

Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients With Extended-Spectrum β -Lactamase Bacteremia

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(See the Editorial Commentary by Perez and Bonomo on pages 1326–9.)

Background. The effectiveness of piperacillin-tazobactam (PTZ) for the treatment of extended-spectrum β -lactamase (ESBL) bacteremia is controversial. We compared 14-day mortality of PTZ vs carbapenems as empiric therapy in a cohort of patients with ESBL bacteremia who all received definitive therapy with a carbapenem.

Methods. Patients hospitalized between January 2007 and April 2014 with monomicrobial ESBL bacteremia were included. A decrease of >3 doubling dilutions in the minimum inhibitory concentration for third-generation cephalosporins tested in combination with 4 $\mu\text{g/mL}$ of clavulanic acid was used to confirm ESBL status. The primary exposure was empiric therapy, defined as antibiotic therapy administered to a patient before ESBL status was known. Patients were excluded if they did not receive a carbapenem after ESBL production was identified. The primary outcome was time to death from the first day of bacteremia. Propensity scores using inverse probability of exposure weighting (IPW) were used to estimate the probability that a patient would receive PTZ vs carbapenems empirically. We calculated overall hazard ratios for mortality censored at 14 days using Cox proportional hazards models on an IPW-adjusted cohort.

Results. A total of 331 unique patients with ESBL bacteremia were identified. One hundred three (48%) patients received PTZ empirically and 110 (52%) received carbapenems empirically. The adjusted risk of death was 1.92 times higher for patients receiving empiric PTZ compared with empiric carbapenem therapy (95% confidence interval, 1.07–3.45).

Conclusions. PTZ appears inferior to carbapenems for the treatment of ESBL bacteremia. For patients at high risk of invasive ESBL infections, early carbapenem therapy should be considered. Our findings should not be extended to β -lactam/ β -lactamase inhibitor combinations in development, as limited clinical data are available for these agents.

Keywords. ESBL; piperacillin-tazobactam; carbapenem; gram-negative; resistance.

The prevalence of gram-negative bacteria resistant to broad-spectrum β -lactams has increased at a rapid

pace over the past decade [1]. Such is the case with extended-spectrum β -lactamase (ESBL)-producing bacteria. ESBL-producing organisms have been associated with poorer clinical outcomes compared with more susceptible organisms [2–6], partially attributable to a delay in initiating appropriate antimicrobial therapy [7–9]. The existing literature indicates that carbapenems have a relatively high rate of clinical success among patients infected with ESBL-producing organisms [10–13]. However, indiscriminant carbapenem use is not without consequence. Increased carbapenem use has

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contributed to the emergence of carbapenem-resistant Enterobacteriaceae [14, 15].

The role of piperacillin-tazobactam (PTZ) for patients infected with ESBL-producing pathogens remains unclear. Although ESBLs are generally inhibited by tazobactam, many organisms produce multiple ESBLs simultaneously, which may reduce the effectiveness of PTZ [16]. The presence of additional mechanisms of resistance (eg, AmpC β -lactamases) may further limit the activity of PTZ against ESBL-producing organisms [16]. Several studies suggest moderate to high in vitro activity of PTZ against ESBLs [17–19], but this does not necessarily translate to clinical efficacy. An inoculum effect, in which the PTZ minimum inhibitory concentration (MIC) increases when inocula reach 10 colony-forming units per milliliter [7], has been proposed as a possible explanation for reduced efficacy observed in the setting of apparent in vitro susceptibility [1–3].

Existing observational data have demonstrated equivalence between PTZ and carbapenems for the treatment of ESBL infections [4]. However, heterogeneity related to the criteria used to define ESBLs, imbalances between sources of infection, variability in dosing, interval, and duration of therapy, use of additional active antibiotics, differences in end-points evaluated, and residual confounding limit the applicability of these findings [10, 13]. A complicating factor in published studies is the discrepancy between empiric and definitive antimicrobial regimens when comparing outcomes due to ESBL-producing bacteria [13]. Very often, patients are prescribed cephalosporins or PTZ empirically, and only after it is known that an organism is an ESBL producer, generally 72–96 hours after blood cultures are obtained, are patients transitioned to carbapenem therapy, making it challenging to conduct fair comparisons of patients receiving carbapenem therapy and alternate agents. To overcome these limitations, we sought to determine the impact of empiric PTZ therapy compared with empiric carbapenem therapy on 14-day mortality in a stabilized inverse probability-weighted (IPW) cohort of patients with ESBL bacteremia who all received culture-directed “definitive” therapy with a carbapenem.

