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Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections

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Background. We conducted this study to describe the clinical characteristics, microbiology, and outcomes of patients treated with ceftazidime-avibactam (CZA) for a range of multidrug-resistant Gram-negative (MDR-GN) infections.

Methods. This is a multicenter, retrospective cohort study conducted at 6 medical centers in the United States between 2015 and 2019. Adult patients who received CZA (≥72 hours) were eligible. The primary outcome was clinical failure defined as a composite of 30-day all-cause mortality, 30-day microbiological failure, and/or failure to resolve or improve signs or symptoms of infection on CZA.

Results. In total, data from 203 patients were evaluated. Carbapenem-resistant Enterobacteriaceae (CRE) and *Pseudomonas* spp were isolated from 117 (57.6%) and 63 (31.0%) culture specimens, respectively. The most common infection sources were respiratory (37.4%), urinary (19.7%), and intra-abdominal (18.7%). Blood cultures were positive in 22 (10.8%) patients. Clinical failure, 30-day mortality, and 30-day recurrence occurred in 59 (29.1%), 35 (17.2%), and 12 (5.9%) patients, respectively. On therapy, CZA resistance developed in 1 of 62 patients with repeat testing. Primary bacteremia or respiratory tract infection and higher SOFA score were positively associated with clinical failure (adjusted odds ratio [aOR] = 2.270, 95% confidence interval [CI] = 1.115–4.620 and aOR = 1.234, 95% CI = 1.118–1.362, respectively). Receipt of CZA within 48 hours of infection onset was protective (aOR, 0.409; 95% CI, 0.180–0.930). Seventeen (8.4%) patients experienced a potential drug-related adverse effect (10 acute kidney injury, 3 *Clostridioides difficile* infection, 2 rash, and 1 each gastrointestinal intolerance and neutropenia)

Conclusions. Ceftazidime-avibactam is being used to treat a range of MDR-GN infections including *Pseudomonas* spp as well as CRE.

Keywords. carbapenem-resistant Enterobacteriaceae; ceftazidime-avibactam; multidrug-resistant *Pseudomonas aeruginosa*.

Multidrug-resistant (MDR) Gram-negative bacteria are a pressing infectious disease challenge [1, 2]. Carbapenems have served as the antibiotics of choice for infections caused by these pathogens for decades. However, the emergence and spread of carbapenemases threatens their utility as our last line of defense against MDR bacteria [2]. The predominant carbapenemase in the United States is *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler class A enzyme that hydrolyses almost all currently available beta-lactams [3]. Bacteria that harbor *bla*KPC often carry other genes that encode resistance to a wide array of other antibiotic classes, posing a serious treatment challenge [2, 3]. Until recently, the only remaining antibiotics with preserved in vitro activity against MDR strains were limited by unfavorable pharmacokinetic properties and/or toxicity [4–6]. The high morbidity and mortality associated with infections caused by MDR Gram-negative bacteria is partly due to the paucity of safe and effective treatment options, attesting to the need for continued antibiotic development [2].

Ceftazidime-avibactam (CZA) is a combination antimicrobial consisting of an established antipseudomonal cephalosporin and a novel non-beta-lactam (diazabicyclooctane) beta-lactamase inhibitor [7]. Avibactam protects ceftazidime from hydrolysis by Ambler class A and some class D carbapenemases [7]. In surveillance studies, CZA has demonstrated in vitro activity against carbapenem-resistant Enterobatceriaceae (CRE) and MDR *Pseudomonas aeruginosa* [8, 9]. Real-world experience

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with CZA for the treatment of CRE infections is slowly accumulating, but data on its use for other MDR Gram-negative pathogens including *P aeruginosa* remain limited [10–16]. We sought to add to these data and describe the clinical characteristics, microbiology, and outcomes of patients treated with CZA for a range of MDR Gram-negative bacterial pathogens.

METHODS

Study Design and Population

This was a multicenter, retrospective, observational cohort study conducted at 6 geographically diverse academic medical centers in the United States between 2015 and 2019. Inclusion criteria were as follows: (1) age ≥18 years and (2) receipt of ≥72 hours of CZA. For each patient, only the initial CZA treatment course during the study period was included.

