






Original Article

Re-evaluation of cefepime or piperacillin-tazobactam to decrease use of carbapenems in extended-spectrum beta-lactamase-producing Enterobacterales bloodstream infections (REDUCE-BSI)

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Abstract

Objective: To re-examine the use of noncarbapenems (NCBPs), specifically piperacillin-tazobactam (PTZ) and cefepime (FEP), for extended-spectrum beta-lactamase-producing Enterobacterales bloodstream infections (ESBL-E BSIs).

Design: Retrospective cohort study.

Setting: Tertiary-care, academic medical center.

Patients: The study included patients hospitalized between May 2016 and May 2019 with a positive blood culture for ESBL-E. Patients were excluded if they received treatment with antibiotics other than meropenem, ertapenem, PTZ, or FEP. Patients were also excluded if they were aged <18 years, received antibiotics for <24 hours, were treated for polymicrobial BSI, or received concomitant antibiotic therapy for a separate gram-negative infection.

Methods: We compared CBPs with FEP or PTZ for the treatment of ESBL-E BSI. The primary outcome was in-hospital mortality. Secondary outcomes included clinical cure, microbiologic cure, infection recurrence, and resistance development.

Results: Data from 114 patients were collected and analyzed; 74 (65%) patients received carbapenem (CBP) therapy and 40 (35%) patients received a NCBP (30 received FEP and 10 received PTZ). The overall in-hospital mortality was 6% (N = 7), with a higher death rate in the CBP arm than in the N-CBP arm, (8% vs 3%; $P = .42$). No difference in mortality was detected between subgroups with Pitt bacteremia score ≥ 4 , those requiring ICU admission, those whose infections were caused by a nongenitourinary source or causative organism (ie, 76 had *Escherichia coli* and 38 had *Klebsiella* spp). We detected no differences in secondary outcomes between the groups.

Conclusion: Compared to CBPs, FEP and PTZ did not result in greater mortality or decreased clinical efficacy for the treatment of ESBL-E BSI caused by susceptible organisms.

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Globally, rates of extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E) have increased from 10.3% to 24% over the past 20 years,¹ along with the concomitant increase of carbapenem (CBP)-resistant Enterobacterales, from 0.6% to 2.9% between 1997 and 2016.² However, in areas of the world with endemic carbapenem-resistant strains, these rates are as high as 65%.^{3,4} Although the availability of novel antimicrobial agents

targeting these bacteria remains limited, the incidence of multi-drug-resistant organisms continues to climb. Despite this significant increase in ESBL-E, cephalosporin or β -lactam/ β -lactamase inhibitor (BLBLI)-susceptible organisms are common among ESBL-E. Thus, the selective use of these agents could minimize widespread CBP use and its attendant resistance issues.

However, controversy continues regarding whether noncarbapenems (NCBP) may be used in ESBL-E bloodstream infections (BSIs), regardless of the susceptibility result. In multiple observational studies, BLBLI treatment in this population was an effective alternative.⁵⁻⁷ However, one prospective, randomized controlled trial reported increased 30-day mortality associated with piperacillin-tazobactam (PTZ) compared with meropenem (MER)