METHODS

Setting and Participants

Clinical microbiology laboratory databases were queried to identify ESBL-producing organisms isolated from the bloodstream from January 2007 to April 2014 at the Johns Hopkins Hospital. The primary exposure was empiric therapy with PTZ or a carbapenem. To remain in the cohort, all patients had to receive carbapenem therapy (ertapenem, meropenem, or imipenem-cilastatin) after their bloodstream isolate was identified as ESBL producing. If a patient began therapy with PTZ and therapy was modified to include a noncarbapenem regimen (eg, ciprofloxacin, trimethoprim-sulfamethoxazole) after ESBL status

was known, the patient was excluded from further analysis. Additionally, patients receiving PTZ with a PTZ MIC >16 $\mu\text{g/mL}$ (resistant using the current Clinical and Laboratory Standards Institute [CLSI] breakpoint) were also excluded.

Although an ESBL-producing organism may test susceptible to PTZ in vitro, the Johns Hopkins Hospital microbiology laboratory automatically reports the organism as resistant to PTZ (along with cephalosporins and aztreonam). Thus, patients initiated on PTZ empirically and later found to have ESBL bacteremia would be highly unlikely to continue this agent after susceptibility results were available.

Only the first episode of ESBL bacteremia per patient was included in the analysis. The main outcome of interest was 14-day mortality. Ninety-six percent of patients were either followed until day 14 or had subsequent inpatient or outpatient visits at Johns Hopkins Hospital to document their vital status at 14 days. Death within 14 days of the first day of bacteremia was selected as this was thought to be the time period most reflective of death attributable to suboptimal therapy.

Data Collection

Patient data were extracted from medical records through chart review by an infectious diseases-trained physician into a standardized data collection form. Pertinent demographic, clinical, and treatment data were included. Highest Pitt bacteremia score, intensive care unit (ICU)-level care (which included admission to the ICU, mechanical ventilator, and/or pressor requirement) were recorded on the day the first positive blood culture was drawn as measures of illness severity. The likely source of infection and source control status were also collected. Adequate source control included removal of central lines in cases of central line-associated infections or drainage of intra-abdominal abscesses when such fluid collections were present. Patients without a clear removable or drainable source (eg, urinary sources, pneumonia) were recorded as having adequate source control.

Patients (1) receiving prednisone ≥ 2 mg/kg or ≥ 20 mg daily for at least 14 days, (2) receiving biologic agents in the preceding 30 days, (3) who received a solid organ transplant, (4) who received a hematopoietic stem cell transplant in the preceding 1 year, (5) who received cancer chemotherapy within 6 months, (6) had a congenital immunodeficiency, or (7) had human immunodeficiency virus with a CD4 count ≤ 200 cells/ μL were categorized as immunocompromised [20]. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Microbiology Methods

Blood isolates growing *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* were included. These organisms were selected because the CLSI-recommended

method for initial screening and phenotypic confirmatory testing is confined to these bacteria [21]. Clinical samples were processed at the Johns Hopkins Hospital Microbiology Laboratory according to standard operating procedures. Antimicrobial susceptibility testing was determined by the BD Phoenix Automated System (BD Diagnostics, Sparks, Maryland). *Klebsiella pneumoniae*, *K. oxytoca*, *E. coli*, and *P. mirabilis* organisms with MICs ≥ 2 $\mu\text{g/mL}$ for ceftriaxone or aztreonam underwent further screening for ESBL production. A decrease of >3 doubling dilutions in the MIC for either ceftriaxone or ceftazidime tested in combination with 4 $\mu\text{g/mL}$ of clavulanic acid, vs its MIC when tested alone, was used to confirm ESBL status. In vitro susceptibility was determined according to CLSI recommendations [21].