Ethics

Approval was obtained from each participating center's Institutional Review Board with a waiver for informed consent.

Data Collection and Study Definitions

Pharmacy records were screened for all patients who received at least 1 dose of CZA during the study period. For eligible patients, demographic, clinical, microbiological, and treatment data were extracted from the electronic medical record and entered into a secure data collection form [17]. Bacterial identification and antibiotic susceptibilities were performed at each center according to standard procedures. Ceftazidime-avibactam susceptibility was determined using disk diffusion or gradient strips, where available. Carbapenem-resistant Enterobatceriaceae was defined by current US Centers for Disease Control and Prevention criteria [5]. Infection onset was considered to be when the index culture was collected. Sources of infection were based on the treating physician's notes and available clinical, microbiological, and diagnostic data. The infection was classified as hospital-acquired if the index culture was obtained more than 48 hours after admission. Comorbidity burden was quantified using the Charlson comorbidity score [18]. Severity of illness at infection onset was quantified using the Sequential Organ Failure Assessment (SOFA) score [19]. Ceftazidime-avibactam was administered as a standard dose of 2.5 grams intravenously (IV) every 8 hours with dose adjustments based on estimate creatinine clearance ([CrCl] Cockroft-Gault equation) [20] according to the manufacturer's recommendations [21]. For the purposes of this study, CZA combination therapy was defined as the receipt of a concomitant Gram-negative targeted antibiotic for ≥48 hours with CZA. Receipt of metronidazole was described separately. Microbiological failure was defined as infection recurrence with the same organism as isolated from the index culture after 7 days of CZA therapy to the end of follow-up plus signs and symptoms of infection. Data were collected for up to 30 days after discharge (ie, from health system outpatient clinics, rehabilitation centers, emergency departments, and hospital re-admissions where available). Clinical failure was defined as a composite of all-cause 30-day mortality, microbiological failure, and/or failure to resolve or improve signs and symptoms of infections during CZA therapy. Acute kidney injury (AKI) was evaluated in patients not receiving hemodialysis at the time of CZA initiation and was defined as a serum creatinine increase of ≥0.5 mg/dL or 50% from baseline on 2 consecutive measurements while on CZA and up to 72 hours after the last dose.

Statistical Analysis

Baseline characteristics of the overall cohort and in the CRE and *Pseudomonas* spp subgroups were evaluated using descriptive statistics; discrete data were reported as counts and percentages, and continuous data were reported as medians and interquartile ranges (IQRs). Multivariable logistic regression analysis was performed to identify independent predictors of clinical failure. Because baseline characteristics, management, and outcomes were similar in the overall cohort and the CRE and *Pseudomonas* spp subgroups, this analysis was conducted using the overall cohort. Clinically relevant variables were selected for model entry based on bivariate comparisons ($P < .2$) and biological plausibility. Some variables were collapsed into single composite variables when the number of patients in subgroups was too small to allow for meaningful analysis. The selected model was simplified based on the Akaike information criterion (AIC) in backward fashion. Multicollinearity of candidate regression models was assessed via the variance inflation factor, with values less than 3 considered acceptable. Secondary outcomes of interest included individual components of the composite outcome, discharge disposition, emergence of CZA resistance during treatment, and hospital length of stay. Safety outcomes included AKI, dermatological reactions, cytopenias, central nervous system disturbances, gastrointestinal (GI) intolerance, and *Clostridioides difficile*-associated diarrhea.

All analyses were performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY) and SAS 9.4 Statistical Software (SAS Institute Inc., Cary, NC). A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Patient Characteristics

In total, 203 patients met study inclusion criteria and were evaluated. A complete description of patient baseline demographic and clinical characteristics are displayed in Table 1. Overall, the study cohort had a median age of 62 (IQR, 49–72) years with a high burden of medical comorbidity (median Charlson comorbidity score 4; IQR, 2–6). Approximately half (93, 45.8%) of patients resided in a skilled nursing facility before admission or

