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Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

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ABSTRACT Ceftazidime-avibactam (CAZ-AVI) is a recently approved β-lactam–β-lactamase inhibitor combination with the potential to treat serious infections caused by carbapenem-resistant organisms. Few patients with such infections were included in the CAZ-AVI clinical trials, and clinical experience is lacking. We present a case series of patients with infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) or *Pseudomonas aeruginosa* (CRPa) who were treated with CAZ-AVI salvage therapy on a compassionate-use basis. Physicians who had prescribed CAZ-AVI completed a case report form. We used descriptive statistics to summarize patient characteristics and treatment outcomes. We used the Wilcoxon rank sum test and Fisher's exact test to compare patients by treatment outcome. The sample included 36 patients infected with CRE and two with CRPa. The most common infections were intra-abdominal. Physicians categorized 60.5% of patients as having life-threatening infections. All but two patients received other antibiotics before CAZ-AVI, for a median of 13 days. The median duration of CAZ-AVI treatment was 16 days. Twenty-five patients (65.8%) concurrently received other antibiotics to which their pathogen was nonresistant *in vitro*. Twenty-eight patients (73.7%, 95% confidence interval [CI], 56.9 to 86.6%) experienced clinical and/or microbiological cure. Five patients (20.8%) with documented microbiological cure died, whereas 10 patients (71.4%) with no documented microbiological cure died ($P = 0.01$). In three-quarters of cases, CAZ-AVI (alone or combined with other antibiotics) cured infections caused by carbapenem-resistant organisms, 95% of which had failed previous therapy. Microbiological cure was associated with improved survival. CAZ-AVI shows promising clinical results for infections for which treatment options are limited.

KEYWORDS carbapenem resistance, case series, ceftazidime-avibactam

Ceftazidime-avibactam (CAZ-AVI), a β-lactam–β-lactamase inhibitor combination, was approved by the U.S. Food and Drug Administration (FDA) in February 2015 (1). It is indicated for the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) (in combination with metronidazole) in adults with limited or no other therapeutic options. A promising characteristic of CAZ-AVI is its potential to treat infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenem-resistant *Pseudomonas aeruginosa* (CRPa). Avibactam recovers the activity of ceftazidime by inhibiting Ambler class A, class C, and some class D beta-lactamases, including the KPC and OXA-48 carbapenemases; CAZ-AVI is not active against metallo-β-lactamases (MBLs), such as NDM, IMP, and VIM (2, 3). In an *in vitro* study that included 276 meropenem-nonsusceptible *Klebsiella* species isolates, 98.9% were susceptible to CAZ-AVI (4). In a second study, 67.4% of 396 meropenem-nonsusceptible *P. aeruginosa* isolates were susceptible to CAZ-AVI (5). A third study reported 100% susceptibility to CAZ-AVI among 133 non-carbapenemase-producing *Enterobacteriaceae* isolates in which the mechanism of carbapenem resistance was extended-spectrum beta-lactamase (ESBL) and/or AmpC production together with porin deficiency (6).

Clinical data on the efficacy of CAZ-AVI against carbapenem-resistant organisms in humans are scarce. In phase II trials (7, 8) and recently completed phase III trials (9, 10) of CAZ-AVI to treat cUTI and cIAI, the comparator drug was a carbapenem; therefore, patients with infections caused by carbapenem-resistant organisms were excluded. In a pathogen-directed open-label phase III trial (the REPRISE trial) comparing CAZ-AVI to the best available therapy for treatment of cUTI and cIAI caused by ceftazidime-resistant Gram-negative organisms (11), few patients with carbapenem-resistant infections met the trial's inclusion criteria. Among the 292 *Enterobacteriaceae* isolates recovered from 288 patients in the REPRISE trial, only nine harbored non-MBL carbapenemases: six KPC-producing *Klebsiella pneumoniae* isolates and three OXA-48-producing *K. pneumoniae* isolates (12). In an effort to amass data about the effectiveness of CAZ-AVI against carbapenem-resistant organisms, we present a case series of patients with infections caused by CRE or CRPa who were treated with CAZ-AVI salvage therapy on a compassionate-use basis. Our primary aim was to evaluate three outcomes: clinical cure at the end of treatment, microbiological cure at the end of treatment, and all-cause in-hospital mortality. Our secondary aim was to identify predictors of cure and of survival.