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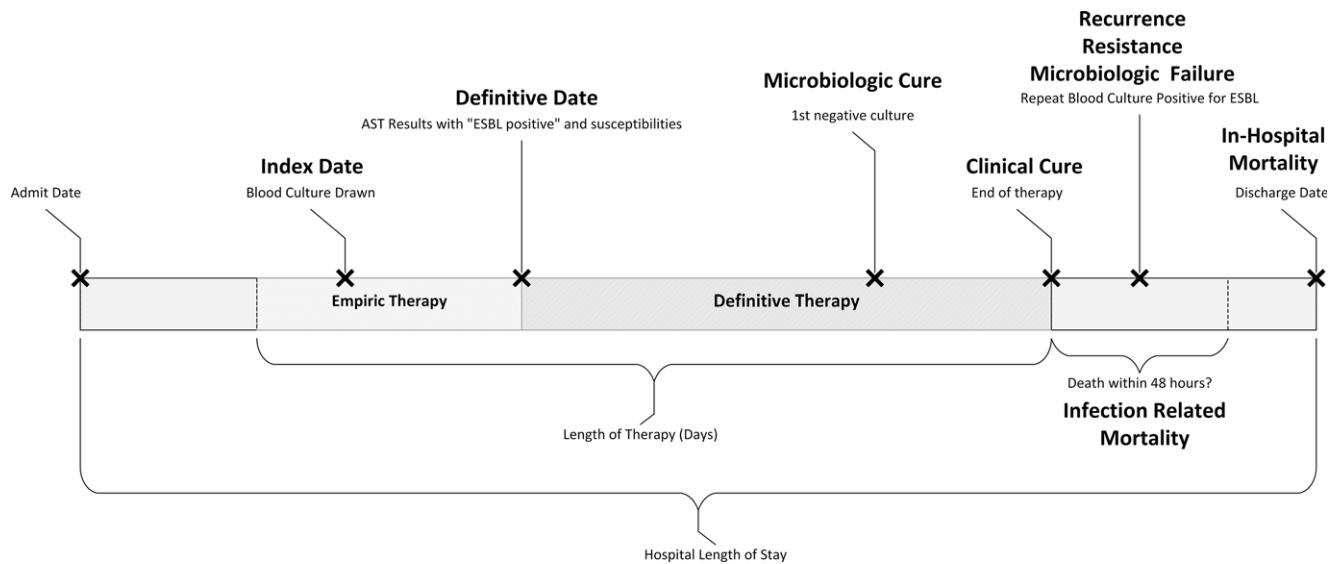


Fig 1. Definitions timeline.

definitive treatment.⁸ However, this study allowed the definitive use of PTZ, even when PTZ resistance was documented, and a large proportion of deaths were due to cancer, not infection. Data from meta-analyses including >20 studies concluded that BLBLI therapy did not increase mortality compared to CBPs.^{9,10}

Data for cefepime (FEP) are not as robust, but in a few available studies, FEP use was associated with an increased risk of mortality.¹¹⁻¹⁴ These studies were limited by small FEP arms, insufficient dosing regimens, outdated Clinical and Laboratory Standards Institute (CLSI) break points, and the absence of minimum inhibitory concentration (MIC) data to guide appropriateness of FEP usage. In an effort to augment stewardship efforts by reducing CBP use, we examined clinical and microbiological outcomes associated with the use of FEP and PTZ for ESBL-E BSI in susceptible isolates. Susceptibility data (ie, MIC values) are routinely used at our institution to determine the appropriate dosing of FEP, and β -lactam therapeutic drug monitoring (TDM) has been incorporated into our practices to optimize exposures related to organism MICs.

Materials and methods

Re-evaluation of cefepime or piperacillin-tazobactam to decrease use of carbapenems in ESBL-producing Enterobacterales bloodstream infections (REDUCE-BSI) was an IRB-approved, observational cohort study conducted at an 1,162-bed academic medical center. Data were collected retrospectively from electronic medical records. All hospitalized patients with a positive blood culture for ESBL-E from May 2016 to May 2019 were screened for inclusion. Patients were excluded if they were not receiving any of the following study drugs: meropenem, ertapenem, cefepime, or piperacillin-tazobactam. Patients were also excluded if they were aged <18 years, had received antibiotics for <24 hours, had carbapenem-resistant Enterobacterales in their blood culture, had a polymicrobial bacteremia, or had received a concomitant antibiotic with activity against gram-negative organisms (eg, trimethoprim-sulfamethoxazole, levofloxacin, aminoglycosides, etc) for a separate infection.

Data were collected for 2 nonmutually exclusive cohorts: an empiric therapy cohort and a definitive therapy cohort.

Antibiotic therapy given prior to susceptibility results were considered “empiric,” and antibiotics administered after this time were considered “definitive” (Fig. 1). In patients with multiple definitive antibiotics, the agent used for >50% of the inpatient definitive duration was the definitive assignment. Dosing was adjusted for renal function based on a pre-established renal dosing protocol.

Organism identification, antimicrobial susceptibility testing, and presence of ESBL phenotypes were determined by VITEK 2 AST-GN73 cards (bioMérieux, Durham, NC). Phenotype interpretations followed break points recommended by CLSI in 2020.¹⁵ Other patient data collected were concomitant infection and the use of combination therapy. Combination therapy was defined as at least 1 dose of a fluoroquinolone or aminoglycoside given in conjunction with a β -lactam for treatment of the ESBL-E BSI.