Table 1. Demographic and Clinical Characteristics

Characteristics	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection[a] N = 63
Age, years	62 (49–72)	63 (52–73)	62 (43–74)
Age ≥65 years	90 (44.3)	53 (45.3)	28 (44.4)
Male gender	39 (61.9)	63 (53.8)	39 (61.9)
Race			
African American	93 (45.8)	57 (48.7)	30 (47.6)
White	79 (38.9)	41 (35.0)	21 (33.3)
Latino	8 (3.9)	6 (5.1)	3 (4.8)
Other	22 (10.8)	13 (11.1)	9 (14.3)
BMI	27 (22–35)	27 (22–34)	25 (21–35)
Obese (BMI ≥30 kg/m^2)	77 (37.9)	40 (34.2)	23 (36.5)
Estimated CrCl (mL/min)[b]	65 (34–105)	60 (29–101)	13 (20.6)
CrCl ≤30 mL/min	40 (19.7)	25 (21.4)	10 (15.9)
CrCl 31–50 mL/min	28 (13.8)	14 (12.0)	15 (23.8)
CrCl 51–90 mL/min	50 (24.6)	27 (23.1)	7 (11.1)
CrCl 91–130 mL/min	28 (13.8)	18 (15.4)	11 (17.5)
CrCl >130 mL/min	27 (13.3)	13 (11.1)	7 (11.1)
Hemodialysis	30 (14.8)	20 (17.1)	
Residence Before Admission			
Community	101 (49.8)	59 (50.4)	25 (39.7)
SNF/LTAC	65 (32.0)	38 (32.5)	23 (11.3)
Transferred from outside	28 (13.8)	14 (12.0)	11 (5.4)
Hospital	9 (4.4)	6 (3.0)	4 (2.0)
Other			
Comorbid Conditions			
Diabetes	85 (41.9)	46 (39.3)	33 (52.4)
Heart failure	37 (18.2)	20 (17.1)	12 (19.0)
Chronic kidney disease	65 (32.0)	40 (34.2)	19 (30.2)
Chronic lung disease	74 (36.5)	40 (34.2)	29 (46.0)
Malignancy	27 (13.3)	19 (16.2)	6 (9.5)
Liver disease	21 (10.3)	15 (12.8)	2 (3.2)
Charlson comorbidity score	4 (2–6)	4 (2–7)	4 (2–6)
Charlson comorbidity score > 4	85 (41.9)	51 (43.6)	25 (39.7)
Immunocompromised	22 (10.8)	16 (13.7)	4 (6.3)
MDRO infection or colonization within 1 year	97 (47.8)	56 (47.9)	34 (54.0)
Recent antibiotic exposure (≥24 hours within 90 days)	157 (77.3)	96 (82.1)	51 (81.0)
Recent hospitalization (≥48 hours within 90 days)	151 (74.4)	94 (80.3)	46 (73.0)
Recent surgery (within 30 days)	38 (18.7)	23 (19.7)	10 (15.9)
ICU at index culture	102 (50.2)	62 (53.0)	35 (55.6)
SOFA score	5 (2–8)	5 (2–8)	5 (2–8)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; CRE, carbapenem-resistant Enterobacteriaceae; ICU, intensive care unit; LTAC, long-term acute care hospital; MDRO, multidrug-resistant organism; SNF, skilled nursing facility; SOFA, Sequential Organ Failure Assessment.

[a]All values represent number (%) or median (interquartile range).

[b]Estimated by using the Cockroft-Gault equation [20]; creatinine measured within 24 hours of first dose ceftazidime-avibactam.

were transferred from an outside hospital, and the majority of patients had a recent (90 day) history of hospitalization or systemic antibiotic exposure (151, 74.4% and 157, 77.3%, respectively). Many patients had a high severity of illness at infection onset with 102 (50.2%) residing in the intensive care unit (ICU) and a median SOFA score of 5 (IQR, 2–8). Baseline characteristic of patients with CRE or *Pseudomonas* spp infections were similar (Table 1).

