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CLINICAL THERAPEUTICS

Multicenter Study of Outcomes with Ceftazidime-Avibactam in Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

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ABSTRACT Ceftazidime-avibactam is a novel cephalosporin–beta-lactamase inhibitor combination that is active against many carbapenem-resistant *Enterobacteriaceae* (CRE). We describe a retrospective chart review for 60 patients who received ceftazidime-avibactam for a CRE infection. In-hospital mortality was 32%, 53% of patients had microbiological cure, and 65% had clinical success. In this severely ill population with CRE infections, ceftazidime-avibactam was an appropriate option.

KEYWORDS antibiotic resistance, beta-lactamases, carbapenemase

The pharmacotherapy of carbapenem-resistant *Enterobacteriaceae* (CRE) infections is challenging and has typically included multiple antibiotics (1). Mortality rates as high as 60% have been reported (2, 3). Ceftazidime-avibactam (Avycaz, Allergan) is a cephalosporin–β-lactamase inhibitor combination that has demonstrated efficacy for treatment of infections caused by *Enterobacteriaceae* and *Pseudomonas aeruginosa* that are resistant to other agents, including ceftazidime (4, 5). Avibactam is structurally distinct from other available β-lactamase inhibitors, is reversible (i.e., the avibactam ring is recyclized instead of being hydrolyzed, so it regains its activity and can bind to more β-lactamases), and is able to inhibit many class A, C, and D β-lactamases (6).

We conducted a multicenter, retrospective review of patients who received ceftazidime-avibactam for a CRE infection from any source between March 2015 and April 2016 at 9 health systems in the United States (in Pennsylvania, New Jersey, Delaware, Maryland, Indiana, and Arizona). Patients ≥18 years old who received at least 24 h of ceftazidime-avibactam therapy were included. Prisoners, pregnant women, and children were excluded from the study. Patients were identified through pharmacy databases. The study was approved by the institutional review boards of each participating site.

Data on baseline and demographic characteristics were assessed from the time of the index infection. We used U.S. Centers for Disease Control and Prevention criteria to define infections (7). The degree of comorbid illness was assessed using the Charlson comorbidity index (CCI), and Pitt bacteremia scores were calculated to assess the severity of illness (8, 9). Dosing of ceftazidime-avibactam was determined by providers at each site based on manufacturer-recommended dosing (10). Concomitant therapy and prior therapy for CRE infections were recorded. Carbapenem resistance was

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TABLE 1 Patient characteristics[a]

Patient characteristic	Values for indicated patient population		
	Total ($N = 60$)	Monotherapy ($n = 33$)	Combination therapy ($n = 27$)
Male gender, *n* (%)	36 (60)	17 (51)	19 (70)
Age, yrs (median, IQR)	60 (51–69)	59 (51–69)	59 (50–69)
Charlson comorbidity index (median, IQR)	4.5 (3–7)	4.5 (2.8–7)	4.5 (2–7)
Pitt bacteremia score (median, IQR)	2 (0–5)	2 (0–5)	2 (0–5)
ICU, *n* (%)	35 (59)	19 (58)	16 (59)
Moderate to severe renal disease, *n* (%)[b]	19 (32)	8 (24)	11 (41)
Moderate to severe liver disease, *n* (%)[c]	8 (13)	2 (6)	6 (22)
Infecting organism (s), *n* (%)			
Klebsiella pneumoniae	50 (83)	29 (88)	21 (78)
Escherichia coli	5 (8)	2 (6)	3 (11)
Enterobacter spp.	4 (7)	1 (3)	3 (11)
Providencia stuartii	1 (2)	1 (3)	0
Serratia marcescens	1 (2)	1 (3)	0
Klebsiella oxytoca	1 (2)	0	1 (4)
Primary infection, *n* (%)			
Bacteremia	23 (38)	13 (39)	10 (37)
Urinary tract	17 (28)	14 (42)	3 (11)
Pneumonia	16 (27)	8 (24)	8 (30)
Wound	8 (13)	3 (9)	5 (19)
Intra-abdominal	4 (7)	0	4 (15)
Bone/joint	2 (3)	1 (3)	1 (4)
Hospital day CRE infection was diagnosed (median, IQR)	1 (1–15)	1 (1–14.8)	1 (1–11)
Hospital day ceftazidime-avibactam was started (median, IQR)	8 (5–22)	7.5 (4.8–21.5)	7 (4–7)