The primary endpoint was in-hospital mortality. Secondary endpoints included clinical cure, microbiologic cure, recurrence of infection, and development of resistance. Clinical cure was defined as complete resolution of all signs and symptoms of infection and no additional antibiotic therapy required. Clinical failure was defined as a persistent or worsening condition for any one of the clinical symptoms, new clinical signs and symptoms of infection, or the requirement for other systemic antimicrobial therapy at the end of therapy. Microbiologic cure was defined as presence of negative blood cultures during the index hospitalization after the index culture. Microbiologic failure was defined as presence of positive blood cultures ≤ 7 days after discontinuation of antibiotics. Recurrence of infection was defined as re-emergence of positive blood cultures with the same organism following clearance of initial blood culture >7 days after completion of antibiotics. Development of resistance was defined as presence of a positive blood culture with the same organism and resistance to the study drug within 30 days of the index culture. Figure 1 includes a timeline illustration for study definitions.

Continuous variables were described as means and standard deviations for parametric data, and median and interquartile ranges were reported for nonparametric data. Normality of the data was assessed by visual inspection of normal quantile plots. Categorical variables were described as frequencies and proportions. Baseline differences between cohorts were assessed by equal

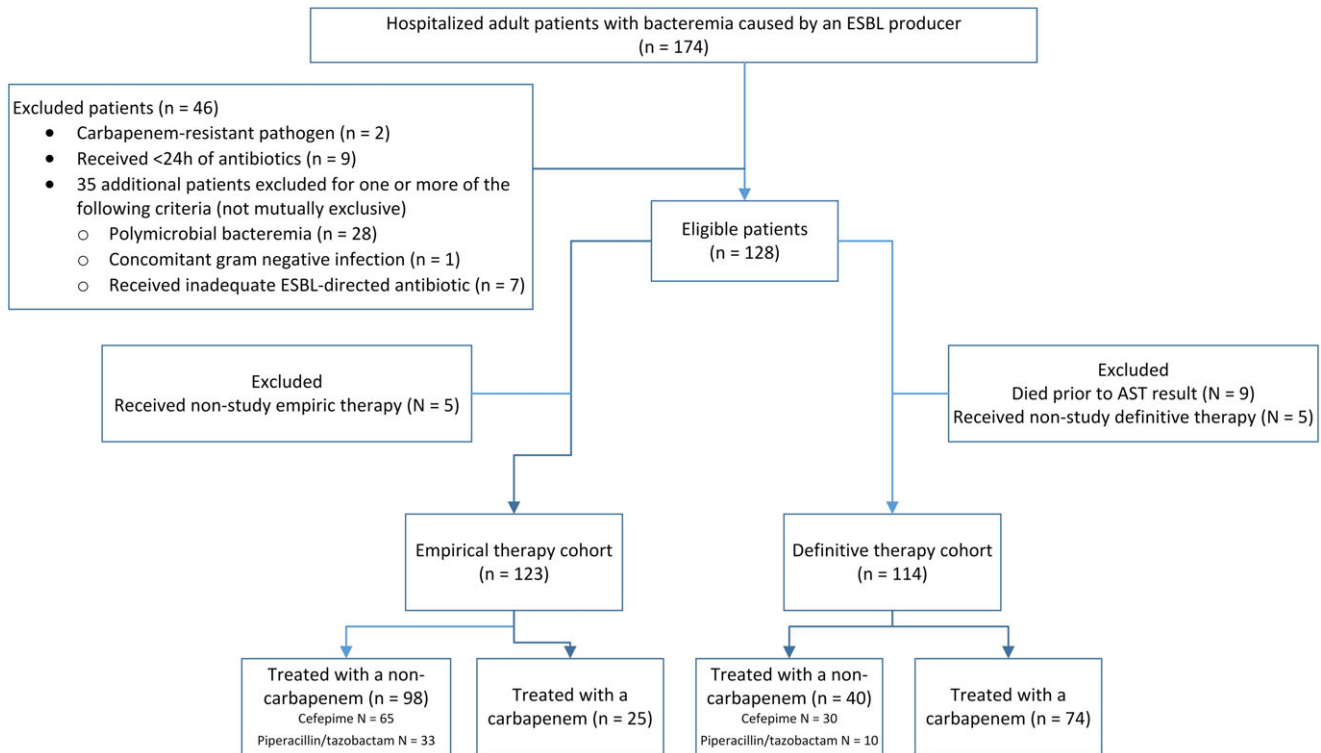


Fig 2. Patient enrollment.

variance, 2-sample *t* tests were used for continuous variables and the χ^2 or Fisher exact test was used for categorical variables, as appropriate.