Statistical Methods

We developed a multivariable logistic regression model to estimate a propensity score for each patient's likelihood of receiving empiric PTZ therapy. Covariates included to generate the propensity score included the following: age, Pitt bacteremia score, ICU level care, profound neutropenia (absolute neutrophil count ≤ 100 $\mu\text{g/mL}$), source of infection, underlying medical conditions, and immunocompromised status. A patient who received PTZ empirically was weighted by the inverse of the probability that he or she would be treated with PTZ, and a patient

who received a carbapenem empirically was weighted by the inverse of the probability that he or she would be treated with a carbapenem, equivalent to 1 minus his or her propensity score. An IPW model can be unduly influenced by extreme weights assigned to patients with a low probability of getting the prescribed treatment. Therefore, stabilized IPWs were created by multiplying the marginal probability of treatment assignment by the IPW. The performance of the propensity model was assessed by comparing baseline characteristics in the 2 treatment groups after applying the stabilized IPW. Baseline characteristics were summarized as percentages or means with standard deviations for categorical and continuous variables, respectively. Comparisons between the treatment groups were made using the Student *t* test for continuous variables and the Pearson χ^2 test for categorical variables.

The primary outcome was mortality within 14 days from the first day of detectable bacteremia. Patients who were alive at 14 days after the first day of antibiotic therapy were administratively censored. Of note, all patients began antibiotic therapy on the first day positive blood cultures were obtained. A stabilized IPW survival curve was developed and comparisons between the exposure groups were made using the log-rank test. A Cox proportional hazards model using the stabilized IPW cohort was used to compare the impact of empiric PTZ and empiric carbapenem therapy on all-cause mortality within 14 days from the first day

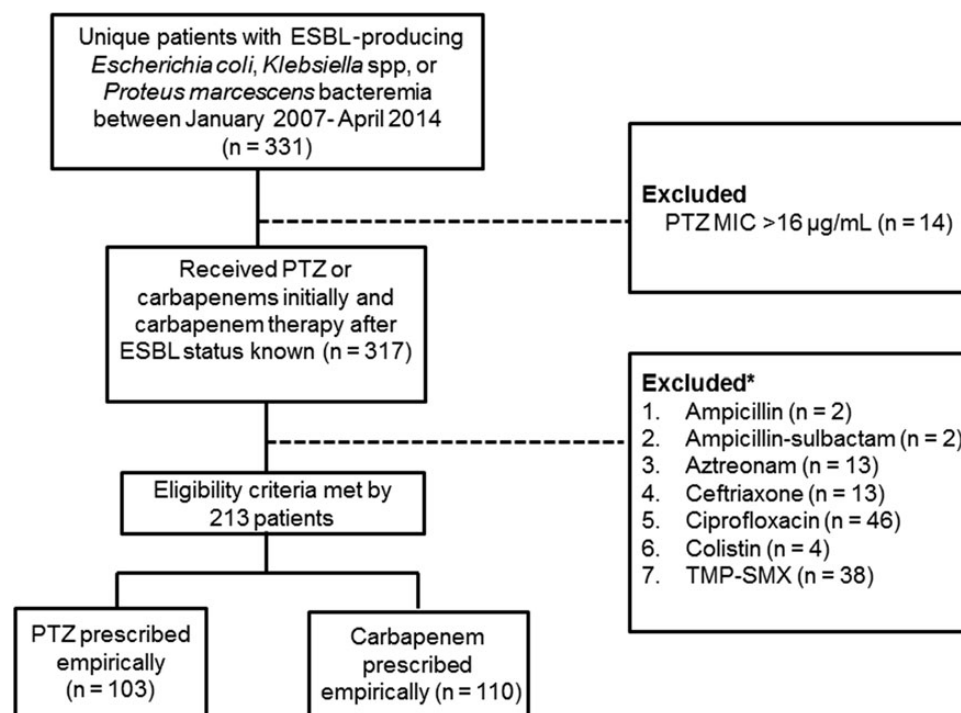


Figure 1. Design of a study of patients receiving piperacillin-tazobactam (PTZ) vs carbapenem therapy for extended-spectrum β -lactamase (ESBL)-producing bacteremia. *Some patients received >1 of the antibiotic agents listed. Abbreviations: MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 1. Baseline Characteristics of 213 Patients With Extended-Spectrum β -Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy, Prior to Culture-Directed Therapy With Carbapenem Therapy^a