[a]Medians (IQRs) are shown for continuous variables.
[b]Serum creatinine level of >3 mg/dl, dialysis, renal transplant, uremia.
[c]Cirrhosis with or without portal hypertension, ascites, chronic jaundice, history of variceal bleeding, liver transplant.

defined as resistance to any carbapenem using current Clinical and Laboratory Standards Institute breakpoints (11). Due to the lack of an FDA-approved susceptibility test at the time of the study, testing for ceftazidime-avibactam susceptibility was not required for enrollment. Some sites used noncommercial Etests to determine susceptibility, and results were collected where available.

The primary outcome was in-hospital mortality. Secondary outcomes were microbiologic cure, defined as a negative culture at the end of therapy, and clinical success, defined as improved signs and symptoms from baseline to the end of therapy with defervescence. Microbiologic cure was evaluated only in patients with repeat cultures available. Descriptive statistics were used for patient characteristics. Comparisons between groups were made using Fisher's exact text or chi-squared tests as appropriate.

In total, 60 patients were included (Table 1). Despite a low median Pitt bacteremia score of 2 points (interquartile range [IQR], 0 to 5 points), there was a high degree of acute illness, with 59% of patients in the intensive care unit (ICU) at the time of receiving ceftazidime-avibactam, 38% requiring mechanical ventilation, and 21% requiring vasopressors. Additionally, 40% of patients had moderate to severe renal disease. 25% of subjects had received a solid-organ transplant. The majority of patients had bacteremia, 17% (8/60) of patients had infections at more than one site, and 67% (32/60) had infections that were concomitant with other organisms reported. The majority of infections were caused by *Klebsiella pneumoniae*. Most isolates were tested

TABLE 2 Patient outcomes

Parameter	Patients, *n*/*N* (%)		
	In-hospital mortality[a]	Microbiologic cure[b]	Clinical success[c]
Overall population	19/60 (32)	32/60 (53)	39/60 (65)
Treatment			
Concomitant therapy	9/27 (33)	17/27 (63)	17/27 (63)
Monotherapy	10/33 (30)	15/33 (45)	22/33 (67)
Location			
ICU	16/35 (46)	16/35 (46)	18/35 (51)
Non-ICU	3/25 (12)	16/25 (64)	21/25 (84)
Renal dose adjustment			
Yes	14/33 (42)	19/33 (58)	18/33 (55)
No	5/27 (19)	13/27 (48)	21/27 (78)
Infection type			
Bacteremia	9/23 (39)	19/23 (82)	14/23 (61)
Urinary tract	2/17 (12)	7/17 (41)	15/17 (88)
Pneumonia	9/16 (56)	7/16 (44)	9/16 (56)
Wound	2/8 (25)	3/8 (38)	5/8 (63)
Intra-abdominal	1/4 (25)	3/4 (75)	3/4 (75)
Bone/joint	1/2 (50)	1/2 (50)	0/2 (0)

[a]For concomitant therapy versus monotherapy, ICU versus non-ICU, and renal dose adjustment versus no renal dose adjustment, $P = 1.0$, 0.01, and 0.057, respectively.
[b]For concomitant therapy versus monotherapy, ICU versus non-ICU, and renal dose adjustment versus no renal dose adjustment, $P = 0.2$, 0.013, and 0.1, respectively.
[c]For concomitant therapy versus monotherapy, ICU versus non-ICU, and renal dose adjustment versus no renal dose adjustment, $P = 0.79$, 0.196, and 0.604, respectively.

for susceptibility to ceftazidime-avibactam (60%, 36/60), and 97% (35/36) of those were susceptible.

