Treatment of Piperacillin-Tazobactam–Nonsusceptible/ Ceftriaxone-Susceptible Infections With Carbapenem Versus Carbapenem-Sparing Antimicrobials

John Cao,[1] Yanina Dubrovskaya,[1] Justin Siegfried,[1] Arnold Decano,[1] Dana Mazo,[2] Sarah Hochman,[2] Ioannis M. Zacharioudakis,[2] Jonathan So,[3] Sadie Solomon,[4] John Papadopoulos,[1] and Kassandra Marsh[1]

[1]Department of Pharmacy, NYU Langone Health, New York, New York, USA, [2]Division of Infectious Diseases, NYU Langone Health, New York, New York, USA, [3]Department of Population Health, NYU Langone Health, New York, New York, USA, and [4]Department of Infection Prevention and Control, NYU Langone Health, New York, New York, USA

Background. *Escherichia coli* and *Klebsiella pneumoniae* with a piperacillin-tazobactam–nonsusceptible/ceftriaxone-susceptible (TZP-NS/CRO-S) phenotype have been increasingly identified, with limited available literature evaluating treatment strategies.

Methods. This was a retrospective study of noncritically ill adults hospitalized between 2013 and 2021 and treated at least 48 hours for TZP-NS/CRO-S *E coli* or *K pneumoniae* infections. The primary composite endpoint included escalation to intensive care unit, infection- or treatment-related readmission, mortality, and infection recurrence. Outcomes were compared between groups who received carbapenem (CG) versus carbapenem-sparing agents (CSG) as targeted gram-negative therapy.

Results. Of 1062 patients screened, 200 were included (CG, n = 51; CSG, n = 149). Baseline characteristics, including Charlson Comorbidity Index (CCI; median [interquartile range], 6 [3–9] vs 6 [4–9]; *P* = .704), were similar between groups, except for more immunocompromised CG patients (29% vs 11%, *P* = .001). The most common infection sources were urinary (31% vs 57%, *P* = .002) and bloodstream (18% vs 17%, *P* = .887). Eighty-eight percent of the CG received meropenem, while 58% of the CSG received ceftriaxone as targeted therapy. There was no statistical difference in the primary endpoint between overall groups (27% vs 17%, *P* = .123), nor when stratified by infection source. More patients in the CSG switched to oral therapy (15 [29%] vs 100 [67%], *P* < .001). In multivariate analysis, CCI was an independent predictor of the primary outcome (odds ratio [OR], 1.199 [95% confidence interval, 1.074–1.340]; *P* = .001), while treatment with carbapenem-sparing therapy was not.

Conclusions. Our study did not find improved clinical outcomes with targeted carbapenem therapy for TZP-NS/CRO-S infections. Carbapenem-sparing agents may be considered to spare carbapenems in noncritically ill patients similar to those included in our cohort.

Keywords. β-lactamases; carbapenems; cephalosporins; *Escherichia*; *Klebsiella*.

Enterobacterales species that include *Escherichia coli* and *Klebsiella pneumoniae* were among the most frequently reported pathogens across all types of adult healthcare-associated infections between 2015 and 2017 [1]. In the New York metropolitan area, there has been an emergence of piperacillin-tazobactam–nonsusceptible (TZP-NS)/ceftriaxone-susceptible (CRO-S) *E coli* and *K pneumoniae* phenotypes, with a prevalence of roughly 4%, as described in an epidemiologic study conducted from 2011 to 2015 [2]. Previous in vitro studies

have hypothesized the mechanism of this phenotypic resistance to result from hyperproduction of Ambler class A (TEM-1/2 and SHV-1) penicillinases, overcoming the inhibitory effect of tazobactam via saturation, without effect on higher-generation cephalosporin activity [3].