Characteristic	Complete Cohort (N = 213)			Cohort Adjusted With the Use of Stabilized Inverse Probability of Exposure Weighting		
	PTZ/Carbapenem (n = 103 [48%])	Carbapenem (n = 110 [52%])	P Value	PTZ/Carbapenem	Carbapenem	P Value
Age, mean (SD)	48.1 (22.8)	48.2 (19.0)	.96	48.2	48.0	.89
Male sex, No. (%)	59 (57.3)	72 (60.5)	.63	56.9	57.4	.94
Pitt bacteremia score, mean (SD)	2.3 (1.9)	2.1 (1.3)	.15	2.2	2.1	.79
ICU-level care, day 1	33 (32.0)	39 (35.5)	.70	33	36	.70
ANC ≤ 100 cells/ μ L, No. (%)	16 (15.5)	16 (13.4)	.66	14.5	14.4	.99
Likely source of bacteremia, No. (%)						
Central line associated	45 (43.7)	52 (43.7)	1.00	46.3	44.1	.77
Urinary tract	20 (19.4)	24 (20.2)	.89	19.3	18.4	.87
Biliary	7 (6.8)	12 (10.1)	.38	8.3	8.3	.98
Intra-abdominal	20 (19.4)	16 (13.4)	.23	16.3	15.1	.82
Pneumonia	11 (10.7)	9 (7.6)	.43	9.8	11.3	.77
Preexisting medical conditions, No. (%)						
End-stage liver disease	16 (15.5)	14 (11.8)	.42	13.8	13.3	.93
End-stage renal disease	4 (3.9)	7 (5.9)	.49	5.3	7.5	.61
Structural lung disease	13 (12.6)	5 (4.2)	.03	7.7	7.0	.86
Neurologic	11 (10.7)	9 (7.6)	.43	7.5	6.6	.77
Congestive heart failure	8 (7.8)	8 (6.7)	.77	6.4	6.2	.93
Immunocompromised ^b , No. (%)	49 (47.6)	76 (69.0)	.04	54.6	57.9	.92

Abbreviations: ANC, absolute neutrophil count; ICU, intensive care unit; PTZ, piperacillin-tazobactam; SD, standard deviation.

^a All patients had isolates susceptible in vitro to both PTZ and carbapenems (ertapenem, imipenem, meropenem).

^b Includes corticosteroid therapy equivalent to prednisone ≥ 2 mg/kg or ≥ 20 mg daily for at least 14 days, (2) biologic agents in the preceding 30 days, (3) solid organ transplant, (4) hematopoietic stem cell transplant in the preceding 1 year, (5) cancer chemotherapy within 6 months, (6) congenital immunodeficiency, or (7) human immunodeficiency virus with CD4 count ≤ 200 cells/ μ L.

of bacteremia. Additional adjustment for any variables with a *P* value $< .20$ on univariable analysis were included in an adjusted Cox regression model. The proportional hazards assumption was checked for all models. All tests were 2-tailed and *P* values $\leq .05$ were used for statistical significance testing. Data were analyzed using the R statistical software package, version 3.0.2.

RESULTS

Antibiotic Data

There were 331 unique patients with ESBL bacteremia during the study period, 213 of whom met eligibility criteria (Figure 1). One hundred three patients (48%) received PTZ empirically and were transitioned to a carbapenem after susceptibility results were available, and 110 (52%) received carbapenems for their entire treatment course. The median time to changing therapy from PTZ to carbapenem therapy was 84 hours. All agents were dose-adjusted for renal insufficiency as appropriate. Of patients receiving PTZ empirically, 61% received 3.375 g every 6 hours and 39% received 4.5 g every 6 hours, or equivalent dosages after accounting for renal insufficiency. Carbapenems prescribed

included meropenem (88%), imipenem-cilastatin (4%), and ertapenem (8%). Meropenem was dosed at 1 g every 8 hours (78%) or 2 g every 8 hours (22%). Imipenem-cilastatin and ertapenem were dosed at 500 mg every 6 hours and 1 g every 24 hours, respectively. No patients received prolonged-infusion PTZ or carbapenem therapy. Twenty-eight (8%) patients received >24 hours of combination therapy with either ciprofloxacin or an aminoglycoside during their treatment course; these patients were equally distributed between the treatment groups. The median duration of the second agent was 36 hours.

