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MAJOR ARTICLE

Clinical Impact of Ceftriaxone Resistance in *Escherichia coli* Bloodstream Infections: A Multicenter Prospective Cohort Study

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Background. Ceftriaxone-resistant (CRO-R) *Escherichia coli* bloodstream infections (BSIs) are common.

Methods. This is a prospective cohort of patients with *E coli* BSI at 14 United States hospitals between November 2020 and April 2021. For each patient with a CRO-R *E coli* BSI enrolled, the next consecutive patient with a ceftriaxone-susceptible (CRO-S) *E coli* BSI was included. Primary outcome was desirability of outcome ranking (DOOR) at day 30, with 50% probability of worse outcomes in the CRO-R group as the null hypothesis. Inverse probability weighting (IPW) was used to reduce confounding.

Results. Notable differences between patients infected with CRO-R and CRO-S *E coli* BSI included the proportion with Pitt bacteremia score ≥4 (23% vs 15%, $P = .079$) and the median time to active antibiotic therapy (12 hours [interquartile range {IQR}, 1–35 hours] vs 1 hour [IQR, 0–6 hours]; $P < .001$). Unadjusted DOOR analyses indicated a 58% probability (95% confidence interval [CI], 52%–63%) for a worse clinical outcome in CRO-R versus CRO-S BSI. In the IPW-adjusted cohort, no difference was observed (54% [95% CI, 47%–61%]). Secondary outcomes included unadjusted and adjusted differences in the proportion of 30-day mortality between CRO-R and CRO-S BSIs (−5.3% [95% CI, −10.3% to −.4%] and −1.8 [95% CI, −6.7% to 3.2%], respectively), postculture median length of stay (8 days [IQR, 5–13 days] vs 6 days [IQR, 4–9 days]; $P < .001$), and incident admission to a long-term care facility (22% vs 12%, $P = .045$).

Conclusions. Patients with CRO-R *E coli* BSI generally have poorer outcomes compared to patients infected with CRO-S *E coli* BSI, even after adjusting for important confounders.

Keywords. bacteremia; ceftriaxone; *Escherichia coli*; ESBL; mortality; resistance.

Escherichia coli is the most common gram-negative pathogen recovered in bloodstream infections (BSIs) [1]. Unfortunately, the incidence of ceftriaxone-resistant (CRO-R) *E coli* BSI continues to rise in the United States (US), with the Centers for Disease Control and Prevention estimating a 53% increase in CRO-R *E coli* in clinical cultures from 2012 through 2017 [2]. Extended-spectrum β-lactamase (ESBL) production is the most common mechanism of ceftriaxone resistance in *E coli*, and ceftriaxone resistance is frequently used as a proxy for the production of ESBLs [3]. Identification of CRO-R *E coli* has important treatment implications because ESBLs hydrolyze a number of β-lactam antibiotics beyond just ceftriaxone, limiting β-lactam treatment options [3]. Additionally, ESBL-encoding genes frequently co-circulate with genes encoding resistance to fluoroquinolones (eg, *gyrA*, *parC*), trimethoprim-sulfamethoxazole (TMP-SMX) (eg, *sul*),

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and aminoglycosides (eg, aminoglycoside-modifying enzymes), further limiting antibiotic choices [3].

Retrospective studies demonstrate that CRO-R *E coli* BSIs are associated with worse clinical outcomes than BSIs caused by ceftriaxone-susceptible (CRO-S) *E coli* isolates [4–8]. It is unclear, however, if poorer outcomes persist after adjustment for confounding factors such as delays in time to active antibiotic therapy, immunocompromise, and challenges with achieving source control—all generally more prevalent in patients infected with drug-resistant phenotypes [9]. Moreover, these variables can be more challenging to accurately capture retrospectively than prospectively.

Furthermore, errors in determination of minimum inhibitory concentrations (MICs) observed with automated susceptibility testing platforms used to define ceftriaxone resistance in the published literature can lead to misclassification of susceptibility, obscuring the findings of outcomes studies [10]. Using a prospective, multicenter cohort of patients from across the US with comprehensive clinical data as well as microbial isolates available for accurate ceftriaxone MIC determination, we sought to compare clinical outcomes of patients with CRO-R *E coli* versus CRO-S *E coli*. These data will help inform the impact of ceftriaxone resistance for clinical prognostication of *E coli* BSI.