Piperacillin-tazobactam is one of the most prescribed antimicrobials in the United States, especially as an empiric agent for sepsis [4]. The emergence of this TZP-NS/CRO-S phenotype may therefore lead to ineffective empiric therapy and, due to this unique susceptibility profile, may cause unnecessary prescription of carbapenem therapy by providers who are unfamiliar with this mechanism of resistance. Downstream complications of increased carbapenem use may include further development of drug resistance and high incidence of *Clostridioides difficile* infection (CDI). A prior retrospective study described treatment outcomes in the TZP-NS/CRO-S phenotype; however, it did not compare outcomes between carbapenems and other classes [5]. The epidemiologic study that identified the prevalence of TZP-NS/CRO-S *E coli* and

K pneumoniae in New York found that definitive therapy with carbapenems was associated with a higher mortality rate (33%) compared to definitive therapy with cephalosporins (17%) [2]. However, potential confounding factors such as baseline and treatment characteristics were not provided for these patient groups. Therefore, the objective of our study was to compare treatment outcomes for noncritically ill patients with TZP-NS/CRO-S *E coli* and *K pneumoniae* infections when using carbapenem versus noncarbapenem therapy to identify whether carbapenem-sparing regimens can be used to treat these infections without affecting patient outcomes.

METHODS

Study Design and Population

This study was an institutional review board–approved, retrospective chart review of unique adult patients admitted to 1 of the 3 New York University Langone Health (NYULH) acute care hospitals located in New York City: Tisch/Kimmel Hospital (800-bed tertiary care facility), Brooklyn Hospital (450-bed community hospital), and Orthopedic Hospital (225-bed specialty hospital), between January 2013 and May 2021, and diagnosed with TZP-NS/CRO-S phenotype *E coli* or *K pneumoniae* infections. Patients were identified through the electronic health record and included if they received at least 48 hours of inpatient antimicrobial therapy. Patients were excluded if they had an emergency department and/or observational unit stay only, were admitted for <48 hours, or were admitted to the intensive care unit (ICU) within 72 hours of culture collection. Patients who had a concomitant infection with third-generation cephalosporin-resistant (3GC-R; extended-spectrum β-lactamase phenotype) Enterobacterales (excluding high-risk AmpC-producing organisms) or polymicrobial gram-negative (GNR) infections, including an organism for which carbapenem therapy would be required due to lack of alternative options based on susceptibility results, were excluded to limit bias of prescribing of carbapenems as targeted therapy. As all included Enterobacterales would be susceptible to 3GC in vitro, the latter polymicrobial exclusion reflects high-risk AmpC-producing organisms with resistance to all of the following: cefepime, fluoroquinolones, sulfamethoxazole-trimethoprim; and *Pseudomonas aeruginosa* resistant to fluoroquinolones, TZP, cefepime, and ceftazidime.

Study Variables

Baseline demographic and clinical characteristics were collected from the NYULH electronic health record including age, sex, race, comorbidities, Charlson Comorbidity Index (CCI), and quick Pitt bacteremia score (qPitt score) [6]. The primary outcome was a composite of in-hospital mortality, need for escalation to ICU-level care, infection- or treatment-related readmission, and infection recurrence. Secondary outcomes evaluated individual components of the primary endpoint, intravenous (IV) to oral (PO) switch, length of stay (LOS) after positive culture, and CDI within 30 days.

Study Definitions

The antimicrobial agent with potential activity against Enterobacterales that was administered for the greatest portion of the first 48 hours from date of culture collection was considered the patient's empiric therapy. The antimicrobial agent with in vitro activity against the *E coli* or *K pneumoniae* isolate that was administered for the greatest portion of time between 48 hours after culture collection and the end of the inpatient index treatment course was considered the patient's targeted therapy and was used to assign the patient to either the carbapenem group (CG) or carbapenem-sparing group (CSG). Patients in both groups may have received additional antimicrobial agents for empiric coverage of gram-positive or anaerobic organisms at the discretion of the treating physician; however, these antimicrobial agents were not collected or described. Isolate minimum inhibitory concentration testing was performed by the NYULH Tisch microbiology laboratory using Vitek2 (bioMérieux, Durham, North Carolina), and susceptibility to an antibiotic was based on published breakpoints from the Clinical and Laboratory Standards Institute M100: Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition. A qPitt score was calculated for each patient as described by Henderson et al, with temperature regarded as <36°C versus ≥36°C, mental status as altered versus normal, and respiratory rate as mechanical ventilation or rate ≥25 breaths per minute versus no mechanical ventilation with rate <25 breaths per minute [6]. Blood pressure was dichotomized as IV vasopressor administration and/or systolic blood pressure (SBP) <90 mm Hg versus no vasopressor administration and SBP ≥90 mm Hg. Cardiac arrest was evaluated within 48 hours prior to the date of index culture while all other variables in the qPitt score were assessed as the worst reading on the calendar day of the index culture [6].