Baseline Characteristics

Notable differences in baseline characteristics between the 2 treatment groups existed. Patients receiving empiric therapy with PTZ were less likely to be immunocompromised and more likely to have underlying structural lung disease (chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis) (Table 1). IPW yielded 2 well-balanced groups with no lingering differences noted between the groups. Common sources of bacteremia included catheter-related (46%), urinary (21%), intra-abdominal (17%), pneumonia (9%), and biliary (9%). In

Table 2. Fourteen-Day Mortality for 213 Patients With Extended-Spectrum β -Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy in a Stabilized Inverse Probability-Weighted Cohort^a

Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P Value	Adjusted HR ^a	95% CI	P Value
Piperacillin-tazobactam	1.78	1.00–3.13	.05	1.92	1.07–3.45	.03
Age (per 10-y increase)	1.28	1.09–1.50	.11	1.18	0.99–1.41	.07
Pitt bacteremia score	1.55	1.39–1.72	<.001	1.49	1.28–1.72	<.001
Intensive care unit level care, day 1	4.49	2.53–7.98	<.001	4.25	1.86–9.71	<.001
Immunocompromised	1.09	0.62–1.93	.76
Inadequate source control ^b	1.18	0.81–1.72	.39

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Inverse probability-weighted sample with additional adjustment for age, Pitt bacteremia score, and intensive care unit-level care.

^b Inadequate source control refers to central lines not removed in the setting of central line-associated bacteremia or intra-abdominal abscesses not drained when intra-abdominal fluid collections were present.

the IPW cohort, approximately 8% and 7% of patients in the PTZ and carbapenem groups, respectively, had inadequate source control during the treatment course.

Mortality

There were 17 deaths (17%) in the PTZ group and 9 deaths (8%) in the carbapenem group within 14 days of the first positive blood culture. Covariates independently associated with a higher risk of death by day 14 included higher Pitt bacteremia scores and ICU-level care needed on day 1 of bacteremia. There was a 1.92 times increased risk of death by day 14 for patients receiving empiric PTZ compared with patients receiving empiric

carbapenems, adjusting for age, Pitt bacteremia score, and ICU level of care (95% confidence interval [CI], 1.07–3.45; Table 2). Figure 2 shows an IPW-adjusted Kaplan–Meier curve depicting vital status at 14 days for patients receiving empiric PTZ compared with empiric carbapenem therapy. The distribution of PTZ MICs were as follows: 2 μ g/ml (1%), 4 μ g/ml (39%), 8 μ g/ml (46%), and 16 μ g/ml (14%).

DISCUSSION

Our results suggest that carbapenems should be used as preferred therapy for patients suspected to have ESBL bacteremia. However, liberal use of carbapenems is not without consequence and can result in the emergence of resistance to this agent [14, 15], severely limiting future treatment options. Therefore, the decision to use empiric carbapenem therapy should be carefully considered after factoring in relevant data such as a previous history of ESBL colonization or infection, prolonged hospital or long-term-care stay prior to infection onset, and recent PTZ or cephalosporin exposure [22–24]. Our findings highlight the need for rapid diagnostics that can detect the presence of resistance mechanisms earlier than traditional phenotypic methods to identify antibiotic resistance.

Although the addition of tazobactam appears to reduce the hydrolyzing effect of β -lactamase enzymes on the β -lactam ring of piperacillin, the activity of tazobactam is diminished when a high concentration of bacteria is present (“inoculum effect”) [25, 26]. The contribution of this proposed phenomenon toward treatment failures, however, has not been the subject of comprehensive clinical evaluation. The presence of other mechanisms of β -lactam resistance in a given bacteria, such as AmpC β -lactamase production or additional ESBLs, further complicates the bacterial environment, reducing the efficacy of PTZ [16].

