolates (aHR, 1.19; 95% CI, 0.52–1.77). Multivariable weighted Cox models identified Pitt bacteremia score >4 (aHR, 1.41; 95% CI, 1.04–1.92), deep infection (aHR, 2.27; 95% CI, 1.21–4.32), and ceftriaxone-resistant AmpC-E (aHR, 1.32; 95% CI, 1.03–1.59) to be independent predictors associated with increased mortality risk, while receipt of prolonged-infusion β-lactam was protective (aHR, 0.67; 95% CI, 0.40–0.89) (Table 4). The weighted standardized differences were below the 0.1 threshold for all investigated covariates (Supplementary Figure 1). An area under

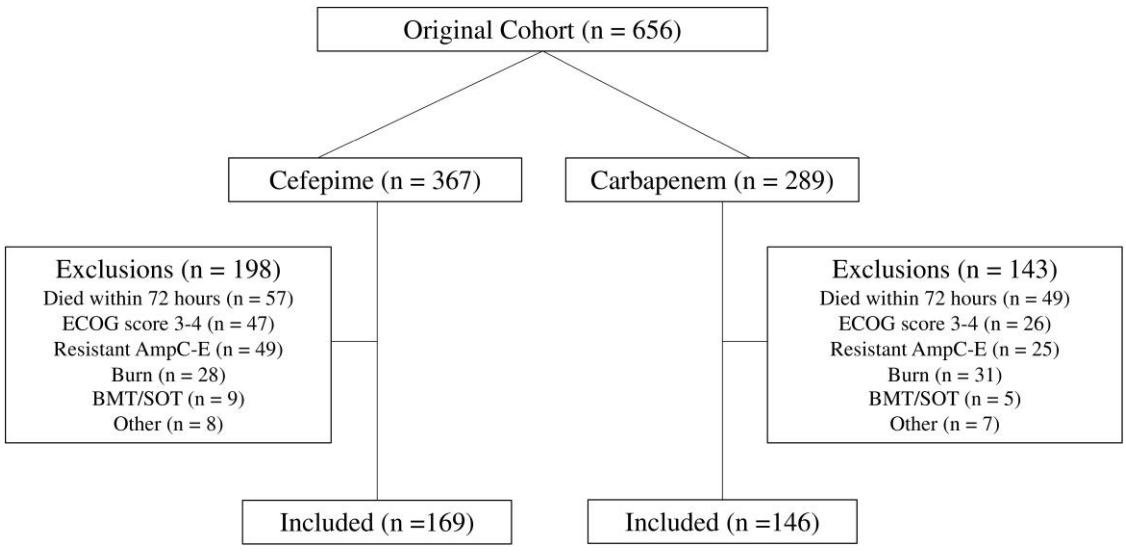

Figure 1. Study flow diagram of patient enrollment. Abbreviations: AmpC-E, AmpC-producing Enterobacterales; BMT, bone marrow transplant; ECOG, Eastern Cooperative Oncology Group; SOT, solid organ transplant.