Infection-related readmission was defined as hospitalization within 30 days of discharge related to either previous or new infection. Treatment-related readmission was defined as hospitalization within 30 days of discharge related to complications of the antimicrobial treatment course, including antibiotic toxicity, antibiotic nonadherence, or IV catheter–related complications. Both readmission variables excluded admissions to hospice or rehabilitation. Infection recurrence was defined as infection with the same isolated bacterial species after completion of index treatment course. LOS after positive culture was calculated from date of culture collection to discharge date.

Statistical Analyses

Categorical variables were described as frequencies and proportions, and continuous variables were described as median

with interquartile range (IQR). Comparisons between the CG and CSG were conducted using χ^2 or Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. Last, individual outcomes were further stratified according to infection type. A univariate analysis was conducted to identify risk factors for the primary composite outcome. All variables with a P value ≤.1 in the univariate analysis were included in a backward stepwise logistic regression model to determine independent predictors of the primary outcome. The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test ($P = .824$). All analyses were performed using SPSS version 28 software (IBM Corp, Armonk, New York). All statistical tests were 2-tailed, and $P < .05$ was considered significant.

RESULTS

Patient Characteristics
A total of 1054 patients with TZP-NS/CRO-S E coli or K pneumoniae infections during the study period were screened and 200 were included, with 51 patients in the CG and 149 in the CSG (Figure 1). Most patients excluded had no inpatient targeted therapy (n = 345), had no inpatient stay (n = 323), or were admitted to ICU within 72 hours of culture collection (n = 97). Demographics and clinical characteristics of included patients are summarized in Table 1. The median patient age for the CG and CSG was 65 (IQR, 52–74) years and 72 (IQR, 56–82) years, respectively. The overall median CCI score in the cohort was 6 (IQR, 4–9), with no difference between groups. More patients in the CG were immunocompromised compared to the CSG (15 [29%] vs 16 [11%]; $P = .001$). The median overall hospital LOS was significantly longer in the CG (14 [IQR, 8–26] vs 10 [IQR, 6–18]; $P = .006$). Finally, while the CG had a statistically higher qPitt score compared to the CSG (median, 1 [IQR, 0–1] vs 0 [IQR, 0–1]; $P = .026$), both groups had

qPitt scores <2, indicating low overall risk for mortality in the cohort. No significant differences between groups were observed with regard to the treating hospital or other underlying comorbidities.

Infection Characteristics
The median time to culture from admission in the CG and CSG was 2 (IQR, 2–9) days and 1 (IQR, 0–4) day, respectively ($P = .006$). The most common organism was E coli in both the CG and CSG (34 [67%] and 110 [74%]), whereas K pneumoniae was isolated in 17 (33%) and 39 (26%) patients, respectively. Fifty-six (28%) patients had a polymicrobial GNR infection, which represented 33% of the CG (17 patients) and 26% of the CSG (39 patients) ($P = .326$). Of the 56 patients with polymicrobial infection, 19 included isolation of *Pseudomonas aeruginosa* (5 [29%] vs 14 [36%], $P = .637$) and 8 included isolation of 3GC/cefepime-susceptible *Enterobacter* spp or *Citrobacter freundii* (3 [18%] vs 5 [13%], $P = .688$). The most common infections were urinary tract infection (UTI) (51%), followed by bacteremia (17%) (Table 2). There were significantly more UTIs in the CSG compared to the CG (85 [57%] vs 16 [31%], $P = .002$), and more intra-abdominal infections in the CG compared to the CSG (10 [20%] vs 12 [8%], $P = .023$). All isolates were susceptible to ceftriaxone, cefepime, and meropenem. The majority of E coli urine isolates were susceptible to nitrofurantoin (90% for CG vs 94% for CSG), and the majority of overall K pneumoniae isolates were susceptible to ciprofloxacin (82% for CG vs 92% for CSG). Of note, a low number of isolates were tested against cefuroxime and levofloxacin given lack of inclusion on the Vitek2 panels utilized at NYULH during the time period of this study. Isolates in this cohort had variable susceptibility to cefoxitin (E coli: 74% for CG vs 85% for CSG; K pneumoniae: 65% for CG vs 74% for CSG). All other antibiotics tested had susceptibilities <80%.
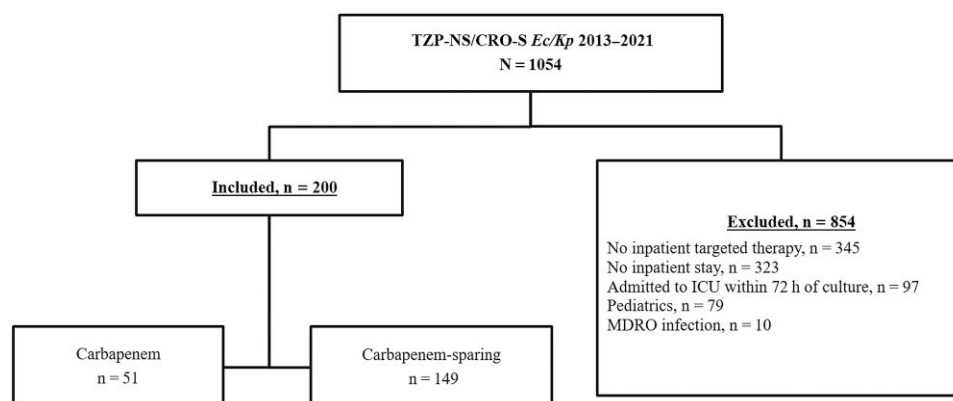

