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CLINICAL THERAPEUTICS

Carbapenem versus Cefepime or Piperacillin-Tazobactam for Empiric Treatment of Bacteremia Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* in Patients with Hematologic Malignancy

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ABSTRACT Infections with extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* are common in patients with hematologic malignancy. The utility of cefepime and piperacillin-tazobactam as empiric therapy for ESBL-producing *E. coli* bacteremia in patients with hematologic malignancy is largely unknown. We conducted a single-center, retrospective cohort review of 103 adult inpatients with leukemia and/or hematopoietic stem cell transplant (HCT) recipients with monomicrobial ESBL-producing *E. coli* bacteremia. No association between increased 14-day mortality and empiric treatment with cefepime (8%) or piperacillin-tazobactam (0%) relative to that with carbapenems (19%) was observed ($P = 0.19$ and $P = 0.04$, respectively). This observation was consistent in multivariate Cox proportional hazards models adjusted for confounding and an inverse probability of treatment-weighted (IPTW) Cox proportional hazards model. Both fever and persistent bacteremia were more common in patients treated empirically with cefepime or piperacillin-tazobactam. Empiric treatment with cefepime or piperacillin-tazobactam did not result in increased mortality relative to that with treatment with carbapenems in patients with hematologic malignancy and ESBL-producing *E. coli* bacteremia, although most patients were changed to carbapenems early in treatment. However, due to prolonged fever and persistent bacteremia, their role may be limited in this patient population.

KEYWORDS antimicrobial stewardship, leukemia, meropenem, propensity score, stem cell transplant

Escherichia coli is one of the most commonly identified causes of bacteremia in patients with hematologic malignancy with neutropenic fever (1, 2). As in general patient populations, the prevalence of extended-spectrum-β-lactamase (ESBL)-producing *E. coli* has increased in recent years in cancer patients, and now nearly 20% of *E. coli* isolates in cancer patients are ESBL producers (3–5). Carbapenems are generally considered to be the treatment of choice for bacteremia caused by ESBL-producing *E. coli*; however, the presence of *E. coli* in the bloodstream and the susceptibility panel are unknown at the time of empiric antimicrobial selection (6). Current guidelines for the management of febrile neutropenia provide equally strong recommendations for the use of antipseudomonal carbapenems (i.e., doripenem, imipenem, or meropenem), cefepime, or piperacillin-tazobactam (7, 8). Therefore, many patients with hematologic malignancy later identified as having bloodstream infection with

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ESBL-producing *E. coli* may receive empiric therapy with cefepime or piperacillin-tazobactam.

Although cefepime and piperacillin-tazobactam are frequently active *in vitro* against ESBL-producing *E. coli*, clinical data regarding their use in patients with bacteremia caused by ESBL-producing *Enterobacteriaceae* are conflicting (6). Retrospective studies comparing cefepime to carbapenems as empiric treatment for ESBL-producing *E. coli* bacteremia have identified increased mortality in patients treated with cefepime; therefore, cefepime is not generally recommended in this situation (9). A large, single-center study identified increased mortality in patients treated empirically with piperacillin-tazobactam compared to that for patients treated empirically with meropenem for bacteremia caused by ESBL-producing *Enterobacteriaceae*, although a multicenter study conducted primarily in Europe did not identify significantly increased mortality in patients treated empirically with β-lactam–β-lactamase inhibitor (BLBLI) combinations, including piperacillin-tazobactam (10, 11). To date, only one study has addressed the use of BLBLIs as carbapenem-sparing alternatives in patients with hematologic malignancy, and none have addressed the use of cefepime (12). Thus, there is a significant need to determine if cefepime or piperacillin-tazobactam is effective as empiric treatment in patients with hematologic malignancy and ESBL-producing *E. coli* bacteremia.

The purpose of this study was to compare mortality in patients with hematologic malignancy and ESBL-producing *E. coli* bacteremia treated empirically with carbapenems or the potential carbapenem-sparing alternative cefepime or piperacillin-tazobactam. Secondarily, we sought to compare other clinically relevant outcomes achieved with these agents, including the persistence of bacteremia and fever.

