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

Sarah C. J. Jorgensen, Trang D. Trinh, Evan J. Zasowski, Abdalhamid M. Laght, Sahil Bhatia, Sarah M. Melvin, Molly E. Steed, Samuel P. Simon, Sandra J. Estrada, Taylor Morrisette, Kimberly C. Claey, Joshua R. Rosenberg, Susan L. Davis, and Michael J. Rybak

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 was a multicenter, retrospective cohort study conducted at 6 medical centers in the United States between 2015 and 2019. Adult patients who received CZA (272 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 = 1.181–1.362, 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 carbapenemase threats 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 blaKPC 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 Enterobacteriaceae (CRE) and MDR Pseudomonas aeruginosa [8, 9]. Real-world experience...
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 Enterobacteriaceae 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
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 1. Demographic and Clinical Characteristics**

| Characteristics                          | Total Cohort<sup>a</sup> N = 203 | CRE Infection<sup>a</sup> N = 117 | Pseudomonas spp Infection<sup>a</sup> 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 (BMI ≥30 kg/m²)                      | 27 (22–35)                       | 27 (22–34)                       | 25 (21–35)                       |
| Obese                                    | 77 (37.5)                        | 40 (34.2)                        | 23 (36.5)                        |
| Estimated CrCl (mL/min)<sup>b</sup>      | 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 (31.3)                        |
| Transferred from outside                 | 28 (13.8)                        | 14 (12.0)                        | 11 (17.4)                        |
| Hospital                                 | 9 (4.4)                          | 6 (3.0)                          | 4 (2.0)                          |
| 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)                        |
| Immuno compromised                       | 22 (10.8)                        | 16 (13.7)                        | 4 (6.3)                          |
| MDRO infection or colonization within 1 year | 97 (47.9)                       | 56 (47.9)                        | 34 (54.0)                        |
| Recent antibiotic exposure               | 157 (77.3)                       | 96 (82.1)                        | 51 (81.0)                        |
| Recent hospitalization                    | 151 (74.4)                       | 94 (80.3)                        | 46 (73.0)                        |
| Recent surgery (within 30 days)          | 38 (18.4)                        | 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.

<sup>a</sup> All values represent number (%) or median (interquartile range).

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

**Table 3. Treatment Information**

| Parameter                              | Total Cohorta |
|----------------------------------------|---------------|
|                                       | N = 203       |
| Infectious disease consult             | 199 (98.0)    |
| Time to infectious disease consult (hours) | 28 (4–63)b |
| Surgical consult                       | 58 (28.6)     |
| Source control pursued                 | 54 (26.6)     |
| Active antibiotic(s) before CZA        | 54 (26.6)     |
| Time to active antibiotic(s) (hours)   | 55 (7–102)    |
| Active antibiotic(s) within 48 hours   | 91 (44.8)     |
| Time to CZA (hours)                    | 85 (42–146)   |
| CZA within 48 hours                    | 59 (29.1)     |
| Renal CZA dose adjustment              | 92 (45.3)     |
| CZA combination therapy                | 68 (33.5)     |
| Aminoglycoside                         | 21 (10.3)     |
| Colistin/polymyxin B                   | 17 (8.4)      |
| Fluoroquinolone                        | 10 (4.9)      |
| Tigecycline                            | 16 (7.9)      |
| Minocycline                            | 2 (1.0)       |
| Aztreonam                              | 3 (1.5)       |
| Inhaled antibiotic therapy in patients with a respiratory tract infectiond | 19/76 (25.0) |
| CZA duration (days)                    | 9 (6–16)      |

