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Outcomes analysis in patients with extended-spectrum beta-lactamase bacteremia empirically treated with piperacillin/tazobactam versus carbapenems

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ABSTRACT

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria are associated with worse outcomes and have limited treatment options. Carbapenems remain the drug of choice for these infections due to evidence of a mortality benefit and the mixed clinical efficacy associated with piperacillin/tazobactam (PTZ). Though definitive treatment for ESBL infections is well defined, evidence for appropriate empiric therapy remains inconclusive, and the role of rapid molecular assays that identify ESBL has not been evaluated. This multicenter retrospective study at nine Baylor Scott & White Health sites included patients who had positive blood cultures with ESBL-producing bacteria identified by rapid molecular assay and were empirically prescribed PTZ or carbapenems. A total of 117 patients were included in the study; 66 received empiric PTZ and 51 received carbapenems. Results showed no difference in hospital mortality (3% vs 7.8%, $P = 0.4$), hospital length of stay (6.1% vs 5.9%, $P = 0.88$), intensive care unit length of stay (4.7% vs 3.3%, $P = 0.39$), or recurrent ESBL bacteremia (7.6% vs 7.8%, $P = 0.99$) between the PTZ and carbapenem empiric treatment groups, respectively. In the era of rapid molecular assays, these results suggest that empiric PTZ use and avoidance of empiric carbapenem therapy in the first 24 hours of infection can be considered until a microbiological diagnosis is confirmed.

KEYWORDS Bacteremia; carbapenems; empiric therapy; extended-spectrum beta-lactamase; piperacillin/tazobactam; rapid diagnostics

Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are becoming increasingly problematic. In certain areas of the USA, rates of ESBL infections have nearly doubled (11.1–22.2 per 100,000 patient days) over the span of 5 years.[1] In a study conducted in 2012 that analyzed over 5000 isolates, the most common organisms and the overall frequency of ESBLs was 16% for *Klebsiella pneumoniae* and 11.9% for *Escherichia coli*.[2] Not only are these infections associated with worse outcomes, such as increased mortality, but their ability to hydrolyze and inactivate beta-lactam antibiotics leaves clinicians with limited treatment options.[3]

Though penicillins on their own are not appropriate for these infections, studies have shown that when combined with beta-lactamase inhibitors, such as piperacillin/tazobactam (PTZ), they have moderate to high in vitro activity against ESBL organisms; however, this does not necessarily translate to clinically significant outcomes.[4,5] Studies investigating outcomes of ESBL bacteremia have shown mixed clinical efficacy of beta-lactam/beta-lactamase inhibitor (BLBLI) combinations when compared to a carbapenem, with some showing no difference in mortality and others showing a benefit to carbapenem therapy.[6–9] Reasons often cited for the difference in efficacy of BLBLI combinations include production of multiple types of ESBLs in the same isolate and an inoculum effect—both potentially rendering BLBLI combinations less effective than carbapenems. Carbapenems, on the other hand, are highly stable against the hydrolysis mediated by ESBLs and are not as susceptible to the inoculum effect as PTZ. Studies have also illustrated a

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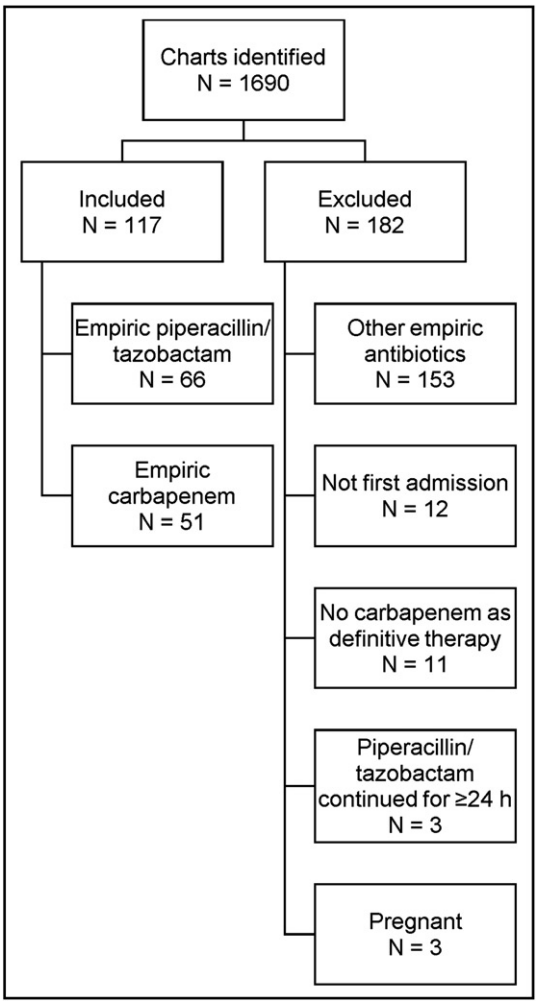