Figure 1. Study flowchart. Abbreviations: CRO-S, ceftriaxone susceptible; *Ec*, *Escherichia coli*; ICU, intensive care unit; *Kp*, *Klebsiella pneumoniae*; MDRO, multidrug-resistant organism; TZP-NS, piperacillin-tazobactam nonsusceptible.

Table 1. Baseline Characteristics

Characteristic	Total (N = 200)	Carbapenem (n = 51)	Carbapenem-Sparing (n = 149)	P Value
Patient characteristics				
Institution				
Tisch/Kimmel Hospital	157 (79)	43 (84)	114 (77)	.242
Langone Brooklyn Hospital	31 (16)	5 (10)	26 (17)	.193
Langone Orthopedic Hospital	12 (5)	3 (6)	9 (6)	1
Age, y, median (IQR)	69 (52–82)	65 (52–74)	72 (56–82)	.059
Male sex	101 (51)	29 (57)	72 (48)	.292
Weight, kg, median (IQR)	71 (59–91)	72 (60–91)	71 (59–85)	.402
BMI, kg/m^2, median, (IQR)	26 (22–30)	26 (22–30)	26 (22–30)	.820
Comorbidities				
COVID-19 infection during admission	6 (3)	1 (2)	5 (3)	1
Hospitalization in last 90 d	65 (33)	19 (37)	46 (31)	.401
Hospital LOS, d, median (IQR)	12 (6–26)	14 (8–26)	10 (6–18)	.006
Diabetes mellitus	83 (42)	18 (35)	65 (44)	.297
Moderate to severe CKD	54 (27)	17 (33)	37 (25)	.238
COPD	41 (21)	14 (28)	27 (18)	.154
Solid tumor	25 (13)	7 (14)	18 (12)	.759
Liver disease	24 (12)	6 (12)	18 (12)	.952
Immunocompromised[a]	31 (16)	15 (29)	16 (11)	.001
Solid organ transplantation	16 (8)	7 (14)	9 (6)	.130
HSCT	13 (7)	7 (14)	6 (4)	.023
Leukemia	10 (5)	6 (12)	4 (3)	.019
Lymphoma	4 (2)	1 (2)	3 (2)	1
AIDS	1 (1)	1 (2)	0 (0)	.255
CCI, median (IQR)	6 (4–9)	6 (3–9)	6 (4–9)	.704
qPitt, median (IQR)	0 (0–1)	1 (0–1)	0 (0–1)	.026

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; LOS, length of stay; qPitt, quick Pitt bacteremia score.

[a]Defined as solid organ transplantation, hematopoietic stem cell transplant, leukemia, lymphoma, or AIDS.