To determine the difference in 30-day mortality between treatment groups, Kaplan-Meier right-censored time-to-event curves were generated, and log-rank was used to test statistical significance. To account for covariates that affected survival, a Cox proportional hazards model was fit. Univariate analyses were performed to identify covariates that had an impact on mortality. Outcomes for variables with $P < .10$ were analyzed as subgroups for the primary and secondary outcomes. Statistical significance was defined a priori by a threshold of $\alpha < .05$. All statistical analyses were performed using SAS JMP version 15.0 software (SAS Institute, Cary, NC).

Results

In total, 174 patients met the inclusion criteria for screening (Fig. 2). Two patients were excluded due to CBP-resistance: one had a *K. pneumoniae* carbapenemase-producing organism confirmed by Cepheid Xpert CarbaR and the other was confirmed with a modified Hodge test. Another 35 patients were excluded for various overlapping criteria (Fig. 2).

In the included patient population, the mean age was 61 years old; 56% percent of patients were male; 68% were white; 25% had a Pitt score ≥ 4 ; 67% were infected with *E. coli*; and the most common source was genitourinary (52%). After adjustment for renal function, the most common dosing regimens were ertapenem (ERT) 1 g every 24 hours, MER 1 g every 8 hours, FEP 2 g every 8 hours, and PTZ 3.375 mg every 6 hours (Supplementary Table S1). The primary analysis of the study was conducted on the definitive cohort after cultures returned positive for ESBL-E. For completeness, analyses are also reported in the empiric cohort in the Supplementary

Materials. Of the 31 patients with FEP-resistant organisms, 10 received cefepime empirically; 90% of these patients survived to discharge after escalation to susceptible antibiotic therapy. One patient elected comfort care and ultimately died in the hospital. Of the 16 patients with PTZ resistant isolates, 2 received PTZ empirically: one patient died prior to susceptibility results (not included in the definitive analysis) and the other patient escalated to ceftazidime-avibactam and survived to discharge.

The definitive therapy cohort included 114 patients: 74 (65%) received CBP (25 received MER and 49 received ERT) therapy and 40 (35%) received an NCBP (of whom 30 received FEP and 10 received PTZ). Of the 74 patients included in the CBP definitive therapy arm, 52 (70%) received an NCBP empirically. Of the 40 patients included in the NCBP definitive therapy arm, only 2 (5%) received empiric CBP.

Baseline characteristics were similar between the 2 arms, including age, sex, race, weight, and source control (Table 1). *Escherichia coli* was the predominant organism in both CBP and NCBP groups, and most bacteremia cases were secondary to genitourinary source. Of the “other” source in Table 1 in the CBP arm, 6 cases were line-associated infections and 1 case was an endovascular infection. For the NCBP arm, 4 cases were line-associated, 2 cases were bone-joint infections, 1 case was a CNS infection, and 1 case was of unknown source. Although numerically higher, we detected no statistically significant difference between the 2 arms for Charlson comorbidity index, Pitt score ≥ 4 , or ICU admission. Table S5 contains the baseline demographics of the FEP and PTZ definitive arms. Figure 3 demonstrates the MIC distribution for FEP and PTZ. Almost all isolates (97%) were within the susceptible range for FEP (ie, MIC ≤ 2 $\mu\text{g}/\text{mL}$). We did not utilize FEP for any isolate with an FEP MIC within the susceptible dose-dependent range (ie, 4–8 $\mu\text{g}/\text{mL}$). Only 1 FEP-resistant isolate (MIC = 32 $\mu\text{g}/\text{mL}$) was treated definitively with FEP; this