METHODS

Study Population

We conducted a prospective multicenter study of unique adult and pediatric patients with monomicrobial *E coli* BSI hospitalized at any of the 14 participating acute care facilities in the US between 12 November 2020 and 28 April 2021 (Figure 1). A target enrollment of 300 patients—150 each with CRO-R *E coli* BSI and CRO-S *E coli* BSI—was selected to ensure at least 90% power to detect a 20% difference in desirability of outcome ranking (DOOR) outcomes between the 2 groups, using a 2-sided exact test at the $\alpha = .05$ level. For each patient with a CRO-R *E coli* BSI enrolled from a participating site, the next consecutive patient with a CRO-S *E coli* BSI at the same site was also enrolled. Clinical and Laboratory Standards Institute (CLSI) criteria were used to categorize isolates as CRO-R *E coli* (ie, ceftriaxone or cefotaxime MIC ≥4 μg/mL) or CRO-S *E coli* (ie, ceftriaxone or cefotaxime MIC ≤1 μg/mL) [11].

Eligibility Criteria

Patients meeting any of the following criteria were excluded from enrollment: (1) infection with *E coli* isolates with ceftriaxone MICs of 2 μg/mL (ie, CLSI intermediate category); (2) infection with *E coli* exhibiting nonsusceptibility to at least 1 carbapenem agent; (3) *E coli* isolates not available for confirmatory antibiotic susceptibility testing by the central laboratory; and (4) polymicrobial BSI.

Microbiological Analysis

Genus and species identification of the index *E coli* isolate and antimicrobial susceptibility testing were initially performed at local microbiology laboratories. Isolates were shipped to the central research laboratory where frozen isolates were subcultured twice and nonfrozen isolates once to tryptic soy agar with 5% sheep blood and eosin-methylene blue agar. Bacterial genus and species were confirmed by matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (Bruker Daltonics). Broth microdilution (BMD) was performed to confirm ceftriaxone MICs [12]. Isolates with ceftriaxone MICs not achieving categorical agreement (ie, MICs not within the same susceptibility category) when comparing local laboratory and BMD results underwent replicate BMD testing [12].

Outcomes

The primary outcome for the analysis was DOOR based on disposition at day 30 after collection of the index blood culture (ie, day 1), comparing patients with CRO-R *E coli* versus CRO-S *E coli* BSI [13]. The DOOR was reported as 4 ordinal levels as described in Table 1. Additionally, the following were evaluated: (1) 30-day mortality; (2) postculture length of stay (ie, days from index blood culture collection to hospital discharge, for patients who survived until hospital discharge); (3) recurrence of *E coli* BSI over the subsequent 30 days (and with an intervening gap of 7 days from collection of the index blood culture); and (4) hospital readmission within 30 days (excluding patients who died prior to or were still hospitalized at day 30).

Data Collection

Data collection occurred locally and was entered into a central, secure, and standardized database following criteria in a detailed data dictionary developed to maximize valid data entry across the 14 sites. Data cleaning and validation occurred in real time by a central team. Local study teams were requested to reenter outlier or conflicting data. The following information was collected on all patients: (1) demographic data; (2) preexisting medical conditions (Charlson Comorbidity Index [CCI] and severe immunocompromise, defined as solid organ or stem cell transplant, human immunodeficiency virus infection, chemotherapy within 6 months, or receipt within 30 days of prednisone ≥10 mg/day or equivalent corticosteroid dose, or tumor necrosis factor α inhibitor or other directed monoclonal immunomodulatory antibody); (3) severity of illness at the time of blood culture collection (Pitt bacteremia score, intensive care unit [ICU] admission on day 1); (4) likely source of BSI and adequate source control (defined as either no source control needed or, for patients in need of source control, drainage of infected fluid collections and removal of infected hardware or catheters); (5) detailed antibiotic administration including use of active antibiotic therapy (ie, antibiotics