Treatment Characteristics

The most common empiric regimen in the CG was TZP (35 [69%]), while in the CSG, empiric TZP (56 [38%]) and CRO (53 [36%]) use was more evenly distributed (Supplementary Table 1). Significantly more patients in the CG received TZP (P < .001) and significantly fewer received CRO (3 [6%] vs 53 [36%], P < .001) as empiric therapy compared to the CSG. The carbapenems used as targeted therapy in the CG were meropenem (88%) and ertapenem (12%). The most common targeted therapies in the CSG were ceftriaxone (58%) followed by cefepime (24%) (Supplementary Table 1).

Outcomes

The primary composite outcome was similar between the CG and CSG (14 [28%] vs 26 [17%], P = .123) (Table 3) and was not statistically different between groups when stratified by infection type. In-hospital mortality was similar between the CG and CSG (7 [14%] vs 11 [7%], P = .254). Additionally, escalation to ICU care, infection-related readmission, treatment-related readmission, and infection recurrence within 30 days were not statistically different between groups. Individual components

of the primary composite outcome when stratified by infection type can be found in Supplementary Table 2.

The median LOS after positive culture was longer in the CG but not statistically significant (9 [IQR, 6–17] vs 8 [IQR, 6–13] days, P = .207). When stratified by type of infection, patients in the CG with pneumonia had a significantly longer LOS after positive culture compared to the CSG (21 [IQR, 16–40] vs 14 [IQR, 9–18] days, P = .020). No CDI within 30 days was observed in either group. Full inpatient IV courses of antibiotics were administered in 29% and 28% (P = .795) of the CG and CSG, respectively (Supplementary Table 3). Significantly more patients in the CG were discharged on IV antibiotics compared to the CSG (21 [41%] vs 8 [5%], P < .001). The most common infections requiring continuation of IV at discharge in the CG were central nervous system (CNS) (100%); intra-abdominal (70%); and skin and soft tissue (SSTI), bone, and joint infections (67%). Significantly more patients in the CSG were switched from IV to PO antibiotics (15 [29%] vs 100 [67%], P < .001). The vast majority of oral antibiotics in the CSG were fluoroquinolones (41%) or 3GC (40%), while the CG was split between 3GC (33%), sulfamethoxazole-

Table 2. Infection Characteristics

Characteristic	Carbapenem (n = 51)	Carbapenem-Sparing (n = 149)	P Value
Time to culture from admission, d, median (IQR)	2 (2–9)	1 (0–4)	.006
Infection type			
Urinary tract infection	16 (31)	85 (57)	.002
Bacteremia	9 (18)	25 (17)	.887
Urinary source	2 (22)	14 (56)	.125
Intra-abdominal source	3 (33)	5 (20)	.649
Catheter-related	2 (22)	3 (12)	.591
Pulmonary source	2 (22)	1 (4)	.164
SSTI	0	2 (8)	1
Intra-abdominal infection	10 (20)	12 (8)	.023
SSTI/bone/joint	9 (18)	12 (8)	.054
Pneumonia	6 (12)	14 (9)	.626
CNS infection	1 (2)	1 (1)	.446
Susceptibility data			
Escherichia coli	34 (67)	110 (74)	.326
Ciprofloxacin	41%	53%	.239
Cefuroxime	0 (n = 1)	88% (n = 16)	.176
Cefoxitin	74%	84%	.187
Nitrofurantoin[a]	90% (n = 10)	94% (n = 66)	.516
Sulfamethoxazole-trimethoprim	41%	40%	.903
Ampicillin-sulbactam	6%	2%	.237
Klebsiella pneumoniae	17 (33)	39 (26)	.326
Ciprofloxacin	82%	92%	.354
Cefuroxime	…	50% (n = 2)	
Cefoxitin	65%	74%	.527
Nitrofurantoin	17% (n = 6)	11% (n = 19)	1
Sulfamethoxazole-trimethoprim	65%	80%	.317
Ampicillin-sulbactam	6%	0	.304

Data are presented as No. (%) unless otherwise indicated. Susceptibility data are reported as % susceptible.

Abbreviations: CNS, central nervous system; IQR, interquartile range; SSTI, skin and soft tissue.