Table 1. Patient Characteristics in Definitive Cohort

Variable	CBP (N = 74)	NCBP (N = 40)	P Value
Age, mean y \pm SD	61.1 \pm 15	62.6 \pm 17	.64
Sex, male, no. (%)	42 (57)	21 (53)	.66
Race, white, no. (%)	48 (65)	32 (80)	.42
Admission weight, median kg (IQR)	79.0 (66–90)	77.9 (63–89)	.91
CCI, median (IQR)	3 (2–5)	2.5 (1–5)	.53
Pitt score \geq 4, no. (%)	19 (26%)	6 (15%)	.19
WBC, median (IQR)	13.1 (7–18)	11.5 (9–19)	.60
CRP, mean \pm SD	174.4 \pm 120	160.9 \pm 100	.62
Procalcitonin, median (IQR)	3.9 (0.5–22)	1.5 (0.4–8.5)	.16
ICU admission, no. (%)	34 (46%)	16 (40%)	.54
ID consultation, no. (%)	63 (85)	27 (68)	.03
Renal function, no. (%)			.99
eGFR \geq 60 mg/dL	35 (47)	20 (50)	
eGFR 30–59 mg/dL	16 (22)	9 (23)	
eGFR 10–29 mg/dL	19 (26)	9 (23)	
eGFR <10 mg/dL	2 (3)	1 (3)	
RRT	2 (3)	1 (3)	
Source, no. (%)			.30
Genitourinary	42 (57)	22 (55)	
Intra-abdominal	17 (23)	6 (15)	
Respiratory	4 (5)	2 (5)	
Skin	4 (5)	1 (3)	
Other	7 (9)	8 (21)	
Concomitant infection, no. (%)	25 (34)	8 (20)	.12
Source control at 72 h, no. (%)	14 (19)	5 (13)	.38
Organism, no. (%)			.78
<i>Klebsiella</i> spp	24 (32)	14 (35)	
<i>E. coli</i>	50 (68)	26 (65)	
β -lactam TDM, no. (%)	12 (16)	9 (23)	
Hospital length of stay, median d (IQR)	12.0 (6–21)	10.0 (5–20)	.92
Length of therapy, median d (IQR)	9.0 (7–13)	8.5 (6–11)	.24
Combination therapy, no. (%)	14 (19)	3 (8)	.10

Note. CBP, carbapenem; NCBP, noncarbapenem; SD, standard deviation; IQR, interquartile range; CCI, Charlson comorbidity index; WBC, leukocyte count; CRP, C-reactive protein; ICU, intensive care unit; ID, infectious disease; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; TDM, therapeutic drug monitoring. Bold for ID consultation data indicates statistical significance.

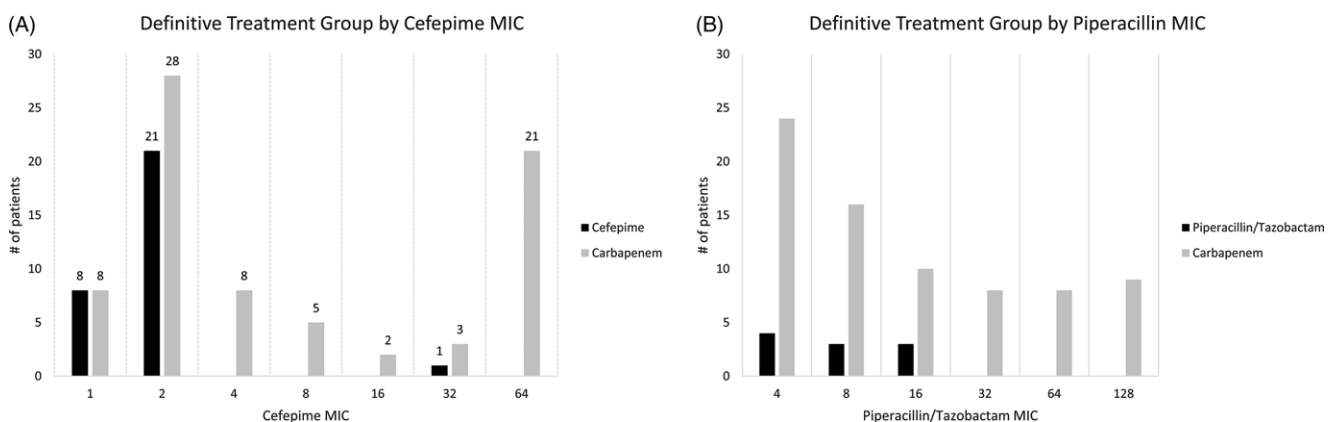
**Fig 3.** Definitive treatment group allocation by (A) cefepime MIC and (B) piperacillin MIC.