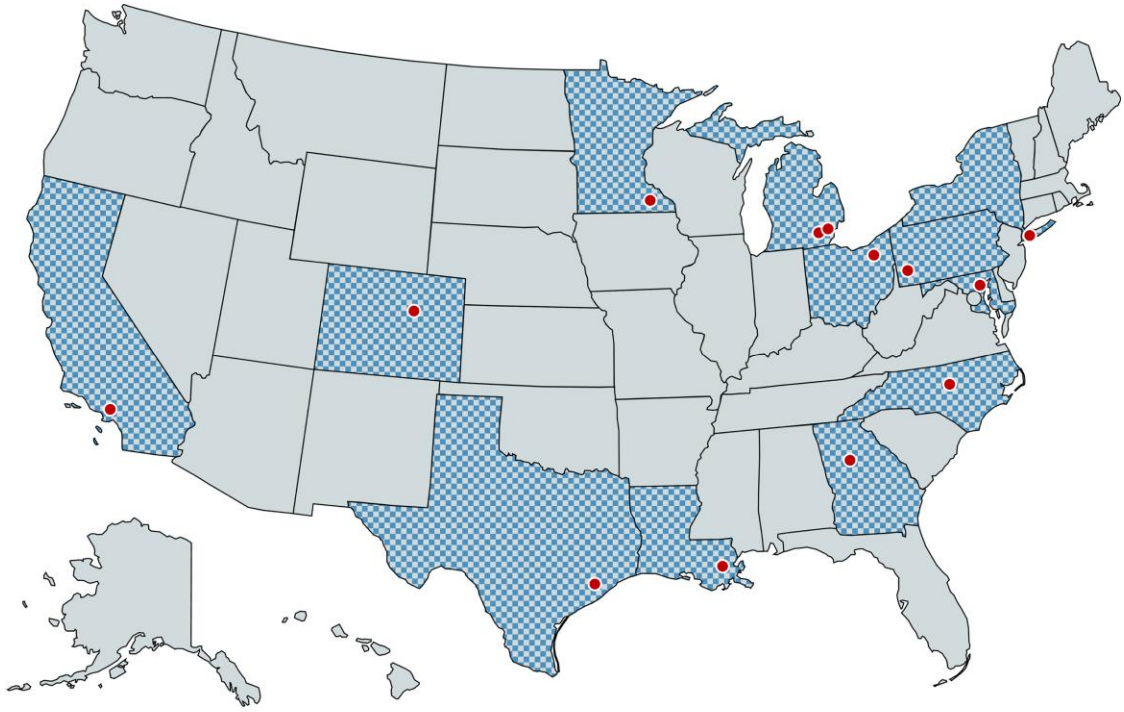

Figure 1. Location of the 14 hospitals (note, two hospitals located in Detroit, MI represented by a single dot) contributing patient data and clinical isolates for the current study.

exhibiting in vitro susceptibility when applying CLSI criteria), duration of active antibiotic therapy (including antibiotic therapy continued after hospital discharge), and use of oral step-down therapy (ie, the discontinuation of all intravenous antibiotic therapy on or before day 5 and transition to an active oral antibiotic); and (6) clinical outcomes data [11, 14–16].

Table 1. Ordinal Outcomes for Desirability of Outcome Rankings in a Cohort of 300 Patients Infected With Ceftriaxone-Resistant Versus Ceftriaxone-Susceptible *Escherichia coli* Bloodstream Infections

Category	Criteria[a,b]
1 (Most desirable)	Alive and no events
2	Alive and 1 event
3	Alive and at least 2 events
4 (Least desirable)	Death
Events definition	
• Failure to achieve a favorable clinical response within 30 d	
• New *Escherichia coli* bloodstream infection within 30 d	
• Remaining in the hospital at day 30 and/or readmission to the same hospital within 30 d	
• Discharge to a nursing home or skilled nursing facility (if originally admitted to the hospital from home)	

[a]All criteria evaluated compared to day 1, with day 1 being the first day a positive blood culture was collected.

[b]If the reason for hospital readmission was a new *E coli* bloodstream infection, it is counted as a single event.

Analytic Approach

The Pearson χ^2 test was used to compare proportions between categorical variables. The Wilcoxon rank-sum test was used to compare distributions between continuous and ordered categorical variables. As it was hypothesized that patients with CRO-R *E coli* BSI would be more likely to have characteristics independently associated with poor outcomes compared to those with CRO-S *E coli* BSI (eg, complex underlying medical conditions), adjustment using inverse probability weighting (IPW) based on propensity scores was undertaken. The following variables were selected in calculating propensity scores: age ≥65 years, preadmission location other than home, hospital-onset infection (defined as blood cultures collected on or after day 3 of hospitalization), CCI, Pitt bacteremia score ≥4 on day 1, ICU status on day 1, severe immunocompromise, diabetes, cirrhosis, chronic renal replacement therapy, urinary source, and adequate source control. Patients in the CRO-R group were weighted by the inverse of the propensity score and patients in the CRO-S group were weighted by the inverse of 1 minus the propensity score. A new, weighted pseudo-population was created in which individuals in the CRO-R and CRO-S groups were up-weighted or down-weighted to ensure that both groups were as similar as possible for all variables in the propensity score at baseline, except for the susceptibility of the *E coli* isolate to ceftriaxone. The primary efficacy analysis was an IPW-adjusted disposition plot illustrating the probability of outcomes at day 30. The probability that a randomly