Infection Characteristics

The majority of infections (117, 57.6%) were hospital-acquired with the median time from admission to infection onset of 3 (IQR, 2–16) days. The most common infection sources were respiratory tract (76, 37.4%), followed by urinary tract (40, 19.7%), intra-abdominal (38, 18.7%), skin and soft tissue (18, 8.9%), and osteoarticular (14, 6.9%) (Table 2). Blood cultures were positive in 22 (10.8%) patients. Carbapenem-resistant

Table 2. Infection Characteristics

Characteristic	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection[a] N = 63
Hospital-acquired infection	117 (57.6)	71 (60.7)	38 (60.3)
Hours from admission to culture collection	3 (2–16)	6 (2–17)	73 (2–13)
Infection Source			
Primary bacteremia	10 (4.9)	7 (6.0)	1 (1.6)
Respiratory	76 (37.4)	39 (33.3)	38 (60.3)
Intra-abdominal	38 (18.7)	26 (22.2)	3 (4.8)
Skin and soft tissue	18 (8.9)	8 (8.8)	6 (9.5)
Osteoarticular	14 (6.9)	7 (6.0)	6 (9.5)
Urine	40 (19.7)	24 (20.4)	7 (11.1)
Prosthetic device	2 (1.0)	2 (1.7)	0
Intravenous catheter	4 (2.0)	3 (2.6)	2 (3.2)
Other[b]	1 (0.5)	1 (0.9)	0
Positive blood cultures	22 (10.8)	10 (8.5)	3 (4.8)
Organism			
Enterobacteriacea	159 (78.3)	117 (100)	
Klebsiella pneumoniae	89 (43.8)	74 (63.2)	
Klebsiella oxytoca	8 (3.9)	5 (4.3)	
Escherichia coli	23 (11.3)	17 (14.5)	
Enterobacter spp	29 (14.3)	15 (12.8)	
Proteus mirabilis	8 (3.9)	1 (0.9)	
Citrobacter spp	9 (4.4)	5 (4.3)	
Serratia marcescens	6 (3.0)	4 (3.4)	
Providentia stuarti	4 (2.0)	0	
Morganella morganii	4 (2.0)	0	
Pseudomonas spp	63 (31.0)		
Acinetobacter spp[c]	12 (5.9)		
Stenotrophomonas maltophilia[d]	5 (2.5)		
Gram positive	30 (14.8)		
Polymicrobial infection	48 (23.6)	30 (25.6)	17 (27.0)
K pneumoniae CZA MIC (mg/L)			
MIC_{50}	1[e]	1[f]	
MIC_{90}	2[e]	4[f]	
Pseudomonas aeruginosa CZA MIC (mg/L)			
MIC_{50}			2[g]
MIC_{90}			6[g]

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CZA, ceftazidime-avibactam; MIC, minimum inhibitory concentration.

[a]All values represent number (%) or median (interquartile range).

[b]Perinephric abscess.

[c]Eleven of 12 patients had polymicrobial infections and received additional other antibiotics targeting *Acinetobacter* spp. The remaining patient had monomicrobial *Acinetobacter* urinary tract infection. They received CZA (surprisingly, MIC 8 mg/mL) plus minocycline. The rationale for using CZA was not explicitly stated.

[d]All patients had polymicrobial infections and received additional other antibiotics targeting *S maltophilia*.

[e]n = 51 isolates tested.

[f]n = 43 isolates tested.

[g]n = 19 isolates tested.

Enterobatceriaceae was isolated from 117 (57.6%) of culture specimens. Most CRE were *K pneumoniae* (74 of 117, 63.2%), followed by *Escherichia coli* (17 of 117, 14.5%) and *Enterobacter* spp (15 of 117, 12.8%). Among the 50 carbapenem-resistant *K pneumoniae* isolates tested, 48 (96.0%) were susceptible to CZA. One resistant isolate (CZA minimum inhibitory concentration [MIC] >256 mg/L) harbored both New Delhi metallo-beta-lactamase (NDM) and oxacillinase (OXA) carbapenemases. The mechanism of resistance in the second isolate is currently unknown.

Ceftazidime-avibactam was used to treat 63 patients with *Pseudomonas* spp infections. The majority of *Pseudomonas* spp infections had a respiratory tract source (38, 60.3%). Among the *P aeruginosa* isolates for which the CZA susceptibility testing was performed (n = 27), 25 (92.6%) were susceptible. One isolate demonstrated intermediate CZA susceptibility (zone diameter 18 mm) and a second was CZA resistant (MIC >256 mg/L, positive for NDM and OXA carbapenemases). Of 40 *P aeruginosa* isolates tested, 21 (52.5%) were susceptible to ceftazidime itself. The most common reason for the use of CZA in these patients was coinfection with CRE (n = 11)

and cefepime resistance or failure in hospitals that did not carry ceftazidime on the formulary (n = 6). *Klebsiella pneumoniae* and *P aeruginosa* antibiograms are shown in Supplementary Appendix 1.