[a]Susceptibility based only on urine cultures.

trimethoprim (27%), and fluoroquinolones (20%). Time to PO switch was shorter in the CSG but not statistically significant (median, 6 [IQR, 3–9] vs 4 [IQR, 3–6] days, $P = .196$).

In a multivariate analysis (Table 4), calculated CCI was identified as the only independent predictor of the primary composite outcome (OR, 1.199 [95% confidence interval {CI}, 1.074–1.340]; $P = .001$) after adjusting for comorbidities, qPitt score, immunocompromised status, empiric therapy, and infection source. Of note, while TZP empiric therapy was identified as a risk factor for the primary outcome in univariate analysis (OR, 2.082 [95% CI, 1.027–4.219]), this did not remain as an independent predictor on multivariate analysis. Additionally, CS treatment was not identified as a risk factor associated with the primary composite outcome in either univariate (OR, 0.560 [95% CI, .27–1.18]) or multivariate analyses (removed on step 4 backward stepwise logistic regression).

DISCUSSION

In this retrospective review of noncritically ill admitted patients treated for TZP-NS/CRO-S *E coli* and *K pneumoniae* infections, we found similar clinical outcomes with higher rates of PO transition among patients receiving carbapenem-sparing therapies compared to treatment with carbapenems. To our knowledge, this is the largest published study describing treatment selection and comparing clinical outcomes among patients with TZP-NS/CRO-S *E coli* and *K pneumoniae* infections treated with carbapenem versus carbapenem-sparing therapies. Our multivariate model showed no association between definitive treatment group and the primary composite outcome. In contrast to our findings, Baker et al described an overall higher mortality rate in patients receiving carbapenems compared to cephalosporins (33% vs 17%) for bacteremia caused by these organisms. However, they did not provide baseline demographics or infection characteristics for these groups, limiting the ability to assess for potential confounding factors that could have biased these results [2].

We observed an overall in-hospital mortality rate of 9%, which is lower than that described (25%) in Baker and colleagues' epidemiologic study of 78 bacteremic episodes caused by TZP-NS/CRO-S *E coli* or *K pneumoniae* [2]. This finding is perhaps due to our inclusion of other sources of infection such

Table 3. Outcomes

Outcome	Carbapenem (n = 51)	Carbapenem-Sparing (n = 149)	P Value
Primary composite outcome	14 (28)	26 (17)	.123
In-hospital mortality	7 (14)	11 (7)	.254
Escalation to ICU	4 (8)	3 (2)	.072
Infection-related readmission	3 (6)	11 (7)	1
Treatment-related readmission	1 (2)	1 (0.7)	.446
Infection recurrence within 30 d	2 (4)	5 (3)	1
Primary composite outcome by infection type			
Urinary tract	4/16 (25)	15/85 (18)	.495
Bacteremia	3/9 (33)	4/25 (16)	.348
Intra-abdominal	4/10 (40)	4/12 (33)	1
SSTI/bone/joint	2/9 (22)	1/12 (8)	.553
Pneumonia	1/6 (17)	2/14 (14)	1
CNS	0/1 (0)	0/1 (0)	
LOS after positive culture, d, median (IQR)	9 (6–17)	8 (6–13)	.207
LOS after positive culture by infection type			
Urinary tract	9 (6–17) (n = 16)	8 (6–11) (n = 85)	.286
Bacteremia	7 (5–21) (n = 9)	7 (5–12) (n = 25)	.848
Intra-abdominal	8 (6–15) (n = 10)	11 (8–18) (n = 12)	.314
SSTI/bone/joint	9 (7–11) (n = 9)	9 (6–13) (n = 12)	.602
Pneumonia	21 (16–40) (n = 6)	14 (9–18) (n = 14)	.020
CNS	25 (25–25) (n = 1)	9 (9–9) (n = 1)	1
CDI within 30 d	0	0	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CDI, *Clostridioides difficile* infection; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SSTI, skin and soft tissue.