(This work was presented, in part, at the 2017 Annual Meeting of the American College of Clinical Pharmacy [13].)

RESULTS

A total of 109 patients with hematologic malignancy and a first episode of monomicrobial ESBL-producing *E. coli* bacteremia were identified. After excluding six patients with cefepime-resistant isolates treated empirically with cefepime, 103 patients meeting the eligibility criteria were identified (cefepime, $n = 40$; piperacillin-tazobactam, $n = 21$; carbapenem, $n = 42$). Ten of 42 patients treated empirically with carbapenems also received cefepime or piperacillin-tazobactam on the day of collection of samples for culture, with no significant differences in markers of severity of illness among those who received both empiric treatments being detected (data not shown). All but one patient in the carbapenem group received meropenem; the remaining patient was treated empirically with ertapenem. Patients treated empirically with carbapenems were more acutely ill (median Pitt bacteremia score, 3; interquartile range [IQR], 1 to 3) than patients treated with piperacillin-tazobactam (median Pitt bacteremia score, 1; IQR, 1 to 2; $P = 0.01$) or cefepime (median Pitt bacteremia score, 2; IQR, 1 to 3; $P = 0.03$). More patients treated with meropenem than those treated with cefepime (93% versus 65%, $P < 0.01$) had leukemia. Other baseline characteristics were similar between the groups (Table 1). Among the 40 patients treated empirically with cefepime, 37 (93%) were switched to a carbapenem in a median of 2 days (IQR, 1 to 3 days), while 18 of the 21 (86%) treated empirically with piperacillin-tazobactam were switched to a carbapenem in a median of 1 day (IQR, 1 to 2 days).

Among the patients treated with cefepime, the cefepime MIC_{50} and MIC_{90} were 4 μg/ml and 8 μg/ml, respectively (MIC range, 1 to 8 μg/ml). Twenty-seven of 40 (68%) isolates had MICs of >2 μg/ml (i.e., susceptible dose dependent). Among the patients treated with piperacillin-tazobactam, the piperacillin-tazobactam MIC_{50} and MIC_{90} were 8 μg/ml and 16 μg/ml, respectively (MIC range, 0.75 to 16 μg/ml). Owing to differences in quantitation ranges over time, the MIC_{50} and MIC_{90} were not calculated for meropenem. Fifteen of 40 isolates (38%), all obtained prior to 2012, had a listed MIC value of ≤ 2 μg/ml.

TABLE 1 Patient characteristics by empiric treatment[a]

Characteristic	Values for patients treated with:		*P* value for carbapenem vs cefepime	Values for patients treated with piperacillin-tazobactam (*n* = 21)	*P* value for piperacillin-tazobactam vs a carbapenem
	Carbapenem (*n* = 42)	Cefepime (*n* = 40)			
Median (IQR) age (yr)	52 (31–61)	54 (38–61)	0.42	54 (35–59)	0.77
No. (%) of male patients	25 (59)	26 (65)	0.65	14 (67)	0.78
Median (IQR) Pitt bacteremia score	3 (1–3)	2 (1–3)	0.03	1 (1–2)	0.01
Median (IQR) CL_{CR} (ml/min)	115 (76–165)	115 (76–171)	0.22	120 (100–150)	0.47
No. (%) of patients with:					
Leukemia diagnosis	39 (93)	26 (65)	<0.01	21 (100)	0.29
Prior HCT	18 (43)	23 (58)	0.26	3 (14)	0.27
Median (IQR) ANC (no. of cells/mm^3)	0 (0–0)	0 (0–0)	0.09	0 (0–20)	0.38
No. (%) of patients in ICU	15 (36)	6 (15)	0.04	4 (19)	0.25
No. (%) of patients receiving chemotherapy	36 (86)	30 (75)	0.27	19 (90)	0.71
No. (%) of patients receiving combination aminoglycoside	24 (57)	13 (33)	0.03	7 (33)	0.11
No. (%) of patients with the following duration of neutropenia[b] of:			0.27		0.14
≥7 days	22 (52)	15 (38)		10 (48)	
<7 days	17 (40)	24 (60)		6 (29)	
No. (%) of nonneutropenic patients	2 (5)	1 (3)		5 (24)	
No. (%) of patients with the following source of bacteremia:			0.43		0.14
Central line	7 (17)	9 (23)		0 (0)	
Respiratory	6 (14)	1 (3)		1 (5)	
Abdominal[c]	16 (38)	19 (48)		9 (43)	
Urinary	4 (10)	2 (5)		2 (10)	
Skin/soft tissue	2 (5)	3 (8)		4 (19)	
Unknown	7 (17)	6 (15)		5 (24)	