selected patient with a CRO-R versus a CRO-S *E coli* BSI had a less desirable DOOR was determined. A probability of 50% implied no difference between DOOR distributions of the 2 groups, whereas a probability >50%, with a 95% confidence interval (CI) that excludes 50%, implied inferiority of the CRO-R versus CRO-S group over the other. Confidence intervals were calculated using 4000 bootstrap resamples. The difference in proportions and 95% CI of 30-day mortality between CRO-R and CRO-S *E coli* BSI was determined. Markers of severity of illness on the causal pathway between the exposure and outcome (eg, ICU transfer after day 1) were not included in the development of propensity scores. However, as active empiric therapy was considered an important confounder between patients infected with CRO-R and CRO-S *E coli*, a subgroup analysis was performed in which the IPW-adjusted DOOR probability was estimated in the subgroup of patients receiving active empiric therapy. *P* values of ≤.05 were considered statistically significant for all analyses. All tests were 2-sided. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Overall Cohort

In total, 300 patients with *E coli* BSI, including 150 patients with CRO-R *E coli* and 150 with CRO-S *E coli*, were enrolled from 14 participating sites (Table 2). The median age of participating patients was 68 years (interquartile range [IQR], 55–76 years). Follow-up blood cultures were obtained in 210 (70%) patients on hospital days subsequent to the collection of the index blood culture; of these 210 patients, 1 patient (0.5%) had a positive follow-up blood culture.

Microbiology

In CRO-R *E coli*, the median ceftriaxone MIC was ≥32 μg/mL (IQR, ≥32–≥32) versus 0.06 μg/mL (IQR, 0.03–0.06) in CRO-S *E coli*. CRO-R *E coli* isolates were less likely to be susceptible to several other antibiotics as compared to CRO-S isolates: aztreonam, 4% versus 100%; cefepime, 13% versus 100%; ciprofloxacin, 21% versus 85%; gentamicin, 67% versus 95%; levofloxacin, 20% versus 87%; piperacillin-tazobactam, 85% versus 98%; and TMP-SMX, 42% versus 73%.

Baseline Characteristics

Overall, patients with CRO-R and CRO-S *E coli* were similar with regard to age, sex, and race/ethnicity (Table 2). Patients with CRO-R *E coli* BSI were more likely to be admitted from nursing homes compared to those with CRO-S *E coli* BSI (20 [13%] vs 6 [4%], $P = .013$). Patients with CRO-R isolates were also more likely to have hospital-onset BSI, compared with patients with CRO-S isolates (41 [27%] vs 21 [14%], $P = .004$). While the median CCI was the same in both groups, the distribution of values indicated that patients with CRO-R *E coli* had overall more comorbidities than patients infected with CRO-S *E coli* ($P = .021$). There were no statistically significant differences between groups in the proportion of individuals with specific underlying medical conditions, including the proportions of patients with severe immunocompromise (38 [26%] vs 30 [20%], $P = .27$). Patients with CRO-R *E coli* BSI had a nonsignificant trend toward being more acutely ill on the day of first positive blood culture compared to patients with CRO-S *E coli* BSI; the proportion of patients with CRO-R *E coli* and CRO-S *E coli* BSI with Pitt bacteremia score ≥4 was 35 (23%) and 23 (15%), respectively ($P = .079$). Common sources of *E coli* BSI in the cohort as a whole were urinary (186 [62%]), intra-abdominal (29 [10%]), presumed (after no other source was identified) intestinal translocation (41 [14%]), and biliary (18 [6%]), with similar distributions between both groups (Table 2). Adequate source control was achieved in 117 (78%) versus 119 (79%) patients in the CRO-R and CRO-S *E coli* BSI groups, respectively ($P = .778$).

