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Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

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IMPORTANCE Extended-spectrum β-lactamases mediate resistance to third-generation cephalosporins (eg, ceftriaxone) in *Escherichia coli* and *Klebsiella pneumoniae.* Significant infections caused by these strains are usually treated with carbapenems, potentially selecting for carbapenem resistance. Piperacillin-tazobactam may be an effective "carbapenem-sparing" option to treat extended-spectrum β-lactamase producers.

OBJECTIVES To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E coli* or *K pneumoniae*.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority, parallel group, randomized clinical trial included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017. Adult patients were eligible if they had at least 1 positive blood culture with *E coli* or *Klebsiella* spp testing nonsusceptible to ceftriaxone but susceptible to piperacillin-tazobactam. Of 1646 patients screened, 391 were included in the study.

INTERVENTIONS Patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants) or meropenem, 1 g, every 8 hours (n = 191 participants) for a minimum of 4 days, up to a maximum of 14 days, with the total duration determined by the treating clinician.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality at 30 days after randomization. A noninferiority margin of 5% was used.

RESULTS Among 379 patients (mean age, 66.5 years; 47.8% women) who were randomized appropriately, received at least 1 dose of study drug, and were included in the primary analysis population, 378 (99.7%) completed the trial and were assessed for the primary outcome. A total of 23 of 187 patients (12.3%) randomized to piperacillin-tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]; *P* = .90 for noninferiority). Effects were consistent in an analysis of the per-protocol population. Nonfatal serious adverse events occurred in 5 of 188 patients (2.7%) in the piperacillin-tazobactam group and 3 of 191 (1.6%) in the meropenem group.

CONCLUSIONS AND RELEVANCE Among patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

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Gram-negative bacteria that produce extended-spectrum β-lactamase (ESBL) enzymes are a global public health concern.[1] Based on national surveillance data from 2011, the US Centers for Disease Control and Prevention estimated that ESBL producers accounted for at least 26 000 infections and 1700 deaths annually.[2] A key feature of ESBL-producing *Enterobacteriaceae* is phenotypic resistance to oxyiminocephalosporins, in addition to penicillins.[3] ESBL producers are increasingly commonplace in both community and health care settings.[4] Carbapenems have been regarded as the treatment of choice for serious infections caused by ESBL producers.[3,5] However, increased use of carbapenems may select for carbapenem resistance in gram-negative bacilli,[6,7] which currently represents the greatest threat in terms of antibiotic resistance.

One strategy to reduce the global use of carbapenems could be to reevaluate alternative agents (ie, carbapenem-sparing regimens). β-Lactam/β-lactamase inhibitor (BLBLI) combination antibiotics, such as piperacillin-tazobactam, have been considered a carbapenem-sparing option for treatment of ESBL producers.[8,9] ESBL enzymes are inhibited by tazobactam, and ESBL producers are frequently susceptible to BLBLIs in vitro.

Some observational studies have suggested that BLBLIs may be clinically effective for treating infections caused by ESBL producers,[10-13] but conflicting results have been reported.[14] This study aimed to test the hypothesis that a carbapenem-sparing regimen (piperacillin-tazobactam) is noninferior to a carbapenem (meropenem) for the definitive treatment of bloodstream infection (BSI) caused by ceftriaxone-nonsusceptible *Escherichia coli* or *Klebsiella* spp that test susceptible to piperacillin-tazobactam.

Methods

Study Design and Inclusion Criteria

The trial protocol was developed by the Australasian Society for Infectious Disease Clinical Research Network and has been previously published.[15] The full protocol is provided in Supplement 1. The protocol was designed to be pragmatic and reflect usual clinical care (PRECIS-2 diagram[16]; eFigure 7 in Supplement 2). The institutional review board for each recruiting center approved the protocol. Written informed consent was obtained from all patients or their appropriate representative. The results are reported in accordance with the CONSORT statement extension for Non-inferiority and Equivalence Trials.[17]

This was an international, multicenter, open-label, parallel group, randomized clinical trial of piperacillin-tazobactam vs meropenem for the definitive treatment of BSI caused by ceftriaxone-nonsusceptible *E coli* or *Klebsiella* spp. Adult patients (aged ≥18 years or ≥21 years in Singapore) were eligible for enrollment if they had at least 1 positive blood culture with *E coli* or *Klebsiella* spp that was nonsusceptible to ceftriaxone or cefotaxime, but remained susceptible to piperacillin-tazobactam and meropenem according to local laboratory protocols. Patients had to be randomized within 72 hours of initial positive blood culture collection. Exclusion criteria included

Key Points

Question Can piperacillin-tazobactam be used as carbapenem-sparing therapy in patients with bloodstream infections caused by ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae*?

Findings In this noninferiority randomized clinical trial that included 391 patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, the 30-day mortality rate for patients treated with piperacillin-tazobactam compared with meropenem was 12.3% vs 3.7%, respectively. The difference did not meet the noninferiority margin of 5%.