Table 4. Univariate and Multivariate Analysis of Primary Outcome

Variable	Met Primary Outcome (n = 40)	Did Not Meet Primary Outcome (n = 160)	Univariate Analysis		Multivariate Analysis[a]	
			OR (95% CI)	P Value	OR (95% CI)	P Value
qPitt	1 (0–2)	0 (0–1)	1.654 (1.116–2.452)	**.012**	1.493 (.970–2.296)	.068
CCI	8 (6–11)	6 (3–8)	1.188 (1.069–1.320)	**.001**	1.199 (1.074–1.340)	**.001**
Empiric ceftriaxone	7 (18)	49 (31)	0.481 (.199–1.161)	.098	0.438 (.169–1.135)	.089
Immunocompromised	3 (8)	28 (18)	0.382 (.110–1.328)	.118	0.308 (.084–1.132)	.076
Empiric cefepime	1 (2.5)	20 (13)	0.179 (.023–1.38)	**.083**	0.137 (.017–1.097)	.137
Solid tumor	11 (28)	14 (9)	3.956 (1.633–9.58)	**.001**	…	
COPD	13 (33)	28 (18)	2.27 (1.043–4.938)	**.036**	…	
Empiric piperacillin-tazobactam	24 (60)	67 (42)	2.082 (1.027–4.219)	**.039**	…	
Carbapenem-sparing definitive treatment	26 (65)	123 (77)	0.560 (.27–1.18)	**.123**	…	
Intra-abdominal infection	8 (20)	14 (9)	2.61 (1.009–6.736)	**.051**	…	
Urinary tract infection	19 (48)	82 (51)	0.86 (.43–1.72)	.671	…	
Bacteremia	7 (18)	27 (17)	1.05 (.42–2.6)	.925	…	
SSTI/bone/joint	3 (8)	18 (11)	0.64 (.179–2.29)	.773	…	
Pneumonia	3 (8)	17 (11)	0.682 (.19–2.45)	.770	…	

Bolded P Values denote variables that were included in the multivariate analysis.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; qPitt, quick Pitt bacteremia score; SSTI, skin and soft tissue.

[a]Multivariate analysis (backwards selection): Variables entered on step 1: solid tumor, intra-abdominal infection, COPD, empiric piperacillin-tazobactam, qPitt score, CCI, carbapenem-sparing definitive treatment, empiric ceftriaxone, immunocompromised, empiric cefepime. Variable removed on step 2: empiric piperacillin-tazobactam. Variable removed on step 3: solid tumor. Variable removed on step 4: carbapenem-sparing definitive treatment. Variable removed on step 5: intra-abdominal infection. Variable removed on step 6: COPD.

as urine, which is associated with lower mortality rates compared to bacteremia. Differences in baseline demographics, such as the Baker et al study including more patients with hematologic malignancy (42%), could also contribute to mortality differences between studies [2]. Conversely, mortality rate in our study was higher than the 5.5% described in the 2017 retrospective study by Stainton et al [5]. This may be explained by the larger proportion of UTIs (70.9% vs 51%) in Stainton and colleagues' study and fewer patients who received carbapenems (18.2% vs 25.5%), which may indicate an overall lower severity of infection [5]. Readmission rates due to infection among our cohort were similar to the prior study (10.9% vs 7%) [5].

Our study is the first to include both bloodstream and non-bloodstream infections and to describe antibiotic IV to PO switch in infections caused by TZP-NS/CRO-S *E coli* and *K pneumoniae*. The CSG had a significantly greater proportion of UTIs, whereas the CG had significantly more patients with intra-abdominal infections or SSTI, bone, and joint infections. We hypothesize that this difference may account for the lower usage of PO agents in the CG, as patients with these infection types are frequently discharged with outpatient parenteral antimicrobial therapy at our institution. However, given the high rate of PO switch in the CSG with comparable outcomes to prior studies of similar patient populations and infection types, we hypothesize that PO switch to a 3GC or fluoroquinolone may be appropriate for UTIs with this phenotype. During the study collection period, cefuroxime susceptibility was not captured for all isolates. Therefore, we cannot comment on whether cefoxitin could be a surrogate agent for second-generation cephalosporin susceptibility, allowing cefuroxime as an appropriate step-down therapy.