RESULTS

Sample. Of the 25 physicians contacted, 17 responded and 15 contributed data for at least one patient with an infection caused by CRE or CRPa that was sensitive to CAZ-AVI, for a total of 38 patients. Included patients had been treated in Europe and Australia in the years 2013 to 2016. Fifteen patients came from a single hospital in Spain that had an outbreak of KPC-producing *K. pneumoniae*; the characteristics of this strain have been previously described (13). Thirty-six patients (94.7%) received CAZ-AVI as salvage therapy after treatment with other antibiotics had failed; in the other two patients, CAZ-AVI was the first antibiotic chosen because no other appropriate treatment was available. Three patients were treated at institutions where CAZ-AVI clinical trials were conducted, but they were treated on a compassionate-use basis because they met the trial's exclusion criteria.

Organisms. Thirty-four patients were infected with *Klebsiella pneumoniae*, one with *Klebsiella oxytoca*, one with *Escherichia coli*, and two with *P. aeruginosa*. Antimicrobial susceptibilities are presented in Table 1. All isolates but one were classified by the local laboratories as resistant to imipenem. In the patient with an imipenem-susceptible carbapenemase-producing organism (OXA-48-producing *E. coli*), treatment with imipenem had resulted in microbiological failure. All isolates were resistant to ceftazidime alone, with MICs ranging from 8 to $\geq$64 μg/ml. Only 14 of 34 isolates tested (41.2%) were susceptible to colistin. Table 2 summarizes the MICs of carbapenems in the 33 isolates for which carbapenem susceptibility was reported quantitatively. One patient

TABLE 1 Antimicrobial susceptibility of isolates from patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Antibiotic	No. of isolates tested[a]	% Susceptible
Imipenem	36	2.8[b]
Meropenem	33	0.0
Ceftazidime	38	0.0
Colistin	34	41.2
Gentamicin	37	51.4
Amikacin	38	31.6
Tigecycline	32	62.5
Fosfomycin	29	55.2

[a]Sample included 34 *K. pneumoniae*, 1 *K. oxytoca*, 1 *E. coli*, and 2 *P. aeruginosa* isolates.
[b]Patient with OXA-48-producing *E. coli* who had failed imipenem treatment (MIC not reported).

with KPC-producing *K. pneumoniae* with an imipenem MIC of <2 and a meropenem MIC of 2 had failed treatment with a multidrug regimen that included meropenem; carbapenem treatment was not tried in the other two patients with imipenem MICs of 2. Exact results of disk diffusion testing for CAZ-AVI susceptibility were available for all but five isolates, with zone diameters ranging from 21 to 32 mm for *Enterobacteriaceae* and from 20 to 23 mm for *P. aeruginosa*. (FDA breakpoints are 21 mm and 18 mm, respectively [14].)

Patient characteristics and prior treatment. Patients' demographic and clinical characteristics are shown in Table 3. All but two patients had received antibiotics before CAZ-AVI (median, 3 drugs) and had failed treatment. Among those who received prior antibiotics, the median duration of treatment before CAZ-AVI was started was 13 days. The most commonly prescribed agents were tigecycline ($n = 26$), meropenem ($n = 18$), gentamicin ($n = 16$), fosfomycin ($n = 14$), and colistin ($n = 11$).

CAZ-AVI treatment. Characteristics of CAZ-AVI treatment are presented in Table 3. The minimum length of treatment was 3 days. Twenty-four patients (63.2%) were given the standard dose of CAZ-AVI throughout their treatment (2 g ceftazidime–0.5 g avibactam every 8 h). Fourteen patients with renal impairment received adjusted doses. Twenty-five patients (65.8%) were treated concurrently with at least one other antibacterial to which their organism was nonresistant *in vitro*; the most common agents were tigecycline ($n = 11$), amikacin ($n = 9$), and fosfomycin ($n = 4$).

Outcomes. Treatment outcomes are presented in Fig. 1. Twenty-eight patients (73.7%; 95% confidence interval [CI], 56.9 to 86.6%) experienced clinical and/or documented microbiological cure at the end of treatment. All-cause in-hospital mortality was 39.5% (95% CI, 24.0 to 56.6%). Ten patients died during their hospitalization because of treatment failure, such that infection-related mortality was 26.3% (95% CI, 13.4 to 43.1%). Among these 10 patients, the median time from the start of CAZ-AVI treatment to death was 19 days (interquartile range [IQR], 7 to 31 days). Six of them were still receiving CAZ-AVI within 1 day of their death. Nine of the 13 patients (69.2%) who received CAZ-AVI as monotherapy achieved clinical and/or microbiological cure,

TABLE 2 MICs (in μg/ml) of carbapenems in 33 isolates for which susceptibility was reported quantitatively

Organism and antibiotic[a]	No. of isolates with MIC of:			
	<2	2	4 to 8	>8
Enterobacteriaceae				
Imipenem ($n = 29$)	1	2	2	24
Meropenem ($n = 27$)	0	1	2	24
P. aeruginosa				
Imipenem ($n = 2$)	0	0	0	2
Meropenem ($n = 1$)	0	0	0	1

[a]n, number of isolates.