Table 1. Baseline Characteristics

Characteristics[a]	Total (n = 315)	Cefepime (n = 169)	Carbapenem (n = 146)	*P* Value
Age, y	63 (53–74.5)	64.5 (55–77)	62 (53–71.8)	.182
Male	174 (55.2)	94 (55.6)	80 (54.8)	.883
Race				
African American	158 (50.2)	83 (49.1)	75 (51.4)	.689
Caucasian	128 (40.6)	74 (43.8)	54 (37)	.220
Other/unknown	29 (9.2)	12 (7.1)	17 (11.6)	.164
BMI, kg/m^2	27.3 (22.8–33.3)	26.4 (22.8–33.8)	27.7 (23–33.1)	
Admitted from				
Home	242 (76.8)	137 (81.1)	105 (71.9)	.055
NH/LTCF	34 (10.8)	19 (11.2)	15 (10.3)	.782
LTAC	3 (1)	1 (0.6)	2 (1.4)	.598
Referral from clinic	16 (5.1)	3 (1.8)	13 (8.9)	.005
Transfer from hospital	20 (6.3)	9 (5.3)	11 (7.5)	.491
Charlson comorbidity index	5 (3–8)	5 (3–8)	5 (3–7)	.692
Immunocompromised[b]	71 (22.5)	39 (23.1)	32 (21.9)	.893
AmpC-E previously isolated	17 (5.4)	8 (4.7)	9 (6.2)	.575
Antibiotic(s) received for ≥24 h in 90 d before hospitalization	137 (43.5)	68 (40.2)	69 (47.3)	.209
Admitting service				
Internal medicine	135 (42.9)	79 (46.7)	56 (38.4)	.134
ICU	120 (38.1)	60 (35.5)	60 (41.1)	.281
Surgery	38 (12.1)	19 (11.2)	19 (13)	.631
Hospitalist	15 (4.8)	8 (4.7)	7 (4.8)	.967
Other	7 (2.2)	3 (1.8)	4 (2.7)	.629
ICU admission during hospitalization	186 (59)	95 (56.2)	91 (62.3)	.271
In the ICU within 24 h of culture collection	160 (50.8)	84 (49.7)	76 (52.1)	.677
Hospital-acquired infection[c]	94 (29.8)	44 (26)	50 (34.2)	.112
Duration of hospitalization before index positive culture collection, d	3 (1.5–10)	2.5 (2–7)	3.5 (1.5–12)	.358
SOFA score	4 (2–7)	4 (2–7)	4.5 (3–6)	.934
APACHE II score	21 (15–25)	23 (16–26)	20 (14–23)	.089
Pitt bacteremia score (initial)	3 (2–5)	3 (2–6)	3 (1–4)	.435
Pitt bacteremia score (follow-up)[d]	2.5 (1–4)	3 (1–4)	2 (1–3)	.146
On ventilator at culture collection	51(16.2)	24 (14.2)	27 (18.5)	.302
Septic shock at culture collection[e]	26 (8.3)	17 (10.1)	9 (6.2)	.210
AmpC-E in blood				
Enterobacter cloacae	159 (50.5)	89 (52.7)	70 (47.9)	.404
Klebsiella aerogenes	78 (24.8)	40 (23.7)	38 (26)	.629
Citrobacter freundii	78 (24.8)	40 (23.7)	38 (26)	.629
AmpC-E cefepime MIC				
4–8 µg/mL	99 (31.4)	48 (28.4)	51 (34.9)	.213
≤2 µg/mL	216 (68.6)	121 (71.6)	95 (65.1)	.213
Polymicrobial blood culture	79 (25.1)	48 (28.4)	31 (21.2)	.143
AmpC-E isolated from nonblood source	92 (29.2)	46 (27.2)	46 (31.5)	.404
Bone	15 (4.8)	6 (3.6)	9 (6.2)	.277
Internal organ abscess	6 (1.9)	4 (2.4)	2 (1.4)	.689
Respiratory	27 (8.6)	15 (8.9)	12 (8.2)	.836
Skin and skin structure	12 (3.8)	4 (2.4)	8 (5.5)	.237
Urine	24 (7.6)	14 (8.3)	10 (6.8)	.632
Other	8 (2.5)	3 (1.8)	5 (3.4)	.479
Primary source of infection				
Bone and joint	42 (13.3)	22 (13)	20 (13.7)	.859
IV catheter	55 (17.5)	29 (17.2)	26 (17.8)	.879
Skin and skin structure	40 (12.7)	19 (11.2)	21 (14.4)	.404
Intra-abdominal	45 (14.3)	25 (14.8)	20 (13.7)	.782
Respiratory/pneumonia	79 (25.1)	42 (24.9)	37 (25.3)	.920
Urinary	30 (9.5)	17 (10.1)	13 (8.9)	.728
Other/unknown	24 (7.6)	15 (8.9)	9 (6.2)	.366

Table 1. Continued

Characteristics[a]	Total (n = 315)	Cefepime (n = 169)	Carbapenem (n = 146)	*P* Value
Deep infection[f]	79 (25.1)	37 (21.9)	42 (28.8)	.160

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation (II score); AmpC-E, AmpC-producing Enterobacterales; BMI, body mass index; ICU, intensive care unit; IV, intravenous; LTAC, long-term acute care facility; NH/LTCF, nursing home/long-term care facility; MIC, minimum inhibitory concentration; SOFA, Sequential Organ Failure Assessment.