Meaning These findings do not support piperacillin-tazobactam compared with meropenem for these infections.

allergy to either trial drug or similar antibiotic classes, no expectation of survival more than 96 hours, treatment without curative intent, polymicrobial bacteremia (likely skin contaminants excepted), previous enrollment in the trial, pregnancy or breastfeeding, or requirement for concomitant antibiotics with activity against gram-negative bacilli. The primary treating clinician also had to agree to enrollment in the study prior to randomization.

Study Population, Stratification, and Randomization

Patients were screened for enrollment in 26 hospitals in 9 countries (Australia, New Zealand, Singapore, Italy, Turkey, Lebanon, South Africa, Saudi Arabia, and Canada) from February 2014 to July 2017 (eFigure 3 in Supplement 2). Patients were stratified according to infecting species (*E coli* or *Klebsiella* spp; groups E or K), presumed source of infection (urinary tract or elsewhere), and severity of disease (Pitt bacteremia score ≤4 or >4). A high-risk stratum (E2 or K2) was defined by nonurinary source for BSI and Pitt score greater than 4 (eFigure 1 in Supplement 2).

Patients were randomly assigned to either meropenem or piperacillin-tazobactam in a 1:1 ratio according to a randomization list prepared in advance for each recruiting site and stratification. The sequence was generated using random permuted blocks of 2 and 4 patients, with the allocated drug revealed using an online randomization module within the REDCap data management system.[18] All records were verified using double-data entry, with reference to the paper clinical record form.

Intervention and Follow-up

Meropenem, 1 g, was administered every 8 hours intravenously. Piperacillin-tazobactam, 4.5 g, was administered every 6 hours intravenously. Each dose of study drug was infused over 30 minutes. Study drug was administered for a minimum of 4 calendar days after randomization and up to 14 days, with the total duration of therapy determined by the treating clinician. Dose adjustment for renal impairment was made according to criteria specified in the trial protocol. The treating clinicians and investigators were not blinded to the treatment allocation.

All patients had a blood culture collected at day 3 after randomization or on any other day if febrile (temperature >38°C) up to day 5. Patients were followed up for 30 days after randomization, by telephone call if the patient was discharged from hospital. All patients had baseline clinical and demographic data recorded, as well as any antibiotics given up to 48 hours prior to initial positive blood culture and for 30 days after randomization. Clinical data were recorded daily from day of initial positive blood culture until day 5 after randomization (with day 1 being the day of randomization, which had to occur within 72 hours of initial blood culture collection) (eTable 1 in Supplement 2). On day 5, the primary treating team had the option to cease all antibiotics, continue the allocated agent or change to step-down therapy (eFigure 2 in Supplement 2).

Definitions

Empirical therapy was defined as antibiotic therapy given in the period prior to enrollment following the collection of the initial positive blood culture. Empirical therapy was defined as "appropriate" if commenced within 24 hours of initial blood culture collection and the blood isolate was susceptible in vitro to the chosen agent(s). Study drug represented definitive therapy, ie, therapy given when results of susceptibility testing were known. Treatment duration included the days of commencement and cessation of the drug.

Outcomes

The primary efficacy outcome was all-cause mortality at 30 days after randomization. Secondary outcomes included (1) time to clinical and microbiologic resolution of infection, defined as the number of days from randomization to resolution of fever (temperature >38.0°C) and leukocytosis (white blood cell count >12 000/μL; to convert to ×10⁹/L, multiply by 0.001) plus sterilization of blood cultures; (2) clinical and microbiologic success at day 4 after randomization, defined as survival plus resolution of fever and leukocytosis plus sterilization of blood cultures; (3) microbiologic resolution of infection, defined as sterility of blood cultures collected on or before day 4 after randomization; (4) relapsed bloodstream infection, defined as growth of the same organism as in the original blood culture after the end of the period of study drug administration but before day 30 after randomization; and (5) secondary infection with a meropenem- or piperacillin-tazobactam–resistant organism or *Clostridium difficile* infection, defined as growth of a meropenem- or piperacillin-tazobactam–resistant gram-negative organism from any clinical specimen collected from day 4 after randomization to day 30 or a positive *C difficile* stool test in the setting of diarrhea. Adverse events were documented for each study group. Other BSI events (caused by organisms other than *E coli* or *Klebsiella* spp) were also recorded up to 30 days. For any missing repeated variable used to define clinical resolution (eg, daily white blood cell count), the last observation was carried forward until a new observation was recorded.

Microbiological Studies

Bacteria isolated from blood cultures in enrolled patients were available for further analysis at the coordinating lab-

oratory. Minimum inhibitory concentrations (MICs) for piperacillin-tazobactam and meropenem were determined by MIC test strips (bioMérieux and Liofilchem) and interpreted according to standards defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[19] ESBL production was confirmed by combination disc testing with clavulanate.[20] Whole-genome sequencing was performed as previously described[21] (eTables 8-10 and eFigure 6 in the "Whole-Genome Sequencing Methods" section of Supplement 2) to determine sequence types (STs) and characterize β-lactamase genes.