TABLE 3 Characteristics of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Characteristic	Value ($n = 38$)[a]
Demographic characteristics	
Age in yr, median (IQR[b])	61 (47–67)
Male sex	25 (65.8)
Location before hospitalization	
Home	33 (86.8)
Transferred from another hospital	5 (13.2)
Comorbidities	
Transplant recipient	5 (13.2)
Diabetes mellitus	8 (21.1)
Immunosuppression[c]	10 (26.3)
Renal disease	7 (18.4)
Cardiovascular disease	11 (28.9)
McCabe score of >1	19 (50.0)
Infection characteristics	
Organism and carbapenemase	
Klebsiella pneumoniae	
KPC	22
OXA-48	12
Klebsiella oxytoca (KPC)	1
Escherichia coli (OXA-48)	1
Pseudomonas aeruginosa	2
Hospital-acquired infection	34 (89.5)
Bacteremia	26 (68.4)
Polymicrobial infection	11 (29.0)
Life-threatening infection (high risk of death within 30 days)	23 (60.5)
Antibiotics before CAZ-AVI	
Received antibiotics before CAZ-AVI for this infection	36 (94.7)
Days of antibiotic treatment before CAZ-AVI, median (IQR)	13 (7–31)
No. of antibiotics before CAZ-AVI, median (IQR)	3 (3–4)
Other treatments before CAZ-AVI	
Surgery to remove the source of infection	16 (42.1)
Removal of foreign body involved in infection	9 (23.7)
Clinical status at start of CAZ-AVI treatment	
Mechanical ventilation	14 (36.8)
Vasopressor support	17 (44.7)
Unconscious	12 (31.6)
CAZ-AVI treatment	
Days of treatment, median (IQR)	16 (14–21)
Extended infusion	36 (94.7)
Concurrent antibiotic treatment[d]	25 (65.8)
Received standard CAZ-AVI dose	24 (63.2)

[a]Values are number (%) of patients unless indicated otherwise.
[b]IQR, interquartile range.
[c]Immunosuppression was defined as posttransplant, chemotherapy in past 6 weeks, systemic steroids (>20 mg of prednisone) or other immunosuppressive agents in past 2 weeks, absolute neutrophil count of <500/μl, or HIV/AIDS.
[d]During CAZ-AVI treatment, patient received another antibiotic to which organism was nonresistant *in vitro*.

compared to 19 out of 25 patients (76.0%) given a concurrent antibiotic with *in vitro* activity against their pathogen ($P = 0.71$).

For three of the four patients with documented microbiological failure, the repeat positive isolates were tested for susceptibility to CAZ-AVI; none had developed CAZ-AVI resistance. Two patients with documented microbiological cure of infections caused by KPC-producing *K. pneumoniae* experienced a relapse, one at 16 days and the other at 30 days after the end of both CAZ-AVI treatment and discharge from the hospital. In the first case, the isolate remained susceptible to CAZ-AVI by disk diffusion testing and the patient experienced clinical and microbiological cure of the relapse infection following dual therapy with CAZ-AVI and gentamicin. In the second case, the relapse isolate was
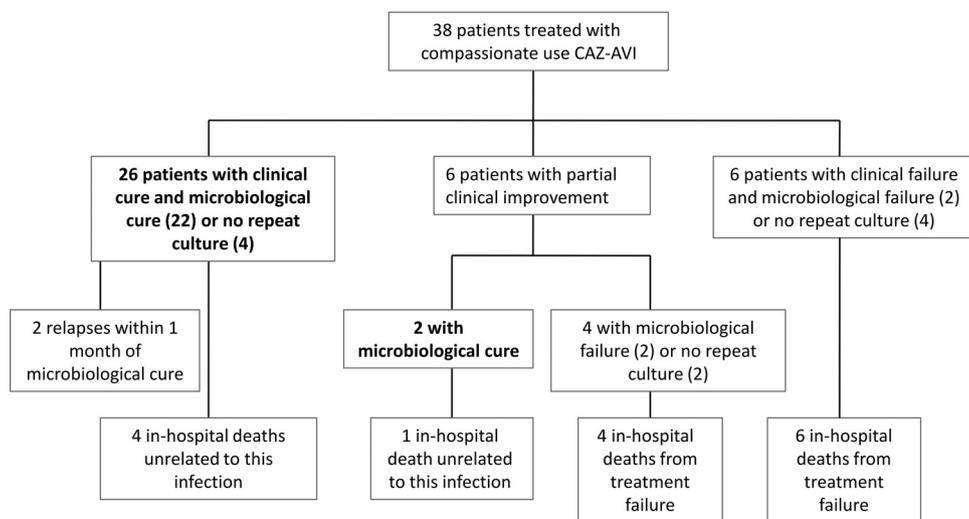
FIG 1 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI.