[a]Data are presented as No. (%) or median (interquartile range), as appropriate.

[b]Immunocompromised: any chemo or radiation therapy within 30 days, HIV/AIDS with CD4 <200, or chronic steroids (equivalent to >40 mg prednisone).

[c]Hospital-acquired infection: index positive blood culture collected 48 hours after hospital admission.

[d]Follow-up Pitt bacteremia score: highest score collected 48 ± 24 hours after definitive antibiotic therapy initiation.

[e]Septic shock at index culture collection: sepsis associated with a systolic blood pressure <90 mm Hg and the need for intravenous hydration and vasopressors for blood pressure resuscitation.

[f]Deep infection: endocarditis, septic pulmonary emboli, osteomyelitis, and hepatic or muscular abscesses presumed to be caused by the AmpC-E blood isolate based on provider documentation and imaging results in the electronic medical record.

the receiver operating curve (AU/ROC) illustrated the model's predictive sensitivity and specificity for AmpC-E cases of 30-day mortality with an AU/ROC of 84.9% (Supplementary Figure 2).

DISCUSSION

This study reported clinical outcomes in hospitalized adult patients infected with AmpC-E blood isolates with moderate to high risk for clinically significant inducible AmpC production treated with high-dose cefepime or carbapenem therapy, as previously described. Upon assessment of the primary outcome, cefepime was not associated with an increased risk of 30-day mortality compared with a carbapenem in both unadjusted and propensity score–weighted Cox regression models with time-varying covariates, which was consistent when comparing patients with cefepime SDD vs cefepime-susceptible isolates. These findings differ from those reported in a 2015 observational study by Lee et al. comparing clinical outcomes in patients infected with ceftriaxone-nonsusceptible cefepime SDD *E. cloacae* isolates and treated with cefepime or carbapenem therapy, which identified increased 30-day mortality in patients treated definitively with cefepime [17]. The authors concluded that cefepime may be considered for infections caused by cefepime-susceptible *E. cloacae* isolates; however, cefepime should be used cautiously for cefepime SDD *E. cloacae* infections. Notably, only 38.9% of patients in that study received high-dose cefepime as definitive therapy compared with 100% of cefepime patients in the current study [17]. To our knowledge, only 1 observational study evaluating cefepime for the treatment of ESBL-producing Enterobacterales included patients receiving cefepime in 8-hour intervals. In that study, inferior outcomes were reported for cefepime compared with carbapenems; however, only 12 patients received cefepime 2 g every 8 hours, and the patients had infections caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *P. mirabilis* infections [29].

Results of the weighted multivariable Cox regression analysis identified the following factors to be independently associated with 30-day mortality: Pitt bacteremia score >4, deep infections, and ceftriaxone-resistant AmpC-E isolates. The association of higher Pitt bacteremia score leading to increased odds of mortality aligns with previous literature, including studies evaluating outcomes in patients with AmpC-E bacteremia [17, 26, 30]. The finding of increased odds of 30-day mortality when treating high-inoculum infections (ie, deep infections) with cefepime or a carbapenem has been heavily debated in recent decades [31]. Studies that evaluated the phenomenon of attenuated antibacterial activity at high bacterial inoculum, referred to as the inoculum effect, demonstrated that cephalosporins, and to a lesser extent carbapenems, were less susceptible and had diminished efficacy at higher bacterial inoculums [32–35]. In a study by Burgess et al., cefepime and meropenem were evaluated against *K. pneumonia* standard and high-inoculum infections. The authors identified that although bactericidal activity for both antibiotics remained the same at standard inoculums, only meropenem sustained bactericidal activity at higher inoculums [36]. Notably, all *K. pneumoniae* isolates in that study were ESBL-producing, and literature evaluating the inoculum effect between cefepime and meropenem for non-ESBL and ESBL-producing AmpC-E is scant.