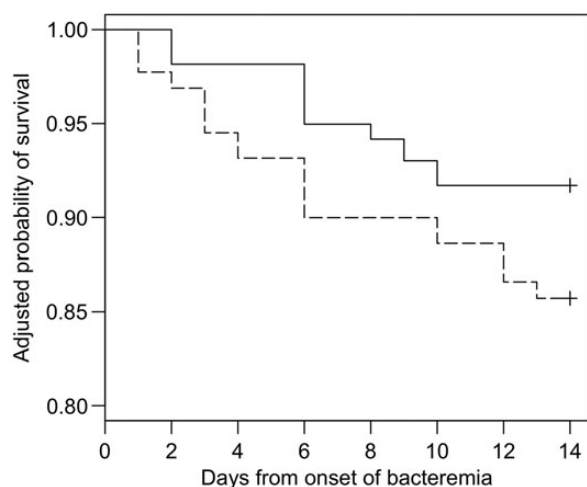


Figure 2. Probability of survival censored at day 14 for patients with extended-spectrum β -lactamase (ESBL)-producing bacteremia in an inverse probability-weighted sample. Solid line represents individuals treated with carbapenems for the entire duration of therapy; dotted line represents individuals treated with piperacillin-tazobactam and converted to carbapenem therapy after ESBL status was known; log-rank test = 0.03.

Published data on the use of PTZ for the treatment of infections caused by ESBL-producing organisms are **conflicting**. An early case report demonstrated treatment failure with PTZ in a patient with prosthetic valve endocarditis caused by ESBL-producing *K. pneumoniae* due to development of resistance during therapy [3]. A prospective, observational study by Rodríguez-Baño et al evaluated 103 patients at 6 Spanish hospitals with ESBL *E. coli* bacteremia receiving either β -lactam/ β -lactamase inhibitor or carbapenem therapy as empiric therapy [27]. No association was found between PTZ and mortality (adjusted hazard ratio, 1.14 [95% CI, .29–4.40]). However, there were only 7 deaths in the β -lactam/ β -lactamase group and 5 deaths in the carbapenem group within 14 days, undermining the ability to detect a difference if one existed. The relatively few events may be due to the predominance of urinary or biliary sources for bacteremia, which was the case for approximately 70% of patients. **Urinary and biliary sources usually result in infections more responsive to therapy** compared with **pneumonia**, **intra-abdominal** infections, or **endovascular** infections [6,7]. The authors acknowledge that more data are needed to guide therapeutic options for deep-seated ESBL infections.

In the Spanish study, >90% of patients received 4.5 g every 6 hours [27]. The generalizability of their findings is limited, as 3.375 g every 6 hours is more traditionally prescribed, particularly for nonpseudomonal infections [28,29]. We did not find a difference in clinical outcomes when comparing patients receiving 4.5 g of PTZ every 6 hours with patients receiving carbapenem therapy (data not shown), but this finding was potentially impacted by the small sample size; only 39% of patients received high-dose PTZ therapy in our cohort. It is unclear if larger quantities of PTZ exceed the capacity of ESBLs to hydrolyze them. More data are needed to evaluate the clinical outcomes of patients with ESBL bacteremia receiving 4.5 g intravenously every 6 hours compared with carbapenem therapy or with extended-infusion PTZ therapy.

Since 2010, phenotypic testing for ESBL status by clinical microbiology laboratories has been considered optional [30], resulting in clinicians often being unaware of which infections are ESBL producing. Approximately **62%–95% of confirmed ESBL-producing organisms are susceptible in vitro to PTZ** [17, 18, 31]. This is **concerning** as clinicians may inadvertently prescribe **suboptimal agents** (ie, **PTZ**) to **critically ill** patients with invasive ESBL infections.

There are some limitations with our study. First, this is a single-center study and our results may not be generalizable to other institutions with a different distribution of PTZ MICs against ESBLs. Second, we do not have molecular analysis to determine the enzymes associated with ESBL production in our study isolates. It is unclear if the utility of PTZ varies depending on the mechanism of ESBL resistance. It is important to emphasize that our findings are specific for PTZ and should not be

extended to newer β -lactam/ β -lactamase inhibitor agents currently being developed, until more data are available.

Due to the **retrospective** nature of our study, we may not have been able to control for all measured and unmeasured confounders that may impact the association of PTZ and 14-day mortality in patients with ESBL bacteremia. However, until more definitive studies are performed, our findings suggest that PTZ is inferior to carbapenem therapy for the treatment of ESBL bacteremia. For patients at high risk of invasive ESBL infections, early carbapenem therapy should be considered.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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