not tested for CAZ-AVI susceptibility; repeat CAZ-AVI treatment was not considered because of the patient's poor prognosis, and the patient died 73 days after infection onset of causes not directly related to the infection.

Table 4 presents treatment outcomes according to infection site. Among the 38 patients, there were 46 infections, not including secondary bacteremia. Eighteen of the 46 infections (39.1%) were either cIAI or cUTI, indications for which CAZ-AVI was approved; 13 patients had only cIAI or cUTI, with or without bacteremia. All-cause mortality was 14.3% in patients with primary or central-line associated bacteremia and 42.3% in patients with any bacteremia. Five out of 24 patients (20.8%) with documented microbiological cure died (of causes unrelated to the infection), whereas 10 of 14 patients (71.4%) with no documented microbiological cure died ($P = 0.01$).

Table 5 compares characteristics of patients by treatment outcome. Patients treated for a longer time with other antibiotics prior to CAZ-AVI administration were less likely to experience clinical cure ($P = 0.06$) and microbiological cure ($P = 0.01$). Among patients infected with *Enterobacteriaceae*, survival was higher in patients with KPC carbapenemase than in those with OXA-48: 17 of 23 patients (73.9%) with KPC-producing organisms survived until discharge, compared to 5 of 13 patients (38.5%)

TABLE 4 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by infection site

| | | No. (%) of cases with: | | | Patients with: | | | | Mortality among patients with microbiological cure | |
| | Total no. of cases | Bacteremia | Life-threatening infection | Documented microbiological cure | Clinical cure | | In-hospital death | | | |
Infection site[a]					No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
All patients	38	26 (68.4)	23 (60.5)	24 (63.2)	26 (68.4)	51.3–82.5	15 (39.5)	24.0–56.6	5 (20.8)	7.1–42.2
Intra-abdominal	15	11 (73.3)	8 (53.3)	6 (40.0)	10 (66.7)	38.4–88.2	6 (40.0)	16.3–67.7	1 (16.7)	0.4–64.1
Pneumonia[b]	7	6 (85.7)	5 (71.4)	3 (42.9)	3 (42.9)	9.9–81.6	5 (71.4)	29.0–96.3	1 (33.3)	0.8–90.6
Skin and soft tissue	4	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0.6–80.6	2 (50.0)	6.8–93.2	0 (0.0)	0.0–97.5
Urinary tract	3	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	9.4–99.2	2 (66.7)	9.4–99.2	1 (50)	1.3–98.7
Primary or catheter-associated bacteremia	7	7 (100)	7 (100)	7 (100.0)	7 (100)	59.0–100	1 (14.3)	0.4–57.9	1 (14.3)	0.4–57.9
Any bacteremia	26	26 (100)	20 (76.9)	18 (69.2)	18 (69.2)	48.2–85.7	11 (42.3)	23.4–63.1	4 (22.2)	6.4–47.6
Endocarditis	2	1 (50.0)	1 (50.0)	2 (100.0)	2 (100.0)	15.8–100	1 (50.0)	1.3–98.7	1 (50)	1.3–98.7
Osteomyelitis	3	0 (0.0)	0 (0.0)	2 (66.7)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	0 (0.0)	0.0–84.2
Surgical site infection	2	1 (50.0)	2 (100)	1 (50.0)	1 (50.0)	1.3–98.7	1 (50.0)	1.3–98.7	0 (0.0)	0.0–97.5
Other[c]	3	1 (33.3)	2 (66.7)	3 (100)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	1 (33.3)	0.8–90.6

[a]Patients may have multiple infection sites.
[b]Pneumonia cases included 6 cases of ventilator-associated pneumonia and 1 case of hospital-acquired pneumonia.
[c]Other infection types (1 patient each) were ventriculitis/subdural abscess, prosthetic joint infection, and mucositis.