Another debated topic regarding AmpC-E is whether carbapenems are necessary for infections caused by all ceftriaxone-resistant Enterobacterales spp. In the current study, ceftriaxone-resistant isolates were independently associated with 30-day mortality in multivariable Cox regression analysis. According to the IDSA, carbapenems are the preferred drugs for moderate to severe infections caused by ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* of which a ceftriaxone MIC of ≥2 μg/mL can be used as a proxy for ESBL production [18]. While most *E. coli*–, *K. pneumoniae*–, *K. oxytoca*–, or *P. mirabilis*–producing ESBLs have ceftriaxone MIC ≥2 μg/mL, data evaluating ceftriaxone resistance and ESBL production in other AmpC-E are lacking.

Administration of prolonged β-lactam infusions for increased exposure and target attainment compared with 30-minute infusions has been discussed previously [37], with prolonged infusions demonstrating decreased mortality in

Table 2. Treatment Characteristics

Characteristics[a]	Total (n = 315)	Cefepime (n = 169)	Carbapenem (n = 146)	*P* Value
Active empiric antibiotic[b]				
Cefepime	179 (56.8)	114 (67.5)	65 (44.5)	<.001
Ceftriaxone[c]	36 (11.4)	23 (13.6)	13 (8.9)	.191
Ertapenem	27 (8.6)	2 (1.2)	25 (17.1)	<.001
Meropenem	24 (7.6)	3 (1.8)	21 (14.4)	.049
Piperacillin-tazobactam	28 (8.9)	17 (10.1)	11 (7.5)	.432
Other	21 (6.7)	10 (5.9)	11 (7.5)	.566
Time elapsed from index positive blood culture collection to active empirical antibiotic, h	2 (0–14)	2 (0–11.5)	3.3 (0–17)	.093
Definitive antibiotic[d]				
Cefepime	169 (53.7)	169 (100)	0 (0)	<.001
Ertapenem	90 (28.6)	0 (0)	90 (61.6)	<.001
Meropenem	56 (17.8)	0 (0)	56 (38.4)	<.001
Time elapsed from active empirical antibiotic to definitive therapy, h	0 (0–20)	0 (0–2.5)	18 (0–37)	<.001
Loading dose[e]	267 (84.8)	142 (84)	125 (85.6)	.695
Extended infusion[f]	144 (45.7)	113 (66.9)	31 (55.4)	.121
Duration of definitive antibiotic, d	5.9 (3.5–12)	5.6 (3.1–9.5)	7.6 (3.3–14)	.076
Postdefinitive antibiotic[g]				
Cefepime	121 (38.4)	121 (71.6)	0 (0)	<.001
Ertapenem	126 (40)	0 (0)	126 (86.3)	<.001
Meropenem	68 (21.6)	0 (0)	68 (46.6)	<.001
Indication for switch to postdefinitive antibiotic				
Lack of clinical improvement[h]	7 (2.2)	5 (3)	2 (1.4)	.340
Treatment-related adverse effect	11 (3.5)	9 (5.3)	2 (1.4)	.057
Discharge/dosing convenience[i]	35 (11.1)	0 (0)	35 (24)	<.001
Practitioner preference[j]	43 (13.7)	34 (20.1)	9 (6.2)	<.001
Total duration of definitive therapy, d	8 (4–14)	7 (4–12)	8.8 (5–18.1)	.001
Surgical source control procedure[k]	122 (38.7)	54 (32)	68 (46.6)	.008
Repeat blood culture	277 (87.9)	151 (89.3)	126 (86.3)	.408
ID consult	275 (87.3)	145 (85.8)	130 (89)	.389
Hospital LOS	13 (6–25)	10 (6–17)	16.5 (8–28)	.021
ICU LOS	11 (5–23)	9 (4–19)	12 (6–32)	<.001
Microbiological failure[l]	11 (3.5)	5 (3)	6 (4.1)	.579
Microbiological relapse[m]	12 (3.8)	5 (3)	7 (4.8)	.396
30-d infection-related readmission[n]	75 (23.8)	37 (21.9)	38 (26)	.391

Abbreviations: AmpC-E, AmpC-producing Enterobacterales; EHR, electronic health record; ICU, intensive care unit; ID, infectious diseases; LOS, length of stay; MIC, minimum inhibitory concentration.