Antibiotic Therapy

Treatment in the first 4 days after obtaining blood cultures is summarized in Figure 2. Empiric carbapenem therapy (ie, carbapenem agents administered within the first 2 days of collection of the index blood culture) was more common in patients with CRO-R *E coli* versus CRO-S *E coli* BSI; 81 (54%) versus 16 (11%), respectively ($P < .001$). In the CRO-R group, fewer patients (31 [21%]) were treated empirically with ceftriaxone as compared to the CRO-R group (65 [44%]) ($P < .0001$). The median number of hours to active antibiotic therapy in the CRO-R and CRO-S groups was 12 hours (IQR, 1–35 hours) and 1 hour (IQR, 0–6 hours), respectively ($P < .001$). Although patients infected with CRO-R *E coli* had a longer time to receipt of active therapy than patients infected with CRO-S *E coli*, a similar proportion in both groups was receiving active therapy by day 3 (139 [97%] vs 145 [99%], respectively, $P = .24$). Durations of active antibiotic therapy were similar between both groups with the median duration of therapy (limited to patients alive beyond day 7) at 13 days (IQR, 8–16 days) and 12 days (IQR, 8–16 days) in the CRO-R and CRO-S groups, respectively ($P = .44$). Patients with CRO-R *E coli* were less likely to be transitioned to oral therapy; 9 (6%) patients with CRO-R *E coli* versus 60 (41%) patients with CRO-S *E coli* were transitioned to oral therapy ($P < .001$).

Impact of Ceftriaxone Resistance on Clinical Outcomes

The DOOR outcomes at 30 days after index blood culture collection both before adjustment and after IPW are illustrated in Figure 3*A* and 3*B*. In the unadjusted DOOR analysis, CRO-R BSI had a 58% probability (95% CI, 52%–63%) for a worse clinical outcome than CRO-S BSI. In the IPW-adjusted DOOR analysis no difference was seen, with CRO-R BSI having an

Table 2. Baseline Characteristics Comparing Patients With *Escherichia coli* Bloodstream Infection, by Ceftriaxone Susceptibility Status

Variable	Ceftriaxone Resistant (n = 150)	Ceftriaxone Susceptible (n = 150)	*P* Value[a]
Age, y, median (IQR)	69 (60–73)	67 (54–78)	.788
Age ≥65 y	90 (60)	78 (52)	.163
Female sex	73 (49)	86 (57)	.133
Weight, kg, median (IQR)	80 (66–94)	75 (63–91)	.271
Race/ethnicity[b]			
White	82 (55)	95 (63)	.127
Black	39 (26)	33 (22)	.417
Latino	12 (8)	11 (7)	.828
Asian	7 (5)	11 (7)	.331
Other/unknown	22 (15)	13 (9)	.106
Preadmission location			.013
Home	120 (80)	136 (91)	
Nursing home	20 (13)	6 (4)	
Skilled nursing facility	10 (7)	8 (5)	
Hospital-onset infection	41 (27)	21 (14)	.004
CCI score, median (IQR)	2 (1–5)	2 (0–4)	.021
Preexisting medical conditions[b]			
Coronary artery disease	21 (14)	30 (20)	.167
Congestive heart failure	25 (17)	22 (15)	.634
Peripheral vascular disease	9 (6)	4 (3)	.156
Diabetes	53 (35)	42 (28)	.172
Cerebrovascular disease	19 (13)	21 (14)	.734
Chronic kidney disease	35 (23)	28 (19)	.321
Chronic renal replacement therapy	9 (6)	3 (2)	.077
COPD	21 (14)	12 (8)	.101
Cirrhosis	9 (6)	10 (7)	.801
Severe immunocompromise[c]	38 (26)	30 (20)	.269
Severity of illness[b]			
Intensive care unit on day 1	41 (28)	39 (26)	.794
Pitt bacteremia score ≥4 on day 1	35 (23)	23 (15)	.079
Vasopressors on day 1	28 (19)	27 (18)	.881
Mechanical ventilation on day 1	25 (17)	19 (13)	.352
Change in mental status on day 1	59 (39)	46 (31)	.116
Highest peripheral WBC count on day 1, cells/mL, median (IQR)	12 600 (6800–19 200)	13 600 (7800–18 000)	.411
Source of bacteremia			.295
Urinary	90 (60)	96 (64)	
Vascular catheter	4 (3)	5 (3)	
Biliary	8 (5)	10 (7)	
Intra-abdominal	16 (11)	13 (9)	
Pneumonia	1 (1)	4 (3)	
Neutropenic fever	7 (5)	2 (1)	
Primary/presumed intestinal translocation[d]	21 (14)	20 (13)	
Adequate source control	117 (78)	119 (79)	.778

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

Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; WBC, white blood cell.

[a]Pearson χ^2 test for categorical variables; Wilcoxon rank-sum test for ordered and continuous variables.

[b]Not mutually exclusive.

[c]Defined by the presence of at least 1 of the following: hematopoietic stem cell transplant within the prior 12 months, chemotherapy within the prior 6 months, solid organ transplant recipient, human immunodeficiency virus infection with a CD4 count <200 cells/μL, receipt of corticosteroids at a dose equivalent to 10 mg daily of prednisone for ≥14 days, or other immunosuppressive therapy (ie, calcineurin inhibitors, mammalian target of rapamycin inhibitors, chemotherapy, monoclonal antibodies, or mycophenolates).