| Parameter                              | CRE Infectiona |
|----------------------------------------|---------------|
|                                       | N = 117       |
| Infectious disease consult             | 117 (100)     |
| Time to infectious disease consult (hours) | 29 (9–65) |
| Surgical consult                       | 32 (27.4)     |
| Source control pursued                 | 29 (24.8)     |
| Active antibiotic(s) before CZA        | 27 (23.1)     |
| Time to active antibiotic(s) (hours)   | 69 (26–103)   |
| Active antibiotic(s) within 48 hours   | 39 (33.3)     |
| Time to CZA (hours)                    | 93 (52–145)   |
| CZA within 48 hours                    | 25 (21.4)     |
| Renal CZA dose adjustment              | 54 (46.2)     |
| CZA combination therapy                | 45 (38.5)     |
| Aminoglycoside                         | 13 (11.1)     |
| Colistin/polymyxin B                   | 10 (8.5)      |
| Fluoroquinolone                        | 8 (6.8)       |
| Tigecycline                            | 10 (8.5)      |
| Minocycline                            | 1 (0.9)       |
| Aztreonam                              | 1 (0.9)       |
| Inhaled antibiotic therapy in patients with a respiratory tract infectiond | 7/39 (79) |
| CZA duration (days)                    | 13 (6–16)     |

| Parameter                              | Pseudomonas spp Infection |
|----------------------------------------|---------------------------|
|                                       | N = 63                    |
| Infectious disease consult             | 59 (93.7)                 |
| Time to infectious disease consult (hours) | 24 (4–86)c              |
| Surgical consult                       | 17 (27.0)                 |
| Source control pursued                 | 19 (30.2)                 |
| Active antibiotic(s) before CZA        | 12 (19.0)                 |
| Time to active antibiotic(s) (hours)   | 72 (12–123)               |
| Active antibiotic(s) within 48 hours   | 24 (38.1)                 |
| Time to CZA (hours)                    | 94 (34–170)               |
| CZA within 48 hours                    | 17 (27.0)                 |
| Renal CZA dose adjustment              | 28 (44.4)                 |
| CZA combination therapy                | 20 (31.7)                 |
| Aminoglycoside                         | 8 (12.7)                  |
| Colistin/polymyxin B                   | 5 (79)                    |
| Fluoroquinolone                        | 2 (3.2)                   |
| Tigecycline                            | 3 (4.8)                   |
| Minocycline                            | 0                         |
| Aztreonam                              | 2 (3.2)                   |
| Inhaled antibiotic therapy in patients with a respiratory tract infectiond | 14/38 (36.8) |
| CZA duration (days)                    | 9 (6–14)                  |

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

aAll values represent number (%) or median (interquartile range).

bN = 199.

cN = 59.

dInhaled tobramycin or colistin.

**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
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.

### 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 bacteria 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 copiededit and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This study was funded by an investigator initiated grant from Allergan USA Inc.