Figure 1. Patient selection. A total of 300 cases were reviewed from the identified charts.

more consistent mortality benefit with carbapenems when compared to other antibiotics.[6,9]

Existing data concerning the use of BLBLI combinations in these infections remain controversial because conflicting outcomes from studies make it difficult to draw definitive conclusions about their place in therapy. The purpose of this retrospective study was to evaluate the outcomes of PTZ versus a carbapenem as empiric therapy in hospitalized patients who develop ESBL bacteremia identified via rapid diagnostic assay.

METHODS

This study was a multicenter, retrospective chart review of patients admitted to Baylor Scott & White Health (BSWH) hospitals in the North Texas division. This study was approved by the institutional review board at Baylor Scott & White Research Institute. Patients were included if they were 18 years of age or older, had a positive ESBL blood culture, and received at least one dose of empiric PTZ or a carbapenem (meropenem or ertapenem) prior to ESBL blood culture between January 1, 2014, and September 22, 2017. Only the first episode of ESBL bacteremia was eligible for inclusion. Patients were excluded if they were pregnant, incarcerated, continued on PTZ for >24 hours after positive ESBL blood culture result, or did not receive a carbapenem as definitive therapy.

Patients were selected utilizing a clinical surveillance software tool (MedMined) that identified patients with blood cultures reported as positive for ESBL-producing bacteria within the study time period. In daily practice, all positive blood cultures were processed through a rapid diagnostic assay that allowed for prompt identification (within 3 hours of positive blood culture) of bacterial species as well as common resistance markers, including CTX-M (Verigene, Nanosphere, Inc., Northbrook, IL). Patients eligible for inclusion were assigned a random number between zero and one using the "RandNum" function within Microsoft Excel. Numbers were fixed and then ordered from smallest to largest to randomize the subjects. This randomization strategy follows the method of simple randomization as described by Altman and Bland.[10] Data were collected until 300 patients were reviewed.

Patient characteristics and culture data were obtained via review of the electronic medical record. Patient data collected included age, gender, and risk factors for ESBL based on prior studies (prior hospitalization and/or antibiotic therapy within 4 weeks of bacteremia onset, residence in nursing homes/long-term care facilities prior to admission, past medical history of diabetes mellitus, intermittent hemodialysis prior to admission, prior history of a positive non-blood culture specimen exhibiting ESBL resistance within 1 year of bacteremia onset, presence of a long-term indwelling urinary catheter/chronic Foley and/or central venous catheter on admission, frequent emergency department visits, immunosuppression, and neutropenia).[11–14] Markers for severity of infection included admission to the intensive care unit (ICU), presence of septic shock, and need for mechanical ventilation within 72 hours of ESBL blood culture collection. The minimum inhibitory concentration (MIC) of PTZ was also evaluated.

Empiric PTZ or carbapenem therapy was defined as administration prior to positive blood culture result. Previous antibiotic therapy with either fluoroquinolones, third-generation cephalosporins, or aminoglycosides within 4 weeks of bacteremia onset was considered a risk factor for ESBL infection. Immunosuppression was defined as ongoing systemic immunosuppressant therapy with tacrolimus, sirolimus, mycophenolate, monoclonal antibodies, or corticosteroids at doses equivalent to ≥2 mg/kg/day of prednisone. Neutropenia was an absolute neutrophil count <100 cells/μL, and a CD4 < 200 cells/μL implied uncontrolled HIV/AIDS. Patients had septic shock if they were administered vasopressors within 72 hours of ESBL blood culture collection or required vasopressors on admission.

The primary outcome of this study was inpatient mortality during the encounter for ESBL bacteremia for which patients received therapy. Secondary outcomes included hospital length of stay; ICU length of stay, defined as admission to the ICU as

Table 1. Baseline characteristics of patients in the two empiric treatment groups[a]