Table 2. Primary and Secondary Outcomes in Definitive Cohort

Variable	CBP, (N = 74), No./Total (%)	NCBP, (N = 40), No./Total (%)	P Value
In-hospital mortality	6/74 (8.1)	1/40 (2.5)	.42
Clinical cure	66/74 (90.4)	36/40 (90.0)	.99
Microbiologic cure	66/68 (97.1)	38/39 (97.4)	.99
Recurrence of infection	3/74 (4.1)	1/40 (2.5)	.99
Development of resistance	1/74 (1.4)	0 (0%)	.99

Note. CBP, carbapenem; NCBP, noncarbapenem.

patient had a genitourinary source and rapidly improved on FEP and the therapy was not changed during inpatient status.

The overall in-hospital mortality rate for the definitive cohort was 6% (N = 7). In the CBP arm, 6 patients (8%) died compared to 1 patient (3%) in the NCBP arm ($P = .42$) (Table 2). Univariate analysis of the entire definitive cohort demonstrated that the following factors were associated with increased in-hospital mortality: Pitt score ≥ 4 , admission to the ICU, nongenitourinary source, combination therapy, higher Charlson comorbidity index, and lack of an infectious disease consultation (Table 3). Due to their significant impact on mortality, these covariates were used for subgroup analyses within NCBP and CBP groups (Table 4). No difference in mortality or secondary outcomes was detected between groups upon subgroup analysis.

Discussion

With ESBL-E posing a serious threat to public health,¹⁶ the observations presented in this paper have major implications for the antimicrobial stewardship community. The results of this study demonstrate that FEP and PTZ are appropriate alternatives to CBP, both empirically and definitively, for the treatment of ESBL-E bacteremia caused by fully susceptible strains.

Using these data, we were not able to detect a difference for empiric therapy when comparing CBP versus NCBP therapy using Cox proportional hazards analysis and adjusting for Pitt score, Charlson comorbidity index, and ICU admission. The greater severity of illness in the CBP arm (Table S2) may explain the decreased likelihood of survival in the Kaplan-Meier analysis (Supplementary Fig. S1). These findings are concordant with numerous retrospective, observational studies that have assessed empiric NCBP therapy in ESBL-E. Multiple analyses, including data from large, international cohorts, have not detected a difference in mortality when NCBPs are used empirically compared to CBP therapy.^{5-7, 17, 18}

Our main outcomes analyses were conducted in the definitive cohort. We report similar baseline characteristics as well as in-hospital mortality when comparing CBP versus NCBP therapy. To determine whether this effect persisted across varying severities of illness, we conducted subgroup analyses in groups in which the univariate analysis signaled a mortality difference in the full population. No differences in outcomes were detected for the primary and secondary endpoints when CBP was compared to NCBP, even among subgroup analyses. Some evidence points to use of FEP or PTZ only in low inoculum, nonsevere infections.¹⁹⁻²² In contrast, our data suggest that treating fully susceptible ESBL-E with CBP-sparing β -lactams results in similar outcomes, even in patients with a high severity of illness and nongenitourinary source.

Table 3. Univariate Analysis for Mortality in Definitive Cohort

Variable	Survivors, (N = 107), No. (%)	Nonsurvivors, (N = 7), No. (%)	P Value
Pitt score ≥ 4 , N = 25	21 (20)	4 (57)	.0404
ICU admission, N = 50	44 (41)	6 (86)	.0422
ID consultation, N = 90	88 (82)	2 (29)	.0044
Nongenitourinary source, N = 50	43 (40)	7 (100)	.0024
Combination therapy, N = 17	12 (11)	5 (71)	.0007
Charlson comorbidity index (IQR)	3 (1-4)	7 (5-9)	.0155
Carbapenem therapy, N = 74	68 (63)	6 (86)	.42

Note. ICU, intensive care unit; ID, infectious disease; IQR, interquartile range.