Infection Management

A summary of infection management is shown in Table 3. Overall, 199 (98.0%) and 58 (28.6%) patients received an infectious disease or surgical consult, respectively, and source control (eg, line removal, abscess drainage) was pursued in 54 (26.6%) patients. The median time from culture collection to CZA initiation was 85 (IQR, 42–146) hours. Approximately 1 in 4 (54, 26.6%) patients received in vitro active antibiotic therapy before CZA with an overall median time to active antibiotic therapy of 55 (IQR, 7–102) hours. The most commonly used active agents before CZA were aminoglycosides (18 of 54, 33.3%). The CZA dose was renally adjusted in 92 (45.3%) patients. Eleven of these patients did not require dose adjustment-based estimated CrCl >50 mL/minute at the start of CZA. Combination IV antibiotic therapy was used in 68 (33.5%) patients, most commonly with an aminoglycoside (21, 10.3%), colistin/polymyxin B (17, 8.4%), or tigecycline (16, 7.9%). Three of 38 patients (7.9%) with an intra-abdominal infection received concomitant metronidazole. Inhaled antibiotics (tobramycin or colistin) were used in 19 of 76 patients (25.0%) with a respiratory tract infection. The median duration of inpatient CZA was 9 (IQR, 6–16) days.

Outcomes

Patient outcomes are displayed in Table 4. As shown, outcomes were similar in patients with CRE and *Pseudomonas* spp infections. Overall, composite clinical failure and 30-day mortality occurred in 59 (29.1%) and 35 (17.2%) patients, respectively. Among patients originally admitted from home (n = 101), 29 (28.7%) and 10 (9.9%) required new nursing home placement or inpatient rehabilitation after discharge, respectively. The highest rates of clinical failure and 30-day mortality were recorded in patients with primary bacteremia (7 of 10, 70.0% and 4 of 10, 40.0%) or a respiratory tract infection (32 of 76, 42.1% and 21 of 76, 27.6%), whereas the lowest rates were documented in patients with intra-abdominal (5 of 38, 13.2% and 2 of 38, 5.3%) or urinary tract infections (6 of 40, 15.0% and 3 of 40, 7.5%). On bivariate analysis, additional variables associated with higher clinical failure included (Supplementary Appendix 2) the following: CrCl ≤30 mL/minute or on hemodialysis, prior hospitalization within 90 days, ICU at infection onset, and SOFA score. Pursuit of source control, active antibiotic therapy within 48 hours of infection onset, and CZA initiation within 48 hours of infection onset were associated with lower clinical failure. The use of CZA combination therapy did not impact clinical failure in the overall patient population or among high-risk subgroups including those with primary bacteremia, a respiratory tract source, or ICU residence at infection onset. Likewise, in patients with CRE or *Pseudomonas* spp infections, combination therapy was not associated with lower

Table 3. Treatment Information

Parameter	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection N = 63
Infectious disease consult	199 (98.0)	117 (100)	59 (93.7)
Time to infectious disease consult (hours)	28 (4–63)[b]	29 (9–65)	24 (0–86)[c]
Surgical consult	58 (28.6)	32 (27.4)	17 (27.0)
Source control pursued	54 (26.6)	29 (24.8)	19 (30.2)
Active antibiotic(s) before CZA	54 (26.6)	27 (23.1)	12 (19.0)
Time to active antibiotic(s) (hours)	55 (7–102)	69 (26–103)	72 (12–123)
Active antibiotic(s) within 48 hours	91 (44.8)	39 (33.3)	24 (38.1)
Time to CZA (hours)	85 (42–146)	93 (52–145)	94 (34–170)
CZA within 48 hours	59 (29.1)	25 (21.4)	17 (27.0)
Renal CZA dose adjustment	92 (45.3)	54 (46.2)	28 (44.4)
CZA combination therapy	68 (33.5)	45 (38.5)	20 (31.7)
Aminoglycoside	21 (10.3)	13 (11.1)	8 (12.7)
Colistin/polymyxin B	17 (8.4)	10 (8.5)	5 (7.9)
Fluoroquinolone	10 (4.9)	8 (6.8)	2 (3.2)
Tigecycline	16 (7.9)	10 (8.5)	3 (4.8)
Minocycline	2 (1.0)	1 (0.9)	0
Aztreonam	3 (1.5)	1 (0.9)	2 (3.2)
Inhaled antibiotic therapy in patients with a respiratory tract infection[d]	19/76 (25.0)	7/39 (7.9)	14/38 (36.8)
CZA duration (days)	9 (6–16)	13 (6–18)	9 (5–14)