[d]No alternative source identified; does not include 1 patient each with a bone and joint infection, skin and soft tissue infection, and endocarditis.

estimated 54% probability (95% CI, 47%–61%) for a worse clinical outcome than CRO-S BSI. The unadjusted and adjusted differences in proportion of 30-day mortality between CRO-R and CRO-S was −5.3% (95% CI, −10.3% to −.4%) and −1.8 (95% CI, −6.7% to 3.2%), respectively. In the IPW-adjusted DOOR analysis limited to patients receiving active empiric therapy, the results were very similar with CRO-R BSI having an estimated 54% probability (95% CI, 48%–61%)

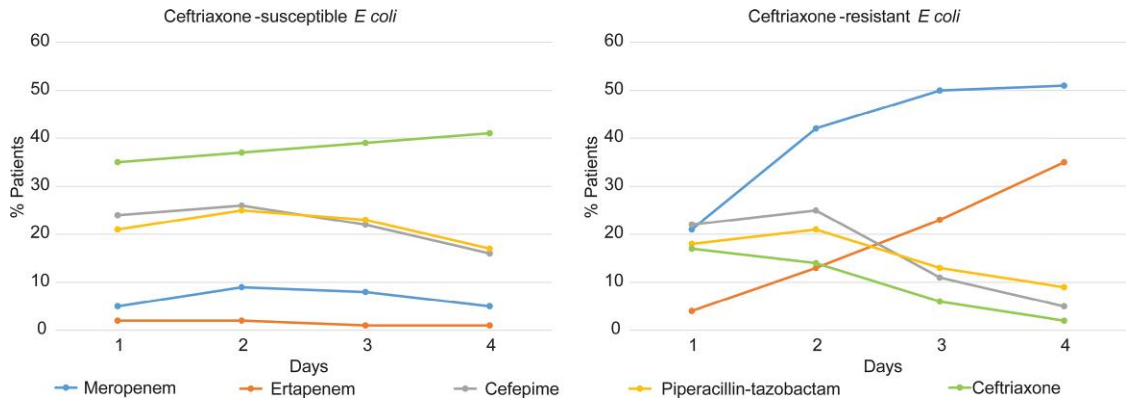

Figure 2. Antibiotic agents administered to patients with *Escherichia coli* bloodstream infections over the first 4 days of antibiotic therapy, by ceftriaxone susceptibility status.

for a poorer clinical outcome than CRO-S BSI. There were 23 (26%) and 23 (22%) hospital readmissions within 30 days among patients discharged alive in the CRO-R and CRO-S groups, respectively. The postculture length of stay was 8 days (IQR, 5–13 days) and 6 days (IQR, 4–9 days), respectively ($P < .001$). Of the 268 (89%) patients alive at day 30, 13 (10%) and 5 (4%) remained in the hospital on day 30 ($P = .037$). Of patients originally admitted to the hospital from their homes and alive at discharge, more patients with CRO-R *E coli* as compared to patients with CRO-S *E coli* were transferred to long-term care facilities (22 [22%] vs 15 [12%], $P = .045$).

DISCUSSION

In this prospective cohort study of 300 patients with *E coli* BSI from 14 hospitals across the US, patients infected with CRO-R *E coli* BSI had worse clinical outcomes compared to patients infected with CRO-S *E coli* BSI in unadjusted analyses. After adjusting for important confounders, no difference was seen in the primary DOOR analysis. However, patients infected with CRO-R BSI were more likely to have prolonged lengths of hospital stays, to remain in the hospital at day 30, and to be newly transferred to long-term care facilities. These findings underscore the importance of judicious antibiotic use to reduce the development of antibiotic resistance and its subsequent negative impacts on patient outcomes [17].