Sample Size Calculation

Because no randomized clinical trials have previously compared treatment options for ESBL producers causing BSI, the sample size estimation was derived from the largest retrospective study available at the time.[10] The overall 30-day mortality in this observational study was 16.7% in those receiving a carbapenem. Based on a mortality rate of 14% in the control group (assuming mortality in observational cohorts may be greater than in trials with exclusion criteria) and a noninferiority margin of 5%, 454 patients were needed in total to achieve 80% power with a 1-sided α level of .025, allowing for 10% dropout.[22] A 5% noninferiority margin was chosen as the maximal difference in mortality between treatments that would be clinically acceptable, by consultation with infectious disease, critical care, and clinical trial specialists of the Australasian Society for Infectious Disease Clinical Research Network involved in the protocol development.[15]

Statistical Analysis

The primary analysis population was defined as any correctly randomized patient receiving at least 1 dose of allocated drug and was used to make inference on noninferiority of the treatment group (piperacillin-tazobactam), compared with control (meropenem), in terms of the primary outcome (30-day mortality). This was supported by an analysis of the per-protocol (PP) population. Protocol deviations defining exclusion from the primary analysis and inclusion in the PP sample were adjudicated by an assessor blinded to treatment allocation. The proportions of deaths in the study groups were calculated, with absolute risk differences determined with the meropenem group as the reference. The Miettinen-Nurminen method (MNM) was used to determine 1-sided 97.5% CIs for risk differences.[23] As a multisite study, alternate methods were also examined including scorebased methods, which extend MNM[24] and logistic regression with sites as fixed and random effects. Because the risk differences and confidence intervals for the primary and secondary outcomes were similar when estimated by MNM or logistic regression, results for the MNM are presented. Noninferiority of all-cause mortality at 30 days would be established if the upper bound of the 1-sided 97.5% CI did not cross the margin of 5%.

For secondary outcomes, parametric and nonparametric tests were used as appropriate, depending on whether the data were normally distributed. Because the secondary outcomes were considered exploratory, adjustments for multiple

comparisons were not made. For secondary outcomes, statistical tests were 2-sided, with a *P* < .05 considered significant. An analysis of the primary end point was undertaken in prespecified subgroups: (1) urinary vs nonurinary source, (2) Pitt bacteremia score of 4 or greater or less than 4, (3) *E coli* vs *K pneumoniae,* (4) appropriate vs inappropriate empirical therapy, and (5) health care–associated vs non–health care–associated BSI. In addition, a post hoc analysis was undertaken of high-income vs middle-income countries (using Organization for Economic Cooperation and Development Development Assistance Committee definitions, http://www.oecd.org/dac) and patients with the presence or absence of immune compromise.

The homogeneity of treatment effects on the primary outcome was explored across subgroups using a test for the intervention by subgroup interaction by adding this term and the subgroup as covariates in a logistic regression model, using a 2-sided significance level of *P* < .05. To quantify the effect of missing data on secondary outcomes, a post hoc sensitivity analysis using multiple imputation was performed using multivariate imputation by chained equations for both discrete and continuous data,[25] with computation via the 'mice' package in R version 3.5.0.[26]

Baseline patient characteristics were tabulated, with proportions for categorical variables, mean and SDs for normally distributed continuous variables, or median and interquartile ranges for skewed data. The influence of clinical variables other than randomized antibiotic therapy on the primary outcome was also explored in a multivariable logistic regression model, including the treatment group as an independent variable. Any variables associated with the primary outcome on bivariable analysis (2-sided *P* < .20) were included in a multivariable logistic regression model (ie, urinary tract source, Pitt score, Charlson Comorbidity Index score, Organization for Economic Cooperation and Development region, immune compromise, and health care–associated infection). The model was optimized using a step-wise approach, beginning with the bivariable model most strongly associated with the primary outcome. The goodness-of-fit of the model after each step was assessed using Akaike's information criteria. Variables that did not improve the model fit were excluded. Adjusted odds ratios for the effect of the intervention on the primary outcome with 1-sided 97.5% CIs were calculated. Analysis of raw data to determine primary and secondary outcomes, including missing value imputation via last value carried forward where appropriate, was performed in R version 4.3.1,[27] with subsequent statistical testing undertaken using Stata version 15.1 (StataCorp). The full statistical analysis plan is provided in Supplement 1.

Study Monitoring
A data and safety monitoring board (DSMB) was established, comprising 2 independent infectious disease physicians with support provided by an independent statistician. Interim analyses were performed after the first 50, 150, and 340 patients completed the 30-day follow-up period. The predefined stopping rule for superiority was a statistically significant difference (at a significance level of *P* < .001) in primary outcome.