[a]CL_{CR}, Cockcroft-Gault creatinine clearance; HCT, hematopoietic stem cell transplant; ANC, absolute neutrophil count; ICU, intensive care unit.
[b]ANC < 500 cells/mm^3.
[c]Includes presumed translocation.

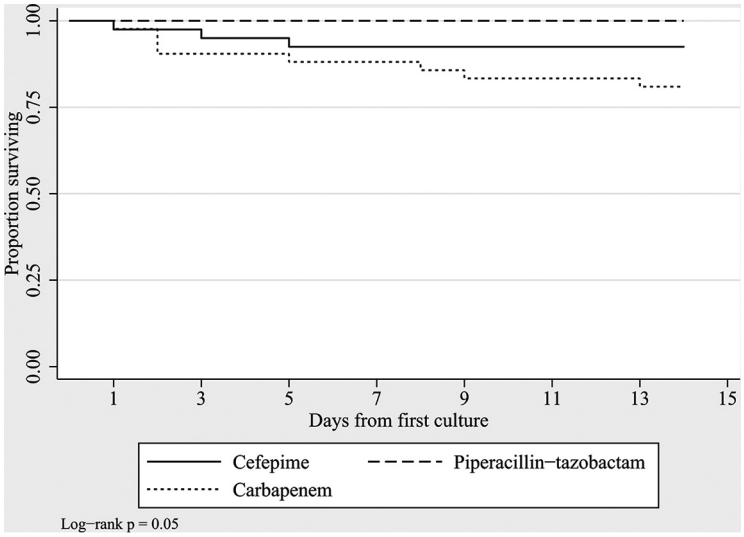

FIG 1 Kaplan-Meier plots for 14-day mortality by empiric treatment choice. *P* was 0.05 by the log-rank test.

Mortality. Fourteen-day mortality was 19% in the carbapenem group, whereas it was 8% in the cefepime group ($P = 0.19$) and 0% in the piperacillin-tazobactam group ($P = 0.04$) (Fig. 1). In the multivariate Cox proportional hazards model, empiric treatment with cefepime was not associated with increased 14-day mortality relative to that with empiric treatment with carbapenems (adjusted hazard ratio [aHR], 0.57; 95% confidence interval [CI], 0.14 to 2.26; $P = 0.42$), while each 1-unit increase in the Pitt bacteremia score was significantly associated with increased 14-day mortality (aHR, 2.21; 95% CI, 1.56 to 3.13; $P < 0.01$). The full univariate and multivariate models are presented in Table 2. As no patients empirically treated with piperacillin-tazobactam died, the adjusted risk of 14-day mortality could not be calculated.

In the first sensitivity analysis, using all significant predictors on univariate analysis in a multivariate Cox proportional hazards model, empiric treatment with cefepime was not associated with increased 14-day mortality (aHR, 0.78; 95% CI, 0.18 to 3.44; $P = 0.75$). The calculated propensity score adequately balanced patient characteristics when incorporating an inverse probability of treatment-weighted (IPTW) Cox proportional hazards model (data not shown). In the second sensitivity analysis, using an IPTW Cox proportional hazards model, cefepime was again not a significant predictor of 14-day mortality (hazard ratio [HR], 0.59; 95% CI, 0.13 to 2.69; $P = 0.50$).