[a]Data are presented as No. (%) or median (interquartile range), as appropriate.

[b]Active empiric antibiotic: antibiotic therapy with in vitro activity received before microbiological identification.

[c]Patients receiving ≤1 dose of ceftriaxone as active empiric therapy were included.

[d]Definitive antibiotic: cefepime or carbapenem therapy received within 48 hours of index culture collection and continued for ≥48 hours following microbiological identification.

[e]Loading dose: receipt of a 30-minute cefepime or carbapenem infusion as the first β-lactam dose.

[f]Prolonged infusion: denominator for carbapenem group includes only meropenem cases as all ertapenem doses were administered as 30-minute infusions.

[g]Postdefinitive antibiotic: cefepime or carbapenem therapy received after ≥48 hours of definitive therapy and continued for at least 48 hours.

[h]Lack of clinical improvement: any of the following after ≥48 hours of definitive therapy: persistent fever, leukocytosis, repeat positive blood culture, follow-up Pitt bacteremia score equal to or higher than the initial Pitt bacteremia score.

[i]Discharge/dosing convenience: EHR documentation that the change from definitive to postdefinitive therapy was for regimen convenience purposes.

[j]Practitioner preference: EHR documentation that the change from definitive to postdefinitive therapy was based on microbiological AmpC-E genus and species data, unrelated to MIC.

[k]Surgical source control procedures included: intravenous catheter removal, valvular repair/replacement, invasive device removal, incision and drainage, drain placement, debridement, resection, excision, or amputation.

[l]Microbiological failure: positive blood culture with index organism after ≥48 hours of definitive therapy with documented source control, if applicable.

[m]Microbiological relapse: growth of index organism in blood culture following negative blood culture.

[n]Patients were considered to have a 30-day infection-related readmission if they were readmitted to the hospital within 30 days of discharge with a positive culture from any source and receipt of in vitro active antimicrobial therapy.

critically ill patients with *P. aeruginosa* infections [38, 39]. The current study demonstrated that receipt of prolonged-infusion β-lactam (eg, cefepime or meropenem) was associated with a protective effect in patients with AmpC-E bacteremia compared with those receiving an intermittent infusion. However, without serum β-lactam concentrations, target attainment

Table 3. Cox Regression Analysis of 30-Day Mortality Among Patients Receiving Cefepime or a Carbapenem for AmpC-E Bacteremia[a]

	Unadjusted Cohort	Propensity Score IPTW Cohort With Time-Varying Covariates[b]			
	Unadjusted Mortality Among Cefepime Patients	Unadjusted Mortality Among Carbapenem Patients	χ^2 *P* Value	aHR (95% CI)	*P* Value
Whole cohort	32/169 (18.9)	25/146 (17.1)	.677	1.45 (0.79–2.14)	.704
Subgroup analysis stratified by cefepime MIC					
4–8 µg/mL (n = 97)	6/48 (12.5)	10/51 (19.6)	.337	1.19 (0.52–1.77)	.551
≤2 µg/mL (n = 218)	26/121 (21.5)	15/95 (15.8)	.289	1.04 (0.69–1.53)	.468

Abbreviations: aHR, adjusted hazard ratio; AmpC-E, AmpC-producing Enterobacterales; IPTW, inverse probability of treatment weighting; MIC, minimum inhibitory concentration.

[a]Thirty-day mortality: mortality within 30 days of index positive blood culture collection.

[b]Propensity score and time-varying covariates: admitted from home, referral from clinic, APACHE II score, surgical source control procedure, active empiric cefepime, ertapenem, or meropenem, and differences in time elapsed from blood culture collection to initiation of active empirical, definitive, and postdefinitive antibiotic.

between groups remains unknown. Additional prospective studies are warranted to examine this question, especially in a critically ill population that has previously demonstrated suboptimal β-lactam plasma concentrations even upon receipt of prolonged β-lactam infusions [40, 41].