Outcomes are listed in Table 2. The overall in-hospital mortality rate in this study was 32% (19/60). The in-hospital mortality rate was highest for patients with pneumonia. Patients who were in the ICU had significantly higher rates of in-hospital mortality than non-ICU patients (46% [16/35] versus 12% [3/25], $P = 0.0102$). There was no significant difference in the rates of in-hospital mortality for patients receiving concomitant therapy versus patients receiving monotherapy with ceftazidime-avibactam (33% [9/27] versus 30% [10/33], $P = 1.0$) or for patients with bacteremia versus patients without bacteremia (39% [9/23] versus 27% [10/37], $P = 0.397$). Patients who required vasopressors and patients who required mechanical ventilation had higher mortality rates than those who did not (79% [11/14] versus 17% [8/46] [$P = 0.001$] and 71% [15/21] versus 10% [4/39] [$P = 0.001$], respectively).

Of the patients with isolates that were tested and susceptible to ceftazidime-avibactam, 51% (18/35) had microbiologic cure, 63% (22/35) had clinical success, and 34% (12/35) died in the hospital. Of the isolates that did not have susceptibility data available (40%, 24/60), 54% (13/24) had microbiologic cure, 67% (16/24) had clinical success, and 25% (6/24) died in the hospital. The patient whose isolate was reported to be resistant had not received ceftazidime-avibactam previously. That patient received concomitant antibiotics and had microbiologic and clinical success but ultimately died in the hospital.

Concomitant antibiotics included ertapenem followed by meropenem with polymyxin B. Many patients (27/60, 45%) received an additional Gram-negative active agent while on ceftazidime-avibactam therapy, most commonly, aminoglycosides, polymyxin, and tigecycline (40%, 26%, and 22%, respectively). There were no statistically significant differences between monotherapy with ceftazidime-avibactam and combination therapy for any of the outcomes.

Renal adjustment for ceftazidime-avibactam occurred in 33 (55%) patients, and 42% (14/33) of those patients received renal replacement therapy. Of the patients who had

the dose adjusted, 58% (19/33) had clinical success, 55% (18/33) had microbiologic cure, and 42% (14/33) died in the hospital. Patients who required a renal adjustment of ceftazidime-avibactam trended toward high in-hospital mortality (42% versus 19% without renal adjustment, $P = 0.0567$). No drug-related adverse events were noted in the study.

In this multicenter evaluation of the use of ceftazidime-avibactam for treatment of CRE infections in acutely ill patients, overall in-hospital mortality was 32%. Outcomes of other studies of CRE infections have been highly variable. Several have found lower mortality rates with combination therapy than with monotherapy, though those studies were conducted prior to the availability of ceftazidime-avibactam. Data with ceftazidime-avibactam are especially lacking. A case series that included 37 patients with a variety of infections due to CRE who were treated with ceftazidime-avibactam demonstrated a 30-day mortality rate of 24% with rates of 59% for clinical success and 27% for microbiologic failure. In 30% of the cases, patients were receiving ceftazidime-avibactam in combination with another agent (12). Notably, 8% of cases developed ceftazidime-avibactam resistance during therapy.

Limitations to this study included its retrospective nature and confounding factors that we were unable to control for. Due to the lack of a commercial test, not all isolates were tested for susceptibility to ceftazidime-avibactam. We did not attempt to determine infection-related mortality, and it is possible that death could be attributed to other disease processes in this patient population. Other confounders include administration of additional antibiotics, which differed between patients, dosing regimens, and comorbidities.

With an overall mortality of 32% in this population, these data suggest that ceftazidime-avibactam is an option for patients with CRE infections, including those who are acutely ill or posttransplant patients. More data on this therapy are urgently needed.

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