TABLE 2 Univariate and multivariate Cox proportional hazards models for 14-day mortality[b]

	Univariate model			Multivariate model		
Factor	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Cefepime treatment	0.38	0.10–1.43	0.19	0.57	0.14–2.26	0.42
Age	1.02	0.98–1.05	0.33			
Neutropenia[a]	0.18	0.04–0.84	0.03			
Pitt bacteremia score	2.22	1.58–3.15	<0.01	2.21	1.56–3.13	<0.01
Leukemia	0.66	0.17–2.48	0.54			
History of HCT	0.83	0.25–2.70	0.75			
Female gender	0.61	0.16–2.29	0.46			
Active chemotherapy	1.05	0.23–4.89	0.94			
ICU residence	6.07	1.78–20.8	<0.01			
Intra-abdominal source	1.18	0.36–3.86	0.79			
Combination aminoglycoside	0.67	0.20–2.29	0.52			

[a]Absolute neutrophil count (ANC) < 500 cells/mm^3.
[b]HR, hazard ratio; CI, confidence interval; HCT, hematopoietic stem cell transplant; ICU, intensive care unit.

TABLE 3 Univariate and multivariate Fine-Gray competing risk models for time to defervescence[b]

Factor	Univariate model			Multivariate model		
	SHR	95% CI	*P* value	SHR	95% CI	*P* value
Cefepime treatment	0.56	0.40–0.77	<0.01	0.56	0.40–0.77	<0.01
Piperacillin-tazobactam treatment	0.37	0.22–0.64	<0.01	0.37	0.22–0.64	<0.01
Carbapenem treatment (reference)						
Age	1.00	0.99–1.01	0.51			
Neutropenia[a]	1.98	1.02–3.82	0.04			
Pitt bacteremia score	1.14	1.04–1.24	<0.01	2.21	1.56–3.13	<0.01
Leukemia	1.06	0.67–1.66	0.81			
History of HCT	1.18	0.87–1.61	0.27			
Female gender	1.24	0.93–1.67	0.14			
Active chemotherapy	0.75	0.58–0.96	0.02			
ICU residence	1.22	0.86–1.73	0.27			
Intra-abdominal source	0.89	0.64–1.24	0.49			
Combination aminoglycoside	0.97	0.70–1.33	0.84			

[a]Absolute neutrophil count (ANC) < 500 cells/mm^3.
[b]SHR, subhazard ratio; CI, confidence interval HCT, hematopoietic stem cell transplant; ICU, intensive care unit.

All three deaths in the cefepime group occurred in patients who never received a carbapenem. One, with a cefepime MIC of 8 μg/ml, presented with severe sepsis and died on the following day. The remaining two, both with a cefepime MIC of 4 μg/ml, were initially stable but progressively worsened on cefepime therapy and eventually died with septic shock (one at day 3 following presentation and the other at day 5 following presentation). A total of eight patients in the carbapenem group died within 14 days of the onset of bacteremia. Among these patients, six of eight had progressive sepsis, and death was likely attributable to ESBL-producing *E. coli* bacteremia (one each at day 1, day 5, and day 9; three at day 2). One patient developed a secondary pneumonia due to *Achromobacter* spp. while on treatment with meropenem and died at day 8. The remaining patient developed a biopsy-proven invasive fungal infection with a dematiaceous mold and was transitioned to hospice care with refractory underlying disease. In total, six of eight (75%) deaths in the carbapenem group could be directly attributed to ESBL-producing *E. coli* bacteremia, while the remaining two had potential alternative immediate causes.

Time to defervescence. A total of 80 patients were febrile at the onset of bacteremia and could be assessed for time to defervescence (cefepime, $n = 30$; piperacillin-tazobactam, $n = 16$; carbapenem, $n = 34$). The median time to defervescence was significantly shorter for patients treated empirically with carbapenems (median, 1 day; IQR 1 to 1 day) than those treated empirically with cefepime (median, 1.5 days; IQR, 1 to 2 days; $P < 0.01$) or piperacillin-tazobactam (median, 2 days; IQR, 1 to 3 days; $P < 0.01$). On Fine-Gray competing risk regression, which accounted for a change in therapy or death, the sole significant predictor of prolonged fever was antibiotic choice (Table 3; Fig. 2).