Results

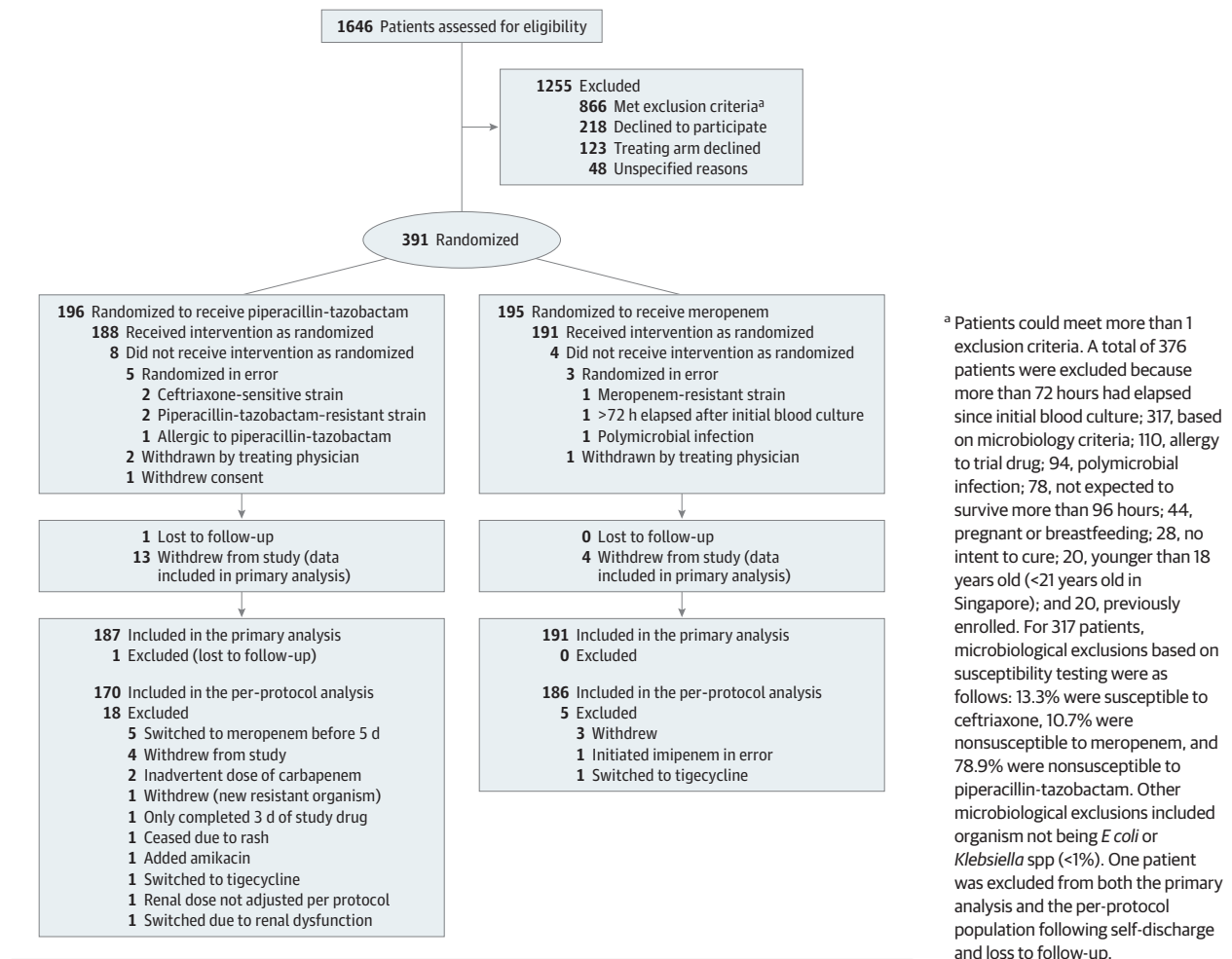### Demographic and Clinical Characteristics of Patients
A total of 1646 patients were screened during the trial period. Of these, 391 (23.8%) were randomized, although 12 patients (8 in the piperacillin-tazobactam group and 4 in the meropenem group) were randomized in error or did not receive the allocated study drug and were therefore excluded from the primary analysis population, which included 379 patients at baseline (191 received meropenem and 188 received piperacillin-tazobactam) (Figure 1). One patient who received piperacillin-tazobactam self-discharged against medical advice and was lost to follow-up, so the total number of patients who were evaluated for the primary outcome was 378. Baseline demographic and clinical details are summarized in Table 1. Overall, treatment groups were balanced with respect to baseline characteristics, although more patients in the meropenem group had diabetes (41.4% vs 31.4%), a urinary tract source for BSI (67.0% vs 54.8%), and higher APACHE II scores (21.0 vs 17.9). More patients in the piperacillin-tazobactam group had immune compromise (27.1% vs 20.9%) but had a shorter time to receipt of microbiologically appropriate antibiotics from onset of infection (5.5 hours vs 9.6 hours). By the day of randomization, 40.7% patients had resolved objective markers of infection (as defined in the secondary outcome measure of clinical and microbiological resolution), although this was similar between groups (40.3% in the meropenem group and 41.2% in the piperacillin-tazobactam group).