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CZA, ceftazidime-avibactam.

[a]All values represent number (%) or median (interquartile range).

[b]N = 199.

[c]N = 59.

[d]Inhaled tobramycin or colistin.

Table 4. Outcomes

Outcome	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection[a] N = 63
Effectiveness			
Discharge Disposition			
Home	57 (28.1)	31 (26.5)	16 (25.4)
SNF/LTAC	90 (44.3)	53 (45.3)	32 (50.8)
Inpatient rehabilitation facility	14 (6.9)	8 (6.8)	3 (4.8)
Hospice	8 (3.9)	5 (4.3)	2 (3.2)
Inhospital mortality	34 (16.7)	20 (17.1)	10 (15.9)
Discharge Disposition Among Patients Admitted From Home			
Home	47/101 (46.5)	25/59 (42.4)	11/25 (44.0)
SNF/LTAC	29/101 (28.7)	18/59 (30.5)	9/25 (36.0)
Inpatient rehabilitation facility	10/101 (9.9)	6/59 (10.2)	3/25 (12.0)
Hospice	2/101 (2.0)	2/59 (3.4)	0
Inhospital mortality	13/101 (12.9)	8/59 (13.6)	2/25 (8.0)
Composite clinical failure	59 (29.1)	34 (29.1)	19 (30.2)
30-day mortality	35 (17.2)	19 (16.2)	11 (17.5)
30-day recurrence	12 (5.9)	7 (6.0)	4 (6.3)
Worsen or failure to improve while on CZA	32 (15.8)	18 (15.4)	12 (19.0)
Development of CZA resistance (n = 61)[b]	0	0	0
Safety			
Acute kidney injury[c]	10/177 (5.6)	5/101 (5.0)	4/56 (7.1)
Clostridioides difficile infection	3 (1.5)	3 (2.6)	0
Rash	2 (1.0)	0	2 (3.2)

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; CZA, ceftazidime-avibactam; LTAC, long-term acute care hospital; SNF, skilled nursing facility.

[a]All values represent number (%) or median (interquartile range).

[b]Evaluated in patients with follow-up cultures.

[c]Patients receiving hemodialysis excluded.

clinical failure or lower 30-day mortality. Among 11 patients who received an inappropriate CZA dose reduction, 5 (45.5%) experienced clinical failure and 3 (27.3%) died by day 30. The final multivariable logistic regression model for clinical failure is shown in Table 5. Primary bacteremia or respiratory tract infection and SOFA score were independently associated with higher clinical failure, whereas CZA within 48 hours of infection onset was protective.

Repeat CZA susceptibility testing was performed in 61 (30.0%) patients. The development of CZA resistance was not detected in any of these cultures.

Table 5. Multivariable Logistic Regression Model for Clinical Failure[a]

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Primary bacteremia or respiratory tract infection	2.270 (1.115–4.620)	<.001
SOFA score	1.234 (1.118–1.362)	.0238
CZA within 48 hours of culture collection	0.409 (0.180–0.930)	.0329

Abbreviations: CI, confidence interval; CZA, ceftzidime-avibactam; SOFA, Sequential Organ Failure Assessment.