Persistent bacteremia. Fifty-eight of 103 (56%) patients had follow-up cultures sufficient to determine if persistent bacteremia existed. Patients treated empirically with carbapenems were less likely than those treated with piperacillin-tazobactam to have persistent bacteremia (1/22 [5%] versus 4/11 [36%], $P = 0.03$), while no significant difference was seen in comparison to those treated empirically with cefepime (5/25 [20%], $P = 0.19$). In multivariate logistic regression, empiric treatment with piperacillin-tazobactam was a significant predictor of persistent bacteremia (adjusted odds ratio [aOR], 27.1; 95% CI, 1.8 to 410.1; $P = 0.02$), and a nonsignificant trend was observed with treatment with cefepime (aOR, 9.7; 95% CI, 0.9 to 108.0; $P = 0.07$). The results of the univariate and multivariate analyses are presented in Table 4.

DISCUSSION

In this study, empiric treatment with cefepime or piperacillin-tazobactam was not associated with increased 14-day mortality in profoundly neutropenic patients with

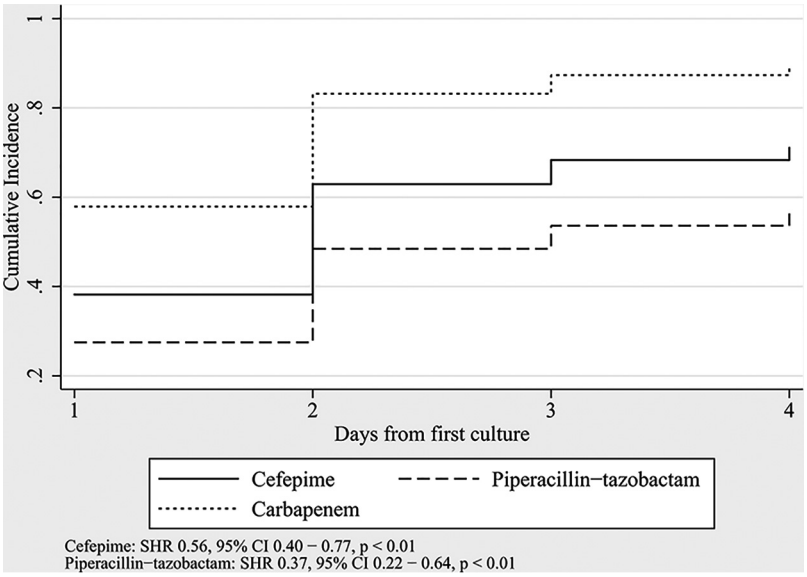

FIG 2 Cumulative incidence of defervescence by empiric treatment choice. For cefepime, the subhazard ratio was 0.56, the 95% CI was 0.40 to 0.77, and *P* was <0.01. For piperacillin-tazobactam, the subhazard ratio was 0.37, the 95% CI was 0.22 to 0.64, and *P* was <0.01.

hematologic malignancy and ESBL-producing *E. coli* bacteremia relative to the 14-day mortality with empiric treatment with a carbapenem. However, other clinically relevant outcomes, including persistent fever and persistent bacteremia, were more common among patients receiving cefepime or piperacillin-tazobactam. To our knowledge, this is the first study simultaneously evaluating the utility of cefepime and piperacillin-tazobactam as carbapenem-sparing alternatives in patients with hematologic malignancy. These findings have important implications for the management of the increasingly common problem of ESBL-producing *E. coli* bacteremia in these vulnerable patients (14).