Following the DSMB review at 340 patients enrolled, a difference in the primary outcome was observed, at a significance level approximating the prespecified stopping rule (*P* = .004). As such, the DSMB recommended temporary suspension of the study on July 8, 2017, pending analysis once all 391 randomized patients had completed 30-day follow-up. This analysis showed that completing full enrollment was highly unlikely to demonstrate noninferiority of piperacillin-tazobactam. If the mortality rate observed in the piperacillin-tazobactam group at the interim analysis were to remain unchanged, it would have required a mortality rate greater than 43% in the meropenem group to conclude noninferiority at the 5% threshold. Even if mortality dropped to 6% in the piperacillin-tazobactam group, mortality greater than 34% in the meropenem group would be necessary. A decision to terminate the study on the grounds of harm and futility was made by the study management team, after discussion with site investigators, on August 10, 2017. This decision was made independently from the DSMB.

Primary Outcome
A total of 23 of 187 patients (12.3%) within the primary analysis population randomized to receive piperacillin-tazobactam as definitive therapy met the primary outcome of all-cause mortality at 30 days compared with 7 of 191 (3.7%) in the meropenem group (risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]; *P* = .90 for noninferiority) (eFigure 4 in Supplement 2). Results were consistent within the PP population, with 18 of 170 patients (10.6%) meeting the primary

Figure 1. Patient Recruitment, Randomization, and Flow Through Study

[a] Patients could meet more than 1 exclusion criteria. A total of 376 patients were excluded because more than 72 hours had elapsed since initial blood culture; 317, based on microbiology criteria; 110, allergy to trial drug; 94, polymicrobial infection; 78, not expected to survive more than 96 hours; 44, pregnant or breastfeeding; 28, no intent to cure; 20, younger than 18 years old (<21 years old in Singapore); and 20, previously enrolled. For 317 patients, microbiological exclusions based on susceptibility testing were as follows: 13.3% were susceptible to ceftriaxone, 10.7% were nonsusceptible to meropenem, and 78.9% were nonsusceptible to piperacillin-tazobactam. Other microbiological exclusions included organism not being *E coli* or *Klebsiella* spp (<1%). One patient was excluded from both the primary analysis and the per-protocol population following self-discharge and loss to follow-up.

outcome in the piperacillin-tazobactam group compared with 7 of 186 (3.8%) in the meropenem group (risk difference, 6.8% [one-sided 97.5% CI, −∞ to 12.8%]; *P* = .76 for noninferiority) (Table 2). Adjustment for a urinary tract source of infection and the Charlson Comorbidity Index score resulted in little change in the findings (unadjusted odds ratio, 3.69 [1-sided 97.5% CI, 0 to 8.82]; adjusted odds ratio, 3.41 [1-sided 97.5% CI, 0 to 8.38]) (eTable 5 in Supplement 2).

Secondary Outcomes

Clinical and microbiological resolution by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin-tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, −6.2% [95% CI, −15.5 to 3.1%]; *P* = .19) (Figure 2). The median day of resolution of signs of infection after randomization was 3 (interquartile range [IQR], 1,5) in the piperacillin-tazobactam group, and 2 (IQR, 1,5) in the meropenem group, but this difference was not significant (*P* = .18) (eFigure 5 in Supplement 2). There were also no significant differences in microbiological resolution by day 4 or rates of microbiological relapse, secondary infection with another multiresistant organism, or *C difficile* (Figure 2). Patients receiving

piperacillin-tazobactam did not have significantly lower rates of subsequent detection of carbapenem-resistant organisms, although this event was infrequent (3.2% vs 2.1%) (Figure 2). The secondary outcomes were also consistent within the PP population. In subgroup analyses of the primary outcome within the primary analysis population, none of the tests for interaction were significant and none of the subgroups met the noninferiority margin. In addition, the direction of risk associated with randomization to piperacillin-tazobactam remained in favor of meropenem across all subgroups (Table 2). Multiple imputation analysis for missing values showed no differences in results for the analysis of secondary outcomes when compared with the last observation carried forward method (Missing Value Method Comparisons section and eTable 11 in Supplement 2).

Adverse Events

Nonfatal serious adverse events occurred in 5 of 188 patients (2.7%) in the piperacillin-tazobactam group compared with 3 of 191 (1.6%) in the meropenem group. Details of all deaths and serious adverse events can be found in eTables 6 and 7 in Supplement 2.

Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a]

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Organism		
Escherichia coli	162 (86.2)	166 (86.9)
Klebsiella pneumoniae	26 (13.8)	25 (13.1)
Stratification[b]		
E1 (*E coli*, less severe infection)	159 (84.6)	162 (84.8)
E2 (*E coli*, more severe infection)	3 (1.6)	3 (1.6)
K1 (*K pneumoniae*, less severe infection)	23 (12.2)	25 (13.1)
K2 (*K pneumoniae*, more severe infection)	3 (1.6)	1 (0.5)
Country		
Singapore	72 (38.3)	82 (42.9)
Australia	42 (22.3)	43 (22.5)
New Zealand	10 (5.3)	9 (4.7)
Canada	1 (0.5)	1 (0.5)
South Africa	5 (2.7)	6 (3.1)
Italy	15 (8.0)	10 (5.2)
Turkey	24 (12.8)	22 (11.5)
Lebanon	8 (4.3)	7 (3.7)
Saudi Arabia	11 (5.9)	11 (5.8)
Age, median (IQR), y	70 (55-78)	69 (59-78)
Male	101 (53.7)	97 (50.8)
Acquisition		
Hospital-acquired	52 (27.7)	46 (24.1)
Health care-associated	55 (29.3)	61 (31.9)
Community-associated	81 (43.1)	84 (44.0)
Source of bacteremia		
Urinary tract	103 (54.8)	128 (67.0)
Intra-abdominal infection	34 (18.1)	28 (14.7)
Vascular catheter–related infection	3 (1.6)	3 (1.6)
Surgical site infection	8 (4.3)	4 (2.1)
Pneumonia	9 (4.8)	3 (1.6)
Mucositis/neutropenia	12 (6.4)	7 (3.7)
Musculoskeletal	1 (0.5)	0 (0)
Skin and soft tissue	4 (2.1)	1 (0.5)
Other	2 (1.1)	1 (0.5)
Unknown	12 (6.4)	16 (8.4)
Surgery within past 14 d	19 (10.1)	14 (7.3)
ICU admission	13 (7.0)	14 (7.5)
APACHE II Score, mean (SD)[c]	17.9 (6.1)	21.0 (6.9)
Charlson Comorbidity Index score, median (IQR)[d]	2.0 (1.0-4.0)	2.0 (1.0-4.0)
Pitt score, median (IQR)[e]	1.0 (0-2.0)	1.0 (0-2.0)
Immune compromise	51 (27.1)	40 (20.9)
Neutropenia	16 (8.5)	9 (4.7)
Central venous catheter	35 (18.6)	20 (10.5)
Urinary catheter/nephrostomy	51 (27.1)	37 (19.4)
Moderate-severe renal dysfunction[f]	31 (16.5)	30 (15.7)
Diabetes[f]	59 (31.4)	79 (41.4)

(continued)

Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a] (continued)

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Liver disease[f]	12 (6.4)	18 (9.4)
qSOFA score ≥2[g]	86 (45.7)	77 (40.3)
Weight, mean (SD), kg	67.2 (18.1)	69.3 (19.3)
Empirical antibiotic category		
β-lactam/β-lactamase inhibitor	38 (20.2)	49 (25.7)
Carbapenem	26 (13.8)	28 (14.7)
Other	124 (66.0)	114 (59.7)
Appropriate empirical antibiotic	126 (67.0)	127 (66.5)
Time to randomization, median (IQR), h	53.6 (44.9-65.6)	52.5 (46.0-63.7)
Time to appropriate antibiotics, median (IQR), h	5.5 (0.4-31.5)	9.6 (0.5-32.1)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation score (only collected in ICU-admitted patients); ICU, intensive care unit; IQR, interquartile range; qSOFA, quick sequential organ failure assessment score.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Stratum designated by infecting species (*E coli* = E, *K pneumoniae* = K) and disease severity (non–urinary tract source and Pitt score >4 designated as stratum 2, otherwise stratum was 1).

[c] Provides an estimate of ICU mortality, with a score ranging from 0 to 71 (scoring 20-24 signifies a mortality risk of approximately 40%)[28]

[d] Provides a 10-year mortality risk, based on weighted comorbid conditions, ranging from 0 to 29, with a score of 4 associated with an estimated 10-year survival of 53%.[29]

[e] Provides a measure of in-hospital mortality risk in patients with bloodstream infections based on clinical variables, ranging from 0 to 14, with a Pitt score ≥4 associated with a risk of mortality of approximately 40%.[30]

[f] These variables were determined at the time of enrollment based on the definitions within the Charlson Comorbidity Index score assessment following clinical review by the site investigator.