[a]Variable considered for model entry were as follows: admission from an outside hospital, creatinine clearance ≤30 mL/min or receipt of hemodialysis, previous hospitalization within 90 days, hospital-acquired infection, primary bacteremia or respiratory tract infection, pursuit of source control, early (≤48 hours) active antibiotic therapy, early (≤48 hours) CZA, Acute Physiological and Chronic Health Evaluation (APACHE) II score, SOFA score, intensive care unit at infection onset.

With regards to safety, 17 (8.4%) patients experienced a potential drug-related adverse effect. Ten patients developed AKI while receiving CZA; 9 of these patients were receiving concomitant nephrotoxic agents around the time of the event. In particular, 5 (25%) patients who received CZA combination therapy with an aminoglycoside or a polymyxin experienced AKI compared with 5 (3.2%) who did not receive either of these antibiotic classes with CZA ($P < .001$). Three patients developed *C difficile*-associated diarrhea (2 of whom received CZA combination therapy). Two patients had a rash, and 1 patient each experienced possible drug-related neutropenia and GI intolerance.

DISCUSSION

Antimicrobial resistance in Gram-negative pathogens has now reached a critical point, and many infections are no longer easily treated with carbapenems, the previous drugs of choice [1, 2]. Fortunately, several novel antibiotics targeted to 1 or more resistant determinants have recently been added to our armamentarium and others are in the pipeline [7, 22–24]. The introduction of these new agents, together with advances in rapid diagnostic techniques and progress in our understanding of pharmacokinetic/pharmacodynamic antibiotic optimization, have changed the landscape of treatment of MDR infections.

Yet, as our struggles with antimicrobial resistance will continue despite the availability of new antibiotics, it is critically important that we learn how to best incorporate new agents into clinical practice. Real-world studies can provide valuable insights into the clinical role of new antibiotics. Therefore, we conducted this study to evaluate the epidemiology and outcomes of patients treated with CZA from across the United States for a range of MDR Gram-negative pathogens.

By some measures, CZA treatment appeared to be both effective and safe. Our primary outcome, composite clinical failure, occurred in 29.1% of patients, and 30-day all-cause mortality was 17.2%. These results are particularly encouraging considering that our cohort comprised patients with high index illness severity and a variety of complex medical conditions. More than half of patients were residents of the ICU at infection onset, the median SOFA score was 5, and more than 40% had a Charlson comorbidity score greater than 4. Ceftazidime-avibactam was also well tolerated. Acute kidney injury occurred in 5.6% of patients not receiving renal replacement therapy at CZA initiation, and the vast majority of these patients were receiving concomitant nephrotoxins. Furthermore, despite extensive prior antibiotic exposure and frequent use of CZA combination therapy, overall *C difficile*-associated diarrhea rates were relatively low (1.5%).

However, on a more sobering note, we observed considerable variation in outcomes by infection source with primary bacteremia and pneumonia portending particularly poor prognoses. Patients with severe renal impairment and those on chronic hemodialysis also did worse. These patterns have been observed by other investigators as well and serve as a reminder that in vitro antibiotic activity is not the only determinant of clinical outcomes in patients with MDR bacterial infections [10, 11, 13, 14, 16].

Also of note, we found that CRE infections accounted for slightly more than half of infections treated with CZA in our cohort. Prior observational studies have focused primarily on CZA for CRE infections [10–16]. Multidrug-resistant *Pseudomonas* spp was also a common indication for CZA in our cohort (n = 63). To the best of our knowledge, this is the largest study of patients treated with CZA for *Pseudomonas* spp infections reported to date. Patient characteristics and outcomes were remarkably similar when stratified by infecting pathogen, with the exception of infection source; a respiratory source of infection was more common in patients with *Pseudomonas* spp infections. Among the *P aeruginosa* isolates tested, CZA susceptibility was high (92.6%) and very similar to that of ceftolozane-tazobactam (85.2%). A great deal of regional variation has been observed with regards to the comparative activity of these antibiotics against MDR *P aeruginosa* [25, 26]. Humphries et al [26] recently evaluated the comparative activity of ceftolozane-tazobactam and CZA against a collection of beta-lactam-resistant *P aeruginosa* isolates recovered from patients treated in Los Angeles, California. Although both agents demonstrated good activity, susceptibility rates were lower than observed in our study, and ceftolozane-tazobactam susceptibility rates were higher than CZA (72.5% and 61.8%, respectively) [26]. None of the centers that contributed cases to this study were located in California or the neighboring states, which may explain the differing results and underscores the importance of considering local resistance patterns to inform decisions at both the health system formulary level and for individual patients. It is also important to point out that our CZA susceptibility rates may be overestimates because we only included patients who received CZA for ≥72 hours (ie, CZA may have not been started or stopped before 72 hours if resistance was detected).