Table 4. Subgroup Analyses for Definitive Cohort

Outcome	CBP, No./Total (%)	NCBP, No./Total (%)	P Value
Pitt score ≥ 4			
In-hospital mortality	3/19 (15.79)	1/6 (16.67)	.99
Clinical cure	14/19 (77.78)	4/6 (66.67)	.61
Micro cure	17/19 (94.44)	5/6 (83.33)	.45
Recurrence	N/A	N/A	...
Resistance emergence	N/A	N/A	...
Admitted to ICU			
In-hospital mortality	5/34 (14.7)	1/16 (6.25)	.65
Clinical cure	27/34 (81.82)	13/16 (81.25)	.99
Micro cure	33/34 (100)	15/16 (93.75)	.33
Recurrence	2/34 (5.88)	0/16 (0)	.99
Resistance emergence	NA	NA	...
Non-GU source			
In-hospital mortality	6/32 (18.75)	1/18 (5.56)	.4
Clinical cure	24/32 (77.42)	15/18 (83.33)	.73
Micro cure	31/32 (96.88)	17/18 (94.44)	.99
Recurrence	NA	NA	...
Resistance emergence	NA	NA	...
Combination therapy			
In-hospital mortality	5/14 (35.71)	0/3 (0)	.51
Clinical cure	10/14 (71.43)	3/3 (100)	.54
Micro cure	14/14 (100)	3/3 (100)	
Recurrence	NA	NA	...
Resistance emergence	NA	NA	...

Note. CBP, carbapenem; NCBP, noncarbapenem; GU, genitourinary; NA, not available.

Only 8.8% of patients in this definitive therapy cohort received PTZ definitively, and 70% of these patients received standard dosing of PTZ 3.375 mg every 6 hours. Although a high dose of PTZ (ie, 4.5 g every 6 hours) is recommended to treat ESBL infections,¹⁹ no patient died and all achieved clinical cure in this arm. The high number of patients with a genitourinary source of infection (90%) in the PTZ group, specifically, could explain these favorable outcomes. Large percentages of both piperacillin and tazobactam

are excreted unchanged in the urine,²³ and prior retrospective studies with predominantly genitourinary sources have endorsed PTZ benefit. Rodríguez-Baño et al⁵ completed a post hoc analysis for ESBL-E bloodstream infections and detected no difference in 30-day mortality between BLBLIs and CBPs, in which ~70% of their population had a urinary or biliary source. Gutiérrez-Gutiérrez et al⁶ conducted an international retrospective analysis and detected no difference in 30-day mortality, with ~45% of infections attributed to a urinary source. In contrast, Tamma et al²⁴ reported increased risk of 14-day mortality in patients treated with PTZ empirically. In their study, only ~20% of patients enrolled had a urinary source. Lastly, the MERINO study group reported increased mortality with PTZ versus MER (12% vs 4%), requiring early termination of the study. Interestingly, a urinary source of bacteremia accounted for most patients in this trial.⁸ However, the high rate of mortality was unrelated to infection, and mortality occurred, on average, after day 15. This study did not exclude patients with PTZ-resistant isolates in the PTZ treatment arm. Additionally, a reanalysis of this data post hoc 2 years after initial publication showed no difference between groups when only susceptible isolates were included.²⁵

New FEP studies in ESBL-E are scarce due to high mortality rates reported in retrospective studies. Chopra et al¹¹ assessed the impact of empiric FEP and found an in-hospital mortality rate of 40%. The FEP MIC was ≥ 16 $\mu\text{g/mL}$ in 56% of isolates, and they utilized 2010 CLSI susceptibility breakpoints.¹¹ Lee et al¹² utilized 2011 CLSI susceptibility breakpoints to retrospectively review FEP definitive therapy. The 30-day mortality rate in the FEP arm was 59%. Of these 17 patients, 4 were treated with FEP and had an MIC ≥ 16 $\mu\text{g/mL}$.¹² Notably, both of these studies utilized CLSI guidance prior to 2014 and dosing regimens were not provided. These historically high mortality rates contrast starkly with the 3% (1 of 30) in-hospital mortality rate of our cohort, in which 97% of isolates had a cefepime MIC of ≤ 2 $\mu\text{g/mL}$.