[g] qSOFA score is a 4-point scale (0-4) used to predict risk in patients with sepsis; a score ≥2 is associated with a 3- to 14-fold increase in mortality.[31]

Microbiology

A total of 306 isolates cultured from the blood of patients in the primary analysis population (80.7%) were available for microbiological analysis (n = 266 *E coli* and n = 40 *K pneumoniae*). The median piperacillin-tazobactam MIC was 2 mg/L (IQR, 1.5 mg/L to 4 mg/L). Twelve isolates (3.9%) tested nonsusceptible to piperacillin-tazobactam according to the EUCAST breakpoint for susceptibility (≤8 mg/L), although only 4 (1.3%) were nonsusceptible if the Clinical and Laboratory Standards Institute breakpoint (≤16 mg/L) was applied[32] (eFigure 6 in Supplement 2). There was no significant difference in the median MICs of piperacillin-tazobactam between the treatment groups (*P* = .64), although the median MIC was significantly greater in *K pneumoniae* than *E coli* (4 mg/L vs 2 mg/L; *P* < .001). Most isolates (99.7%) tested susceptible to meropenem (median MIC, 0.023 mg/L; IQR, 0.016 mg/L

Table 2. Primary Analysis and Subgroup Analyses

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	P Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				P Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	.31
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	.99
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	.99
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	.26
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	.70
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	.44
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	.27

Abbreviations: HAI, health care–associated infection; OECD, Organization for Economic Cooperation and Development; UT, urinary tract.

[a] The absolute risk difference was calculated with a 1-sided 97.5% CI using the Miettinen-Nurminen method. The margin for noninferiority was set at 5%. The upper bound of the CI exceeded this threshold in the primary analysis population, thus excluding noninferiority.

[b] Subgroup analyses performed using primary analysis population.

[c] Immune compromise defined by use of cytotoxic chemotherapy, high-dose corticosteroids (at least 30 mg/d of prednisolone or equivalent), antitumor necrosis factor biological agents (eg, infliximab, etanercept), other immune active monoclonal antibodies (eg, rituximab) or immunosuppressive therapy (eg, tacrolimus, everolimus, methotrexate, cyclosporin, azathioprine, mycophenolate), neutrophil count <500/μL (to convert to ×10⁹/L, multiply by 0.001) on day of bloodstream infection, presence of active solid organ/hematological malignancy, or infection with HIV (with a CD4 count <200/mm³ or an AIDS-defining condition).

to 0.032 mg/L; EUCAST breakpoint for susceptibility ≤2 mg/L). There was no clear relationship between piperacillin-tazobactam MIC and mortality in patients randomized to receive this drug (eTable 9 in Supplement 2). One *K pneumoniae* strain from Singapore (in a surviving patient randomized to meropenem) demonstrated high-level resistance to piperacillin-tazobactam (MIC ≥256 mg/L) via the presence of bla_{DHA-1} (AmpC-type β-lactamase). A single *E coli* strain from Turkey (from a surviving patient randomized to meropenem) demonstrated nonsusceptibility to meropenem (MIC, 4 mg/L) via $bla_{OXA-162}$ (a variant of OXA-48 carbapenemase).

Phenotypic ESBL production was confirmed in 86.0% of isolates (85.0% of *E coli* and 92.5% of *K pneumoniae*). Whole-genome sequencing data were available for 293 (77.3%) of the initial blood culture isolates from patients in the primary analysis population. The dominant *E coli* multilocus ST was ST131 (56.8%), with a small number of multiple other STs represented. For *K pneumoniae*, no ST predominated, although ST25 (16.7%) and ST15 (11.1%) were most common. The K2 capsular serotype, associated with hypervirulence,[33] was the most com-

mon serotype detected in 6 of 36 *K pneumoniae* infections (16.7%); no strains with K1 serotype were identified. ESBL genes were confirmed in 85.3% of isolates, with 10.2% possessing acquired *ampC* genes (predominantly bla_{CMY-2}); 2.0% carried both ESBL and *ampC*. As previously described,[21] the predominant ESBL genes were bla_{CTX-M}-type (83.5%), with the most common subtypes being $bla_{CTX-M-15}$ (54.5%), $bla_{CTX-M-27}$ (13.0%), and $bla_{CTX-M-14}$ (11.0%). The presence of narrow-spectrum oxacillinases (such as bla_{OXA-1} and variants) was also common (seen in 67.6% of all strains), and may compromise β-lactamase inhibition by tazobactam.[34,35]

Discussion

In patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, noninferiority of piperacillin-tazobactam for the primary outcome of 30-day mortality could not be demonstrated when compared with meropenem. The overall mortality in this study (7.9%) was lower

Figure 2. Secondary Outcomes

Measure of Success	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)	
	Piperacillin-Tazobactam	Meropenem		
Clinical and microbiological success at day 4[a]	121/177 (68.4)	138/185 (74.6)	-6.2 (-15.5 to 3.1)	
Microbiological success at day 4	169/174 (97.1)	184/185 (99.5)	-2.3 (-6.1 to 0.4)	

Favors Meropenem | Favors Piperacillin-Tazobactam

-20 -15 -10 -5 0 5 10
Between-Group Risk Difference (95 CI), %

Measure of Failure	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)	
	Piperacillin-Tazobactam	Meropenem		
Microbiological relapse	9/187 (4.8)	4/191 (2.1)	2.7 (-1.1 to 7.1)	
Secondary infection with multiresistant organism or *Clostridium difficile*	15/187 (8.0)[b]	8/191 (4.2)[c]	3.8 (-1.1 to 9.1)	

Favors Piperacillin-Tazobactam | Favors Meropenem

-20 -15 -10 -5 0 5 10
Between-Group Risk Difference (95 CI), %

[a] Clinical and microbiological success defined as survival, negative blood cultures, temperature of 38°C or less, and peripheral white blood cell count of less than or equal to 12 000/μL (to convert to ×10⁹/L, multiply by 0.001).