Variable	Piperacillin/tazobactam ($N = 66$)	Carbapenem ($N = 51$)	P value
Age (years) (range 21–94)	67.9 (14.1)	64.9 (14.9)	0.27
Female	31 (47%)	31 (61%)	0.19
Prior hospitalization	17 (26%)	16 (31%)	0.54
Previous antibiotic therapy	14 (21%)	9 (18%)	0.82
Nursing home/long-term care facility residence	7 (11%)	6 (12%)	0.99
History of diabetes mellitus	29 (44%)	25 (49%)	0.71
History of positive non-blood ESBL culture	8 (12%)	13 (26%)	0.09
Frequent ED visits	4 (6%)	5 (10%)	0.50
ICU admission	25 (38%)	20 (39%)	0.99
Septic shock	12 (18%)	8 (16%)	0.81
Mechanical ventilation	1 (2%)	2 (4%)	0.58
Central venous catheter	0	1 (2%)	0.44
Indwelling/chronic Foley	6 (9%)	0	0.04
Hemodialysis	4 (6%)	1 (2%)	0.39
Devices	0	6 (12%)	0.006
Percutaneous tube	2 (3%)	2 (4%)	0.99
Immunosuppression	7 (11%)	7 (14%)	0.78
Identification of ESBL (hours)	22.5 (9.5)	25.1 (12.4)	0.20
Suspected source of bacteremia			0.34
Urinary	48 (72%)	37 (73%)	
Intra-abdominal	14 (21%)	8 (16%)	
Respiratory	1 (2%)	0	
Other/unknown	3 (5%)	6 (12%)	
Organism			0.29
E. coli	59 (89%)	42 (82%)	
Klebsiella spp.	7 (11%)	9 (18%)	

ED indicates emergency department; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit.
[a]Data presented as *n* (%) or mean (SD).

a result of ESBL bacteremia; and rates of recurrent ESBL bacteremia, defined as readmission within 6 months with positive ESBL blood cultures (same species and resistance pattern). If the patient was in the ICU prior to bacteremia onset, ICU length of stay was defined as the number of days in the ICU after the positive ESBL blood culture.

Patient characteristics were compared between patients who received PTZ and those who received a carbapenem using Fisher's exact tests for categorical variables and *t* tests or Wilcoxon rank sum tests for continuous variables. All analyses were performed using STATA (version 14.0).

RESULTS

The clinical surveillance software identified 1690 patients. Of the 300 charts that were reviewed, 117 patients were included from nine sites in the North Texas division of BSWH. Sixty-six patients received empiric PTZ and 51 received an empiric carbapenem. *Figure 1* depicts the breakdown of patient selection and describes included and excluded patients.

Baseline characteristics were well matched between the study groups *(Table 1)*. There were no significant differences between the groups with respect to potential risk factors for ESBL infection, including prior hospitalization, previous antibiotic therapy, nursing home/long-term care facility residence, history of positive non-blood ESBL culture, hemodialysis, and presence of central venous catheter on admission. More patients who were treated empirically with PTZ had chronic, in-dwelling Foley catheters present on admission (0.9% vs 0%, $P = 0.035$). Conversely, those treated with an empiric carbapenem at baseline had more devices (0% vs 11.8%, $P = 0.006$), which

Table 2. MIC of piperacillin/tazobactam for isolates in each empiric antibiotic study group

MIC (g/mL)	Piperacillin/tazobactam	Carbapenem
≤4	4	3
8	44	37
16	5	3
>16	7	0

MIC indicates mean inhibitory concentration.

Table 3. Outcomes of patients in the two empiric treatment groups[a]

Outcome	Piperacillin/tazobactam ($N = 66$)	Carbapenem ($N = 51$)	*P* value
Hospital mortality	2 (3%)	4 (7.8%)	0.40
Hospital LOS (days)	7.9 (6.1)	7.1 (5.9)	0.88
ICU LOS (days)	4.4 (4.7)	3.4 (3.3)	0.39
Recurrent ESBL bacteremia	5 (7.6%)	4 (7.8%)	0.99

ESBL indicates extended-spectrum beta-lactamase; ICU, intensive care unit; LOS, length of stay.
[a]Data presented as *n* (%) or mean (SD).

included ventriculoperitoneal shunts, bladder implants, implanted surgical hardware, and infected Mediports.

Although patients on empiric PTZ had higher rates of admission to the ICU and septic shock, the results were not statistically significant ($P = 0.99$ and 0.81, respectively). Of those who received an empiric carbapenem, two (3.9%) patients required mechanical ventilation versus one patient (1.5%) in the empiric PTZ group ($P = 0.58$).

ESBL resistance (due to the CTX-M gene) was reported, on average, between 22.5 and 25.1 hours (PTZ vs carbapenem) from blood culture collection ($P = 0.197$). The most commonly isolated organism was *E. coli* (89.4% vs 82.4%, $P = 0.291$), and the most common suspected source of bacteremia was the urinary tract (72.2% vs 72.5%, respectively). *Table 1* lists other suspected sources. The MIC of PTZ was also collected and is depicted in *Table 2*. One of the two patients who received empiric PTZ and died had a PTZ MIC >16 μg/mL. There was no statistically significant difference in the primary outcome of hospital mortality between those started empirically on either PTZ or a carbapenem (3% vs 7.8%, respectively). There was also no statistically significant difference in hospital length of stay (7.9 vs 7.1 days), ICU length of stay (4.4 vs 3.4 days), or rates of recurrent ESBL bacteremia (7.6% vs 7.8%) *(Table 3)*.