We believe that mortality associated with FEP in previous studies was primarily driven by the inability to achieve bactericidal pharmacokinetic/pharmacodynamic (PK/PD) targets. The 2 key contributors of suboptimal PKPD attainment were utilization of high break points and inadequate dosing. In 2014, the CLSI lowered the cefepime susceptible break points for Enterobacterales to 2 $\mu\text{g/mL}$ and created a new susceptible-dose-dependent (SDD) category including isolates with FEP MIC of 4–8 $\mu\text{g/mL}$.²⁶ These changes acknowledged the importance of appropriate dosing to achieve clinical efficacy. Historically, FEP 1 g every 8 hours was the predominant dosing regimen utilized.^{27,28} It is now clear that isolates with higher FEP MICs (ie, 4–8 $\mu\text{g/mL}$) require higher doses of FEP (eg, 2 g every 8 hours) to maintain adequate bactericidal activity.^{29,30}

A study published by Lee et al¹³ had the largest cohort to assess definitive FEP therapy in ESBL-E BSI. Utilizing 2014 CLSI guidance, they observed a 30-day mortality rate of 22% versus 26% for CBP and FEP, respectively ($P = .70$) in a cohort of 144 patients infected with *Enterobacter cloacae*. However, isolates categorized as SDD to FEP according to the CLSI were associated with a much higher mortality rate at 63%, and they were associated with increased mortality on multivariate analysis (HR, 18.04; 95% CI, 2.66–122; $P = .003$).¹³ Similarly, Wang et al¹⁴ observed high mortality in a propensity-matched cohort that assessed 14-day mortality for empiric therapy. Moreover, 41% of FEP-treated patients compared to 20% CBP-treated patients died. However, 76% of the patients in this cohort had FEP MICs of 4–8 $\mu\text{g/mL}$. Although high doses of FEP were administered to 70% of patients,

FEP empiric treatment was still associated with increased risk of death (HR, 2.87; 95% CI, 0.88–9.41). Due to the small sample size ($n = 17$ treated with FEP), these findings were not statistically significant.¹⁴ Treatment failures in these 2 cohorts were largely driven by higher MICs. Because no isolates were within the susceptible-dose-dependent (SDD) range in our study, we cannot make any conclusions about FEP efficacy in ESBL-producing bacteria with FEP MICs within the SDD range.

These clinical data, as well as pharmacokinetic studies assessing FEP in ESBL-E, illustrate the critical role of PK/PD target attainment for β -lactam efficacy. The low MICs and high doses of FEP utilized in our study ensured that optimal bactericidal concentrations were maintained throughout the dosing interval, which can explain our favorable outcomes. The availability of therapeutic drug monitoring at our institution allows us to customize β -lactam doses to account for interpatient variability, taking away much of the guesswork about antibiotic exposure to MIC relationships. The principle of tailoring therapy to MIC, regardless of β -lactamase presence, is supported by in vitro data, which have led CLSI to recommend against routinely testing for ESBL production.³¹ However, debate continues because many institutions still report ESBL detection via phenotypic automated testing.^{32–34}

The strengths of this study include a pragmatic study design, subgroup analyses of high-risk populations, and thorough descriptive data including source control, dosing regimens, and analysis of MIC data.

The study also had several limitations. Even though the findings of this study are encouraging for CBP-sparing therapies, caution must be taken regarding widespread adoption of NCP therapy in ESBL-E bloodstream infections due to the limitations of the study design. Although this is the largest cohort of patients treated with FEP for this patient population to date, it is still a small, non-randomized cohort subject to type II error. No sample size calculation was performed a priori due to the limited number of patients expected for inclusion in a single-center study. Consequently, a larger cohort may have been able to detect a difference between the 2 arms. The largest limitation of this study was the retrospective design and the imperfect statistical methods used to adjust for unequal patient characteristics. We attempted to control for selection bias by incorporating Pitt score, Charlson comorbidity index, and ICU admission, but these characteristics were more prevalent at baseline in the CBP arm. Therefore, patients assigned to the CBP arm were more likely to experience the primary outcome. Other limitations to the external validity of this study include availability of β -lactam therapeutic drug monitoring at our institution, use of automated susceptibility testing to report MIC and phenotypic data, and inclusion of only *E. coli* and *Klebsiella* spp isolates. Due to our lack of genotypic data or confirmation of MICs with broth microdilution, these data cannot be definitively applied to institutions with other Enterobacterales that may express different enzymes.

In conclusion, the results of this study show no difference in in-hospital mortality in patients treated with FEP or PTZ compared to CBP in ESBL-producing *E. coli* and *Klebsiella* spp. bloodstream infections. These observations support the use of cefepime and piperacillin-tazobactam in ESBL-E when isolates are fully susceptible as a strategy to reduce unnecessary carbapenem consumption and preserve their antimicrobial activity.

Supplementary material. For supplementary material accompanying this paper visit <https://doi.org/10.1017/ash.2022.21>

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