Previous studies conducted in general patient populations have identified an increased risk of treatment failure with cefepime as empiric therapy for ESBL-producing *E. coli* bacteremia, while retrospective studies evaluating piperacillin-tazobactam as empiric therapy for these infections have shown conflicting results (6, 9, 11, 15, 16). A recent international, multicenter study conducted by Gudiol et al. comparing BLBLI combination therapy to carbapenems for the treatment of ESBL-producing *Enterobacteriaceae* bacteremia in neutropenic patients with hematologic malignancy identified a

TABLE 4 Univariate and multivariate logistic models for persistent bacteremia[b]

	Univariate model			Multivariate model		
Factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Cefepime treatment	5.25	0.56–49.0	0.15	9.70	0.87–108.04	0.07
Piperacillin-tazobactam treatment	12.0	1.14–126.1	0.04	27.06	1.79–410.08	0.02
Carbapenem treatment (reference)						
Age	0.94	0.89–0.98	0.01	0.92	0.87–0.98	<0.01
Neutropenia[a]	0.84	0.08–8.40	0.88			
Pitt bacteremia score	0.94	0.56–1.57	0.80			
Leukemia	0.92	0.17–5.11	0.93			
History of HCT	0.60	0.14–2.61	0.50			
Female gender	0.35	0.07–1.83	0.21			
Active chemotherapy	0.57	0.10–3.35	0.54			
ICU residence	1.43	0.57–3.56	0.45			
Intra-abdominal source	3.27	0.75–14.20	0.11			
Combination aminoglycoside	0.51	0.12–2.20	0.36			

[a]Absolute neutrophil count (ANC) < 500 cells/mm^3.
[b]OR, odds ratio; CI, confidence interval; HCT, hematopoietic stem cell transplant; ICU, intensive care unit.

similar 14-day mortality in patients treated empirically with BLBLIs in a propensity score-matched analysis (12). These results are in agreement with ours, where no patients who received empiric piperacillin-tazobactam died within 14 days. However, in both our study and the multicenter study, patients treated with carbapenems were more acutely ill than those receiving piperacillin-tazobactam. Thus, despite statistical adjustment, the similar or reduced mortality in patients treated with BLBLIs may be a reflection of patient status rather than treatment efficacy.

In support of this hypothesis, two other measures of antibiotic efficacy (i.e., persistent bacteremia and persistent fever) both favored empiric treatment with carbapenems. These results, again, are generally in agreement with those of the study conducted by Gudiol et al., who demonstrated that persistent bacteremia was numerically more common in patients treated with BLBLIs than in those treated with carbapenems (10.4% versus 3.9%, $P = 0.13$), while persistent fever was not evaluated (12). The apparent disconnect between these relatively softer markers of efficacy and mortality may be reconciled by the timing of carbapenem therapy as well as the clinical status of the patients. In our study, a switch to carbapenem therapy occurred in a median of 2 days for patients empirically treated with cefepime and 1 day for patients receiving piperacillin-tazobactam, and patients receiving both carbapenem-sparing alternatives had lower median Pitt bacteremia scores. These data suggest that selected patients with ESBL-producing *E. coli* bacteremia may be treated empirically with cefepime or piperacillin-tazobactam without increased mortality, although at the potential cost of prolonged fever and bacteremia.

Although this study was not designed to evaluate definitive therapy, two findings are worth noting. First, all three deaths in patients treated with cefepime occurred in those who were never changed to carbapenem therapy. Therefore, despite *in vitro* activity, cefepime appears to be suboptimal and cannot be recommended as definitive therapy. Taken together with the findings of other studies showing the increased failure of cefepime for the treatment of infections caused by ESBL-producing *Enterobacteriaceae* and/or those with MICs in the susceptible dose-dependent range, like two-thirds of the isolates in this study, the adequacy of the recently revised CLSI cefepime breakpoints may be called into question (18, 19). Second, none of the 21 patients who received empiric therapy with piperacillin-tazobactam died, including 3 who never received carbapenem therapy. This finding is in general agreement with the findings of the retrospective study performed by Gudiol et al. (12) but is in sharp contrast to the findings of the prospective, randomized MERINO trial, which identified significantly increased mortality in patients receiving definitive BLBLI therapy relative to that in patients receiving carbapenems (20). Thus, while it appears that some patients may successfully be treated definitively with piperacillin-tazobactam, this approach cannot be generally recommended in the absence of additional prospective data.