The strengths of this study include the consideration of high-dose cefepime as a carbapenem-sparing option for bacteremia caused by AmpC-E with moderate to high risk of clinically significant AmpC β-lactamase production, while prior studies have focused primarily on standard cefepime dosing regimens. Additionally, the number of patients included in the cohort with cefepime SDD blood isolates is 4-fold that previously reported on, augmenting the clinical validity of this study. Further, the inclusion of time-varying covariates in weighted statistical models considers variations in time elapsed from culture collection to β-lactam initiation.

This study is not without limitations. First, while possible AmpC induction across AmpC-E was evaluated by identifying organisms initially susceptible to certain β-lactam agents that on subsequent isolation become resistant, AmpC-E isolate genotyping was not conducted to confirm that the same organism was recovered and that AmpC production had in fact significantly increased. Thus, one cannot eliminate the possible presence of ESBL-producing isolates harboring and expressing β-lactamase genes other than CTX-M. One such β-lactamase gene was SHV, which was previously identified in 33% of ESBL-producing *E. cloacae* isolates, and current multiplex polymerase chain reaction kits that identify SHV are for research use only and not for diagnostic procedures [23, 35]. However, the usefulness of ESBL testing in clinical practice remains debatable as Enterobacterales isolates may have multiple existing mechanisms of resistance including Enterobacterales with chromosomally expressed AmpC, possibly limiting test accuracy and the ability to detect class A enzymes. Additionally, current breakpoints relied on PK/PD data with high-dose cefepime that, if used against ESBL-producing Enterobacterales, may provide a substantial PD cushion. Further, variations in practitioner preference related to the treatment of serious infections caused by AmpC-E may have resulted in treatment selection bias not remedied by methods used to mitigate bias including propensity score weighting and time-varying covariates.

In summary, our results suggest that high-dose cefepime may be a reasonable option for bacteremia caused by AmpC-E with moderate to high risk of clinically significant AmpC β-lactamase production. Additional microbiological and treatment factors may be considered in therapeutic guidance for AmpC-E with moderate to high risk of clinically significant AmpC β-lactamase production including ceftriaxone susceptibility data, β-lactam dose, and duration of infusion. Further large-scale studies are warranted.

Table 4. Cox Regression Multivariable Analysis of Factors Associated With 30-Day Mortality

	Unadjusted Cohort		Propensity Score IPTW Cohort With Time-Varying Covariates[a]	
Variables	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Pitt bacteremia score >4[b]	1.11 (1.02–1.15)	.034	1.41 (1.04–1.92)	.041
Deep infection[c]	1.54 (1.25–1.73)	.018	2.27 (1.21–4.32)	.039
Ceftriaxone-resistant AmpC-E[d]	2.53 (1.32–4.85)	.026	1.32 (1.03–1.59)	.007
Prolonged-infusion β-lactam	0.52 (0.24–0.78)	.002	0.67 (0.40–0.89)	<.001

Abbreviations: aHR, adjusted hazard ratio; AmpC-E, AmpC-producing Enterobacterales; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

[a]Propensity score and time-varying covariates: admitted from home, referral from clinic, APACHE II score, surgical source control procedure, active empiric cefepime, ertapenem, or meropenem, and differences in time elapsed from blood culture collection to initiation of active empirical, definitive, and postdefinitive antibiotic.

[b]Classification and regression tree analysis used to predict the Pitt bacteremia scores associated with mortality.

[c]Deep infection: endocarditis, septic pulmonary emboli, osteomyelitis, and hepatic or muscular abscesses presumed to be caused by the AmpC-E blood isolate based on documentation in the electronic medical record.

[d]Ceftriaxone-resistant AmpC-E: ceftriaxone minimum inhibitory concentration of ≥2 µg/mL for AmpC-producing Enterobacterales in blood culture.

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.

Acknowledgments

Potential conflicts of interest. M.J.R. has received funds for research and consulting or participated in speaking bureaus for AbbVie, Contrafect, Entasis, Ferring, Melinta, Merck, Paratek Pharmaceuticals, Shionogi, Spero, Tetraphase, and T2 Bioscience and is partially supported by National Institute of Allergy and Infectious Diseases R01 AI121400 and R21 AI163726. All other authors report no potential conflicts.

Patient consent. This study does not include factors necessitating patient consent.

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