Changing antimicrobial therapy based on sensitivities from culture results may not reduce the excess risk of hospital mortality associated with inappropriate empiric treatment [7–10]. The most common empiric therapy in the CG was TZP whereas for the CSG was ceftriaxone, which may be explained by a higher proportion of UTI and community-acquired infections in the CSG. Additionally, TZP is recommended as the empiric agent for broad GNR coverage for patients who meet sepsis criteria at our institution. Previous in vitro studies have hypothesized the mechanism of this phenotypic resistance to result from hyperproduction of Ambler class A (TEM-1/2 and SHV-1) penicillinases, overcoming the inhibitory effect of tazobactam via saturation due to low concentrations in vitro [3]. Due to the differences between groups in our cohort, and unidentified confounding factors, our study cannot directly answer whether this effect on tazobactam in vitro is clinically meaningful in vivo. While empiric therapy with TZP was associated with the primary outcome on univariate analysis, it was reassuringly not identified as an independent risk factor in the multivariate, suggesting that the in vitro resistance did not

impact clinical outcomes when using TZP empirically in this noncritically ill cohort. Given the overall low prevalence of this phenotype in the New York metropolitan area (4%), as well as availability of rapid diagnostic testing, our institution has not made any changes to recommended empiric therapy for sepsis to account for the potential for TZP resistance. However, we recommend that individual institutions assess local prevalence of this phenotype and adjust institutional empiric antimicrobial regimens accordingly until prospective trial evidence of the in vivo outcomes associated with TZP empiric therapy in infections with this phenotype is established.

Our study has several limitations that should be considered. Although this is the largest study to date assessing TZP-NS/CRO-S outcomes between CG versus CSG, there is still a possibility for type II error when assessing patients' clinical outcomes due to a relatively small sample size. Due to the retrospective nature of our study, we are unable to exclude the possibility of other baseline differences between groups that bias providers to select carbapenem versus carbapenem-sparing therapies. We limited this bias by excluding critically ill patients who are more likely to have the primary outcome and for whom providers might be more likely to treat with carbapenems. While the groups had similar CCI score and percentage of patients with bacteremia and CNS infections, the CSG had a greater percentage of UTIs and fewer immunocompromised patients. This, along with the higher empiric use of TZP in the CG, which is our institution's empiric recommendation for sepsis, may indicate some bias toward using carbapenems in patients who appeared more severely ill without requiring ICU admission. Furthermore, our study described inpatient treatment of patients with TZP-NS/CRO-S phenotype infections without concomitant 3GC-R infections. Therefore, the impact of carbapenem-sparing regimens in patients with concomitant 3GC-R organisms cannot be stated based on the results of this study. Last, genotypic evaluation of isolates was not performed, and therefore the mechanisms of resistance in these isolates and organism virulence cannot be verified. However, in real-world experience, many institutions may not readily have this information available to make clinical decisions.

Based on the hypothesized mechanisms of TZP resistance in TZP-NS/CRO-S phenotype *E coli* and *K pneumoniae*, cephalosporins may remain active and effective therapies for patients with these infections [2, 3, 5, 11]. Unnecessary prescribing of carbapenems increases the risk of further development of drug resistance. Furthermore, concerns have been raised that antimicrobial IV to PO conversion may lead to need for escalation of care or clinical relapse. In our multivariate analysis, we observed that switching to noncarbapenem antibiotics did not negatively impact mortality, readmission, or recurrent infection in patients with TZP-NS/CRO-S *E coli* and *K pneumoniae* infections. Based on our study, given comparable clinical outcomes to prior studies of gram-negative infections, we hypothesize that

de-escalation and transition to 3GC, fluoroquinolones, or sulfamethoxazole-trimethoprim in noncritically ill patients with these infections may provide a safe carbapenem-sparing option. Ultimately, large multicenter prospective trials are warranted to confirm whether TZP as empiric therapy results in worse clinical outcomes in patients with this infection phenotype and whether carbapenem-sparing options are appropriate treatment options for both critically and noncritically ill patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. C.: methodology, investigation, formal analysis, writing–original draft. Y. D., J. S., A. D., D. M., S. H., and I. Z.: methodology, writing–review and editing. J. S.: methodology, software utilization, investigation. S. S.: software utilization, investigation. J. P.: writing–review and editing. K. M.: conceptualization, methodology, writing–review and editing.

Patient consent. This study did not include factors necessitating patient consent. The New York University Langone Health Institutional Review Board approved this study, which conforms to current standards.

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

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