[b] Twelve patients with meropenem- or piperacillin-tazobactam–resistant organism and 3 with *Clostridium difficile* infection.

[c] Six patients with meropenem- or piperacillin-tazobactam–resistant organism and 2 with *Clostridium difficile* infection.

than expected, likely reflecting barriers to recruiting patients into clinical trials with severe infections, as well as the exclusion of individuals who were deemed unlikely to survive beyond 96 hours. Indeed, few patients (10/379, 2.6%) met stratification criteria for high-risk disease (ie, Pitt score >4 and nonurinary focus of infection). However, this would tend to bias this study toward a lower estimate of the mortality risk. The risk of mortality was lower in patients with urinary source of infection, although noninferiority was not demonstrated in the subgroup analysis (accepting that the study was not powered accordingly).

A recent trial of meropenem-vaborbactam vs piperacillin-tazobactam for complicated urinary tract source found superiority of meropenem-vaborbactam over piperacillin-tazobactam for a composite end point of clinical cure or improvement and microbial eradication, even when few carbapenemase-producing strains (the target of the vaborbactam inhibitor component) were present.[36] Whether piperacillin-tazobactam remains effective for urinary infections caused by ESBL producers in patients without BSI or low mortality risk remains uncertain. Efforts to define alternatives to carbapenems remain a priority. Whether newer BLBLI agents (such as ceftolozane-tazobactam or ceftazidime-avibactam) are useful options in this clinical context remains unknown and conclusions on the efficacy of new BLBLIs for these infections should not be drawn from the results of this trial before evaluation within randomized studies.

Limitations

This study has several limitations. First, the inherent delays in the processing of blood cultures and susceptibility testing means that empirical therapy was not under control of the study team. Many patients (50/191, 26.2%) who were randomized to meropenem received a BLBLI empirically and, con-

versely, 13.8% (26/188) of those randomized to piperacillin-tazobactam received a carbapenem empirically (eTable 3 in Supplement 2). As empirical therapy may have a major influence on outcome, the fact that some "contamination" of drug exposure between the 2 groups exists may complicate inferences. However, this would tend to bias toward noninferiority. This pragmatic study was purposefully designed not to mimic registration drug trials, but to reflect clinical practice where prescribers are faced with a decision point when ceftriaxone nonsusceptibility is known. Second, step-down therapy (which was allowed on day 5 after randomization) with a carbapenem (eg, once-daily ertapenem) occurred in 20.1% (76/379) of all patients, even if randomized to piperacillin-tazobactam (eTable 3 in Supplement 2).

Third, whether adequate source control was achieved in patients with a complex source of BSI is not known and could have influenced mortality if imbalances were present. Fourth, although patients were recruited from diverse geographical and economic regions, only 2 patients were enrolled from North America (Canada), so it is possible that these results are not generalizable to the United States. However, *E coli* strains causing BSI in this study are consistent with the STs and their associated ESBL genes previously described as prevalent in the United States.[37] Piperacillin-tazobactam may be dosed differently in some US hospitals than in this trial (eg, 3.375 g every 6 hours vs 4.5 g of 6 hours),[14] but the lower dosing regimen has been associated with a low probability of achieving optimal drug exposure in ESBL producers.[38] Extended or continuous infusions of piperacillin-tazobactam may optimize drug exposure but the clinical efficacy of this approach remains uncertain.[39]

Fifth, given that the primary treating clinician had to agree to enrollment, this may have introduced spectrum (or case-mix) bias. However, this was a reason for exclusion

in only 123 of 1255 excluded patients (9.8%). Sixth, for missing data variables used to determine clinical and microbiological resolution, imputation by carrying forward the last observation was used, which could bias secondary end point measures. However, a post hoc sensitivity analysis using multiple imputation had no significant effect on these outcomes. Seventh, as an unblinded study, investigators were aware of the treatment allocation and this may have prompted the early cessation of piperacillin-tazobactam if the clinician perceived clinical failure. However, the results were comparable in both the primary analysis and PP populations, suggesting this did not substantially alter the final results. Furthermore, the primary outcome measure was objective (mortality), mitigating any inherent bias that may be introduced by an open-label study.

Conclusions

Among patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

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