Combination therapy was considered standard for the treatment of CRE infections in the pre-CZA era [2, 27]. However, the marginal benefits of this approach were often mitigated by overlapping toxicities [27]. The use of CZA combination therapy was also common in our cohort with 1 in 3 patients receiving a second Gram-negative targeted agent, most often an aminoglycoside or a polymyxin. However, combination therapy was not associated with improved clinical outcomes in the overall cohort nor in subgroups of higher risk patients. This finding is consistent with several recent CZA observational studies [10, 11, 13, 14]. Acute kidney injury was significantly higher in patients who received a concomitant aminoglycoside or polymyxin. Although we cannot exclude confounding by indication, the consistent lack of benefit seen across studies and the potential for harm demonstrated in the present study does call into question the utility of continuing this practice.

We found that early in vitro active antibiotic therapy, and, in particular, early use of CZA (within 48 hours of infection onset), was associated with improved clinical outcomes. Several studies have shown that treatment of serious infections is time sensitive with negative consequences for delays in appropriate therapy [28–31]. This underscores the important role of rapid diagnostic testing for early pathogen identification and susceptibility testing. New agents are often introduced before validated susceptibility testing methods are available, and this may limit the benefit derived from their use. Almost all patients enrolled in this study received an infectious disease consult at a median of 28 hours of infection onset. This was likely very important in ensuring the appropriate and optimal use of CZA.

Rates of recurrence in our study were low (5.6%), and development of CZA on therapy resistance was not detected. These results compare favorably with one of the earliest CZA observational studies by Shields et al [13]. These investigators evaluated 37 patients treated with CZA for CRE infections and found a 30-day recurrence rate of 16.7% including 3 patients with re-infection by a strain that had developed CZA resistance [13]. Differences in patient and infection characteristics as well as study procedures may account for the following discrepancies: (1) the study by Shields et al [13] included a larger proportions

of patients with bacteremia and pneumonia that are characterized by high bacterial burdens; (2) we included patients with infections caused by a variety of pathogens versus only CRE infections in the Shields et al [13] study; and (3) repeat susceptibility testing was performed in less than one third of our patients (30.0%).

This study has several important limitations including its retrospective, observational design. In addition, although this represents one of the largest studies to date evaluating the use of CZA for MDR infections, the sample size was still relatively small, limiting our ability to conduct meaningful subgroup analyses. The use of rapid diagnostics varied across centers, and CZA susceptibility testing was performed on a relatively small proportion of isolates. We also did not have data regarding the mechanisms responsible for resistance. However, this is unfortunately reflective of real-world practice where, as noted previously, validated susceptibility testing methods often lag antibiotic approvals. Finally, the interpretation of CZA effectiveness and safety is limited by the lack of a control group. Comparative outcomes research of newer antibiotics is desperately needed. Indeed, one may reasonably argue that there is no longer equipoise with regards to the comparative safety and efficacy of older more toxic regimens and newly approved CRE-active agents [12, 15, 32, 33]. Clinicians and patients would be better served if regulatory bodies would revise their guidance to the industry to stipulate that agents in late-stage development targeted to MDR pathogens be compared with the new standard.

CONCLUSIONS

In conclusion, our study adds to the growing body of literature describing CZA treatment patterns and outcomes for MDR infections. Our study shows that when patients are managed by infectious diseases physicians, CZA can be an effective therapy for MDR *Pseudomonas* as well as CRE infections. We provide additional data that should prompt clinicians to reassess the anticipated benefits and risks of combination therapy in the era of novel Gram-negative agents. Our study also highlights the need for continued advances to improve outcomes in vulnerable patient groups including those with MDR Gram-negative bacteremia or pneumonia and patients with severe renal impairment.

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.

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