DISCUSSION

This retrospective study found no difference in inpatient mortality between patients empirically treated with PTZ or a carbapenem for suspected ESBL bacteremia identified by rapid molecular assay. To our knowledge, this is the first study that incorporates rapid diagnostic testing for resistant phenotypes in evaluating outcomes with empiric PTZ versus a carbapenem in the setting of ESBL infection.

Previously published reports assessing the role of PTZ versus a carbapenem as empiric therapy illustrated mixed clinical results. A 2012 meta-analysis including 21 studies determined that there was no significant difference in all-cause mortality between a carbapenem and a BLBLI administered as definitive treatment (relative risk 0.52, 95% confidence interval [CI], 0.23–1.13) or empiric treatment (relative risk 0.91, 95% CI, 0.66–1.25).[6] Similarly, a 2016 retrospective study concluded that 30-day mortality was comparable between those empirically treated with either PTZ or a carbapenem (30.9% vs 29.8%, $P = 0.89$).[8] However, the authors acknowledged that their results might not be generalizable to patients with nonurinary sources of bacteremia. On the contrary, a retrospective chart review from 2016 demonstrated an increased 14-day mortality associated with empiric PTZ compared with empiric carbapenem therapy for ESBL bacteremia, with a 1.92 times higher adjusted risk of death for those in the PTZ group (95% CI, 1.07–3.45).[9]

Most recently, the MERINO trial (a prospective, randomized, multicenter, open-label noninferiority trial) evaluated outcomes of PTZ or meropenem as definitive therapy in patients with bloodstream infections caused by ceftriaxone-nonsusceptible *E. coli* or *K. pneumoniae*, of which 86% of isolates were confirmed to have phenotypic ESBL production.[15] The authors found that PTZ did not meet the noninferiority criteria for the primary outcome of 30-day mortality compared to meropenem. Interestingly, 26.2% of patients randomized to meropenem received a BLBLI empirically and were randomized when ceftriaxone nonsusceptibility was identified, which occurred after >52 hours of empiric therapy in each group. Given that patients in our study had identification of ESBL much quicker (<26 hours), this afforded the opportunity to switch to appropriate definitive therapy earlier. This fact by itself may explain why no difference in mortality was seen between the groups in our study.

Though the definition of appropriate antibiotics after ESBL identification varied between studies, at our health system, it is generally accepted that carbapenems are preferred for definitive therapy for ESBL infections. It is also important to note that none of the aforementioned studies evaluated outcomes of empiric treatment with the availability of rapid diagnostic resistance testing. The importance of rapid resistance testing allows for change in antimicrobials to appropriate therapy within approximately 24 hours from blood culture collection. The particular rapid diagnostic assay utilized in this study allowed for detection of the genus and/or species and resistance mechanism within 3 hours of a positive blood culture. The assay was only able to identify resistance due to the CTX-M gene, which is the most

prevalent gene to code for ESBL resistance.[16,17] Thus, if another gene mediating resistance was present, it would prolong the time to identification. Given availability of this technology, the in vitro activity of PTZ may be acceptable within the short window until ESBL resistance can be identified and the patient is transitioned to definitive carbapenem therapy. It should be noted that PTZ had reported in vitro activity against most isolates in this study.

Strengths of this study include its multicenter design, moderate sample size, and extensive assessment of baseline characteristics to account for potential risk factors for ESBL infection as well as severity of presentation. Limitations of this study include its retrospective design as well as the lack of applicability to settings that do not utilize rapid diagnostic testing capable of identifying ESBL resistance. The role of empiric antibiotics other than PTZ or carbapenems was not assessed in this study. We did not collect data with respect to cases of polymicrobial bacteremia. Although the study involved multiple centers, we were not able to access medical records from hospitals outside the network. We could not account for inherent prescriber bias, because providers may be more inclined to prescribe a carbapenem empirically in patients with more severe presentations. However, both groups were well matched at baseline with respect to markers of severity of infection.

Based on the results of this retrospective chart review, the use of empiric PTZ for suspected ESBL infections does not seem to increase the risk of hospital mortality, hospital or ICU lengths of stay, or rates of recurrent ESBL bacteremia and can therefore be considered a viable alternative to carbapenems if rapid diagnostics are available to detect resistance mechanisms. Future research is warranted to determine the role of rapid diagnostics in antimicrobial stewardship efforts, particularly the impact of earlier identification of resistance.

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