All-cause mortality has been evaluated in existing literature investigating outcomes associated with drug resistance. Previous studies have demonstrated that infections exhibiting drug-resistant phenotypes are generally associated with increased mortality compared to infections caused by drug-susceptible isolates [4–8]. Our investigation was not powered to detect a mortality difference. However, all-cause mortality was numerically higher in the CRO-R group, although this difference was not statistically significant. To evaluate additional factors negatively impacting the quality of life of patients infected with drug-resistant organisms, we elected to use DOOR as a primary endpoint to capture a more wide-ranging experience of patients infected with drug-resistant pathogens [18]. Concerns with available observational studies are that they are either missing several key variables due to their retrospective nature or that they insufficiently adjust for important baseline and treatment variables independently associated with mortality (eg, delays in time to active therapy, complex underlying medical conditions, severe immunocompromise, adequate source control measures). We attempted to overcome the first concern by enrolling a prospective cohort with comprehensive data collection occurring in real time. Regarding the second concern, there were differences between patients with CRO-R *E coli* and CRO-S *E coli* at baseline. For example, patients with CRO-R *E coli* tended to be more acutely ill at baseline (ie, higher Pitt bacteremia score), had risk factors increasing their likelihood of drug-resistant infections (ie, long-term care facility residency), and had more underlying medical conditions (ie, higher CCI). By employing IPW, we reduced the impact of the baseline differences and associated confounding by indication between patients infected with CRO-R *E coli* and CRO-S *E coli* BSI.

Clinicians treating patients in our study were reasonably accurate in predicting the antibiotic resistance phenotype on the day of blood culture collection. Treating physicians prescribed empiric carbapenem therapy for most patients with CRO-R *E coli* and only in few patients with CRO-S *E coli*. This accuracy may have contributed to the limited differences observed in 30-day mortality. In an international randomized clinical trial, carbapenem therapy was associated with a significant decrease in 30-day mortality in patients with CRO-R *E coli* BSI [19]. Patients with CRO-R *E coli* bacteremia who receive early carbapenem therapy may have similar 30-day mortality rates as those with CRO-S *E coli* bacteremia.