In concert with data from other published studies, these data provide additional guidance on the management of febrile neutropenia in an era of increasing ESBL prevalence. Both our study and the study performed by Gudiol et al. (12) show that a significant proportion of patients with bacteremia caused by ESBL-producing organisms can be safely treated empirically with noncarbapenems. This approach appears to be particularly well-suited to non-critically ill patients, who represented the majority of our cohort and the general febrile neutropenic patient population.

The relatively low mortality rate observed in this study of patients with ESBL-producing *E. coli* bacteremia, despite being conducted in a patient population generally considered to be at the highest risk of poor outcomes, is also worth noting. The 19% mortality rate in the carbapenem group approximated that seen in general patient populations, while the rates in the cefepime and piperacillin-tazobactam groups were far below the 20% to 40% generally reported (10, 11, 21–23). This relatively low mortality may potentially be explained by rapid antibiotic therapy for neutropenic fever, although considerable controversy exists over the impact of the timing of antibiotic therapy in patients with neutropenic fever (7, 24). Recent data in cancer patients with severe sepsis indicate that neutropenia may not be a negative prognostic

marker, with traditional markers of sepsis more reliably indicating a worse prognosis (25). In our study, an increased Pitt bacteremia score correlated with increased 14-day mortality, while the presence of neutropenia was not a significant predictor of outcomes. The clinical significance of neutropenia in cancer patients with severe infections is an active area of interest for our group.

The strengths of this study include the consideration of both cefepime and piperacillin-tazobactam as carbapenem-sparing alternatives, while prior studies have compared only one of these two alternatives. We additionally used three different statistical models, including a propensity score-based method, to ensure the reliability of our findings. Despite these strengths, there are several limitations. First, this was a single-center study conducted at an NCI-designated Comprehensive Cancer Center. Therefore, these results may not be applicable in other settings. Additionally, as a retrospective study, differences in baseline characteristics between treatment groups, such as unmeasured confounding or unrecognized concomitant infections, and inherent biases with such a study design cannot be fully accounted for with statistical analyses. Antimicrobial susceptibility was determined using automated antimicrobial susceptibility testing, which may have significant discrepancies with reference standards (26–28), although this reflects clinical practice at the majority of hospitals worldwide. Further, as only patients with ESBL-producing *E. coli* were included in this study, these findings cannot be generalized to other *Enterobacteriaceae*, including *Klebsiella* spp. Finally, despite the use of broad inclusion criteria, the sample size was relatively small. However, this study provides the basis for future multicenter studies evaluating this important clinical topic.

In conclusion, empiric treatment with cefepime or piperacillin-tazobactam was not associated with increased 14-day mortality relative to that with empiric treatment with carbapenems in patients with hematologic malignancy and ESBL-producing *E. coli* bacteremia, although most patients were switched to carbapenems early in treatment. Both persistent bacteremia and prolonged fever were more common in patients treated with piperacillin-tazobactam and cefepime. Based on these data, both cefepime and piperacillin-tazobactam remain viable options for empiric therapy for hematologic malignancy patients at risk for ESBL-producing *E. coli* bacteremia.

MATERIALS AND METHODS

Patient selection. This was a single-center retrospective cohort study conducted at The University of Texas MD Anderson Cancer Center, an NCI-designated Comprehensive Cancer Center, between January 2008 and November 2015. Patients were included if they were adult (age $\geq$ 18 years) inpatients with either leukemia or a history of hematopoietic stem cell transplant (HCT) at any time, had monomicrobial bacteremia caused by ESBL-producing *E. coli*, and received empiric treatment with either cefepime, piperacillin-tazobactam, or a carbapenem. Empiric treatment was defined as the receipt of only one of these three agents of interest on the day that the sample for culture was collected. However, if a patient received both cefepime or piperacillin-tazobactam and a carbapenem, the patient was included in the carbapenem group. Only the first occurrence of ESBL-producing *E. coli* bacteremia was assessed in patients with multiple episodes. Patients who received no empiric antimicrobial therapy on the same calendar day that the index isolate was recovered were excluded. Patients were excluded if the *E. coli* isolate was resistant to the empiric antimicrobial chosen. During the time period of this study, standard antimicrobial doses were cefepime at 2 g intravenously (i.v.) every 8 h, piperacillin-tazobactam at 4.5 g i.v. every 6 h, and meropenem at 1 g i.v. every 8 h (or their renally adjusted equivalents), each of which was administered by a 30-min infusion. The specific doses administered to the patients included in this study were not assessed.