Potential conflicts of interest. M. J. R. reports the following: research support and consultant or speaker for Allergan, Melinta, Merck, Motif, Nabriva, Paratek, Tetraphase, and Shionogi. K. C. C. is an ad hoc board member for Melinta Therapeutics. J. R. R. reports consulting agreements or in other speakers bureaus with Allergan, Merck, Shinogi, Tetraphase, Melinta, and Paratek. S. L. D. is a consultant for Allergan, Spero, and Tetraphase. S. J. E. is an employee of T2 Biosoystms. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Munita JM, Aitken SL, Miller WR, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant Pseudomonas aeruginosa. Clin Infect Dis 2017; 65:158–61.
2. Doi Y, Bonomo RA, Hooper DC, et al.; Gram-Negative Leadership Group (AGL). Gram-negative bacterial infections: research priorities, accomplishments, and future directions of the antibiotic resistance leadership group. Clin Infect Dis 2017; 64(Suppl. 1):S30–5.
3. Munnor-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis 2013; 13:785–96.
4. Benattar YD, Omar M, Zusan O, et al. The effectiveness and safety of high-dose colistin: prospective cohort study. Clin Infect Dis 2016; 63:1605–12.
5. Mingorget-Delecreq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother 1999; 43:1003–12.
6. Panidis D, Markantonis SL, Boutzouka E, et al. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest 2005; 128:545–52.
7. Zasowski EJ, Rybak JM, Rybak MI. The β-lactams strike back: ceftazidime/avibactam. Pharmacotherapy 2015; 35:755–70.
8. Karlowsky JA, Biedenbach DJ, Kloviziczk KM, et al. Activity of ceftazidime-avibactam against extended-spectrum- and AmpC β-lactamase-producing Enterobacteriaceae collected in the INFORM Global Surveillance Study from 2012 to 2014. Antimicrob Agents Chemother 2016; 60:2849–57.
9. Nichols WW, de Jonge BL, Kloviziczk KM, et al. In vitro susceptibility of global surveillance isolates of Pseudomonas aeruginosa to ceftazidime-avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 2016; 60:4743–9.
10. Castrén JJ, Lacort-Peralta I, Martín-Dávila P, et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematoletic patients. Int J Infect Dis 2017; 59:118–23.
11. King, M, Heil E, Kuriaisco S, et al. Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother 2017; 61:e00449–17.
12. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother 2016; 60:e00883–17.
13. Shields RK, Potoski BA, Haidar G, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis 2016; 63:1615–8.
14. Temkin E, Torres-Cisneros J, Beovic B, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother 2017; 61:e01964–16.
15. van Duin D, Lok JJ, Earley M, et al.; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. Clin Infect Dis 2018; 66:163–71.
16. Shields RK, Nguyen MH, Chen L, et al. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother 2018; 62:e02497–17.
17. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–81.
18. Charlson ME, Pompei P, Alex KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373–83.
19. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–10.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 19:31–41.
21. Evans SR, Doernberg S, Gouskova NA, et al. Using endpoints to analyze patients rather than patients to analyze endpoints: a pre-trial substudy to develop a global outcome for clinical trials. Society for Clinical Trials 37th Annual Meeting. (Montreal, Quebec, Canada).

22. Abdul-Mutakabbir JC, Kebriaei R, Jorgensen SCJ, Rybak MJ. Teaching an old class new tricks: a novel semi-synthetic aminoglycoside, plazomicin. Infect Dis Ther 2019; 8:155–70.

23. Heaney M, Mahoney MV, Gallagher JC. Eravacycline: the tetracyclines strike back. Ann Pharmacother 2019; 53:1124–35.

24. Jorgensen SC, Rybak MJ. Meropenem and vaborbactam: stepping up the battle against carbapenem-resistant Enterobacteriaceae. Pharmacotherapy 2018; 38:444–61.

25. Buehrle DJ, Shields RK, Chen L, et al. Evaluation of the in vitro activity of ceftazidime-avibactam and ceftolozane-tazobactam against meropenem-resistant Pseudomonas aeruginosa isolates. Antimicrob Agents Chemother 2016; 60:3227–31.

26. Humphries RM, Hindler JA, Wong-Beringer A, et al. Activity of ceftolozane-tazobactam and ceftazidime-avibactam against beta-lactam-resistant Pseudomonas aeruginosa isolates. Antimicrob Agents Chemother 2017; 61:e01858–17.

27. Alexander EL, Loutit J, Tumbarello M, et al. Carbapenem-resistant Enterobacteriaceae infections: results from a retrospective series and implications for the design of prospective clinical trials. Open Forum Infect Dis 2017; 4:ofi063.

28. Bonine NG, Berger A, Altincatal A, et al. Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious Gram-negative bacterial infections. Am J Med Sci 2019; 357:103–10.

29. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017; 376:2235–44.

30. Lodise TP Jr, Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with Pseudomonas aeruginosa bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother 2007; 51:3510–5.

31. Raman G, Avendano E, Berger S, Menon V. Appropriate initial antibiotic therapy in hospitalized patients with Gram-negative infections: systematic review and meta-analysis. BMC Infect Dis 2015; 15:395.

32. Wunderink RG, Giamarellos-Bourboulis EI, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II Randomized Clinical Trial. Infect Dis Ther 2018; 7:439–55.

33. McKinnell JA, Dwyer JP, Talbot GH, et al.; CARE Study Group. Plazomicin for infections caused by carbapenem-resistant Enterobacteriaceae. N Engl J Med 2019; 380:791–3.