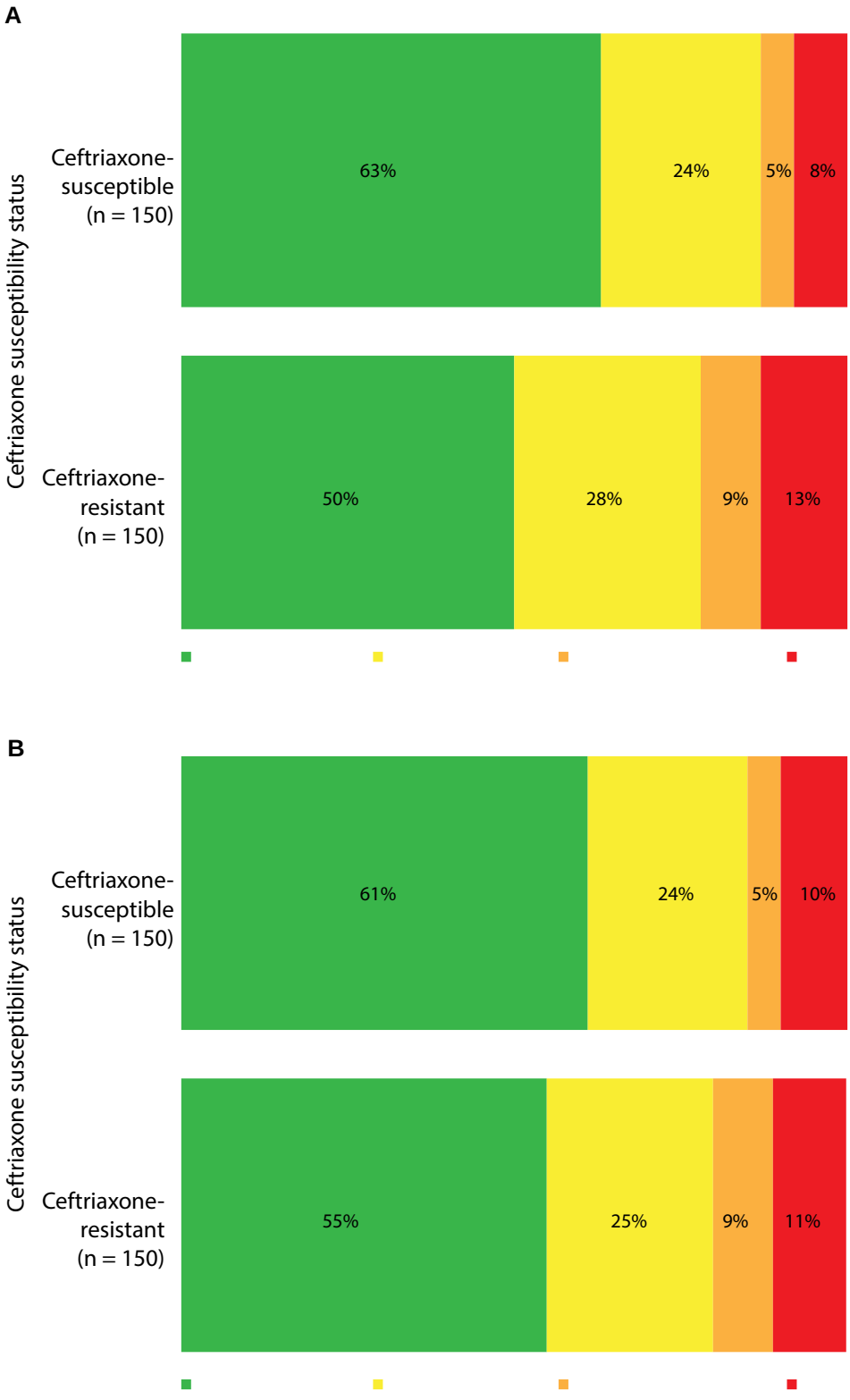

Figure 3. Unadjusted desirability of outcome ranking (DOOR) proportions at day 30 by ceftriaxone susceptibility status (*A*) and inverse probability weighting–adjusted DOOR proportions at day 30 (*B*), by ceftriaxone susceptibility status. Unadjusted DOOR probability: 58% (95% bootstrap confidence interval [CI], 52%–63%). Adjusted DOOR probability: 54% (95% bootstrap CI, 47%–61%).

We decided to focus on ceftriaxone resistance rather than the presence of specific β-lactamase genes as ceftriaxone resistance is more reflective of the ability of a β-lactamase to hydrolyze ceftriaxone. Moreover, as the CLSI does not endorse routine ESBL testing and it is performed by a minority of clinical microbiology laboratories [11, 20, 21], a phenotype-guided study design is more reflective of real-world antibiotic decision making. Although clinicians often equate CRO-R *E coli* with ESBL production, *E coli* can exhibit ceftriaxone resistance due to a number of mechanisms including ESBL genes (eg, $bla_{\text{CTX-M-15}}$, $bla_{\text{SHV-12}}$), plasmid-mediated bla_{ampC}genes (eg, bla_{DHA}, bla_{FOX}), chromosomally derepressed bla_{ampC} genes, and hyperexpressed narrow-spectrum β-lactamase genes with associated mutations in permeability [3].

CRO-R *E coli* often carry additional antimicrobial resistance markers (eg, *qnr,* mutations in *gyrA* and *sul* genes) conferring resistance to oral antibiotics such as ciprofloxacin, levofloxacin, and TMP-SMX [22]. In our cohort, susceptibility of CRO-R *E coli* isolates to fluoroquinolones and TMP-SMX was significantly lower than for CRO-S *E coli* isolates. The limited availability of active oral treatment options likely, at least partially, contributed to the low percentage of patients in the CRO-R *E coli* group transitioned to oral therapy, when compared to the CRO-S *E coli* group (6% vs 41%). Unfortunately, the lack of suitable oral antibiotic treatment options increases the likelihood of placement of peripherally inserted central catheters, prolonged hospital stays, or transfer to long-term care facilities—further contributing to the morbidity associated with CRO-R *E coli* BSI. As oral carbapenem agents are currently in advanced phases of clinical trials, these may help alleviate morbidity associated with CRO-R *E coli* BSI in the future.

There are important limitations to this work. First, although variables expected to be independently associated with poor outcomes for patients with *E coli* BSI were collected, there were likely additional unmeasured confounders that were not accounted for. We attempted to mitigate the impact of cofounders on clinical outcomes through IPW propensity score–adjusted analysis. Nonetheless, residual confounding persists. Second, the associated differential impact of specific antibiotics on clinical outcomes could not be investigated given the heterogeneity of antibiotic therapy prescribed to study participants. Additionally, we were likely underpowered to identify some important clinical differences because of the sample size. For example, 30-day mortality was 13% in patients with CRO-R *E coli* versus 8% in those with CRO-S *E coli*.

In conclusion, this work shows that patients infected with CRO-R *E coli* generally have worse clinical outcomes as compared to patients infected with CRO-S *E coli*. This observation is primarily driven by host factors such as increased comorbidities. Furthermore, effective empiric therapy may further decrease differences in outcomes between groups. These findings highlight the importance of judicious antibiotic prescribing and infection control practices to prevent emergence of antibiotic resistance, and its negative downstream consequences.

Notes

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Patient consent. The study was approved by the institutional review boards (IRBs) of all study sites, with a waiver of informed consent. Duke University was the coordinating IRB (DUHS IRB Pro00106280).

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