Antimicrobial susceptibility testing. All laboratory testing was performed according to routine practice at The University of Texas MD Anderson Cancer Center clinical microbiology laboratory, and the results were interpreted according to the manufacturer's instructions. Antimicrobial susceptibility testing was performed with a Vitek 2 instrument (bioMérieux, Marcy l'Étoile, France). ESBL production was defined as resistance to one or more oxyimino cephalosporins (e.g., ceftazidime, ceftriaxone, cefotaxime) with a positive confirmatory ESBL Etest (bioMérieux). Resistance was determined according to current Clinical and Laboratory Standards Institute (CLSI) susceptibility criteria (https://www.clsi.org/standards/products/microbiology/documents/m100/). For the purposes of this analysis, cefepime-susceptible-dose-dependent isolates were considered susceptible. Prior to 2012, the Vitek panel used did not provide quantitative meropenem MICs below 2 μg/ml; therefore, all isolates with a reported meropenem MIC of $\leq$2 μg/ml during this time period were considered susceptible to meropenem.

Outcomes and statistical analysis. The primary outcome was 14-day mortality from the date of onset of bacteremia. Secondary outcomes were time to defervescence (defined as the first day without

a recorded temperature of ≥38.3°C, limited to patients who were febrile on the day that the sample positive by culture was obtained) and persistent bacteremia. As serial blood samples for culture were not collected from all patients, persistent bacteremia was defined as the presence of a positive blood culture on day 3 or later with no intervening negative blood culture.

All analyses were performed using carbapenem treatment as the reference group. No adjustments were made for multiple comparisons. Demographic characteristics are presented descriptively, with comparisons being made using Fisher's exact test, the Wilcoxon rank-sum test, or *t* test, as appropriate. Analysis of the primary endpoint, 14-day mortality, was performed using a backwards stepwise Cox proportional hazards model. The initial model included all potential explanatory variables, and at each step, the variable with the least significant *P* value was removed and the Bayesian information criterion (BIC) of the subsequent model was assessed. If the BIC increased, the backwards process stopped and the prior model was used. Time to defervescence was assessed using a backwards stepwise Fine-Gray competing risk regression model, treating death or a change to carbapenem as competing risks (29). Backwards stepwise logistic regression was used to assess persistent bacteremia. For both secondary outcomes, a process identical to that used for model selection was employed for selection of the Cox proportional hazards model. Candidate variables included in each of the analyses for the primary outcome and the outcome for persistent bacteremia were age, gender, Pitt bacteremia score (30), neutropenia, cancer diagnosis and status, receipt of prior HCT, current receipt of chemotherapy, the source of infection, and the use of combination aminoglycosides within the first 24 h of culture.

As a sensitivity analysis, two additional methods were used to assess the primary endpoint, 14-day mortality. In the first, any significant predictor of mortality in the univariate Cox proportional hazards model was included in a multivariate Cox proportional hazards model. In the second, a propensity score was calculated using a nonparsimonious logistic regression model incorporating all previously described candidate variables to predict the probability of treatment with cefepime. This propensity score was then used to generate an inverse probability of treatment-weighted (IPTW) univariate Cox proportional hazards model (31). The IPTW Cox proportional hazards model was specifically chosen over propensity score matching to minimize the loss of statistical power that may occur in case matching with small sample sizes.

All study data were collected and maintained using REDCap (Vanderbilt University, Nashville, TN) software, hosted at The University of Texas MD Anderson Cancer Center (32). Statistical analysis was performed using Stata (v14.1) software (StataCorp LP, College Station, TX). This study was approved by the Institutional Review Board (IRB) at The University of Texas MD Anderson Cancer Center with a waiver of the requirement for informed consent (IRB number PA16-0812).

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