TABLE 5 Comparison of characteristics of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by treatment outcome[a]

Characteristic	Clinical cure			Documented microbiological cure			Survival to hospital discharge		
	Yes (n = 26)	No (n = 12)	P value	Yes (n = 24)	No (n = 14)	P value	Yes (n = 23)	No (n = 15)	P value
Age in yr, median (IQR)	54 (46–65)	62 (58–69)	0.25	63 (48–70)	58 (46–63)	0.41	54 (47–66)	61 (44–68)	0.68
Male sex	17 (65.4)	8 (66.7)	1.00	14 (58.3)	11 (78.6)	0.29	16 (69.6)	9 (60.0)	0.73
McCabe score of >1	14 (53.9)	5 (41.7)	0.73	14 (58.3)	5 (35.7)	0.31	12 (52.2)	7 (46.7)	1.00
Days of antibiotic treatment before CAZ-AVI, median (IQR)	9 (5–17)	21 (10–50)	0.06	8 (3–16)	29 (11–45)	0.01	10 (5–20)	15 (6–31)	0.38
No. of antibiotics before CAZ-AVI, median (IQR)	3 (2–3)	3 (3–6)	0.19	3 (2–3)	3 (3–6)	0.15	3 (2–4)	3 (2–4)	0.75
Life-threatening infection	15 (57.7)	8 (66.7)	0.73	14 (58.3)	9 (64.3)	1.00	12 (52.2)	11 (73.3)	0.31
Carbapenemase[b]			0.48			0.07			0.07
KPC	17 (68.0)	6 (54.6)		18 (75.0)	5 (41.7)		17 (77.3)	6 (42.9)	
OXA-48	8 (32.0)	5 (45.5)		6 (25.0)	7 (58.3)		5 (22.7)	8 (57.1)	
Polymicrobial infection	6 (23.1)	5 (41.7)	0.27	4 (16.7)	7 (50.0)	0.06	6 (26.1)	5 (33.3)	0.72
cIAI or CUTI as sole infection site (with or without bacteremia)	10 (38.5)	3 (25.0)	0.49	7 (29.2)	6 (42.9)	0.49	9 (39.1)	4 (26.7)	0.50
Bacteremia	18 (69.2)	8 (66.7)	1.00	18 (75.0)	8 (57.1)	0.30	15 (65.2)	11 (73.3)	0.73
Surgery to remove the source of infection before or during CAZ-AVI	13 (50.0)	6 (50.0)	1.00	11 (45.8)	8 (57.1)	0.74	12 (52.2)	7 (46.7)	1.00
Mechanical ventilation at start of CAZ-AVI	8 (30.8)	6 (50.0)	0.30	8 (33.3)	6 (42.9)	0.73	5 (21.7)	9 (60.0)	0.04
On vasopressors at start of CAZ-AVI	11 (42.3)	6 (50.0)	0.73	10 (41.7)	7 (50.0)	0.74	8 (34.8)	9 (60.0)	0.19
Unconscious at start of CAZ-AVI	6 (23.1)	6 (50.0)	0.14	6 (25.0)	6 (42.9)	0.30	4 (17.4)	8 (53.3)	0.03
Concurrent active antibiotic treatment[c]	18 (69.2)	7 (58.3)	0.71	16 (66.7)	9 (64.3)	1.00	14 (60.9)	11 (73.3)	0.50
Received standard CAZ-AVI dose	17 (65.4)	7 (58.3)	0.73	15 (62.5)	9 (64.3)	1.00	15 (65.2)	9 (60.0)	1.00

[a]Values are number (%) of patients unless indicated otherwise.
[b]Among 36 patients with *Enterobacteriaceae* infections.
[c]During CAZ-AVI treatment, patient received another antibiotic to which the organism was nonresistant *in vitro*.

with OXA-48 producers ($P = 0.07$). These 2 groups of patients did not differ by the proportion with life-threatening infection ($P = 0.73$) or high McCabe score ($P = 0.50$). Neither of the two cases of relapse occurred in patients with OXA-48; one of the four cases of documented microbiological failure occurred in a patient with OXA-48.

Six patients (15.8%) developed adverse events that were attributed to CAZ-AVI. Blood alkaline phosphatase increased in two patients; nausea/vomiting, *Clostridium difficile*-associated diarrhea, convulsions, and disorientation progressing to stupor occurred in one patient each.

DISCUSSION

The proportion of Gram-negative infections caused by carbapenem-resistant strains is increasing. According to U.S. surveillance systems, carbapenem resistance in nosocomial infections caused by *Klebsiella* spp. rose from 1.6% in 2001 to 10.4% in 2011 (15). Regional differences in resistance are striking: in the 2014 report of the EARS-Net European surveillance system, the proportion of *Klebsiella* spp. isolated from blood or cerebrospinal fluid that was carbapenem resistant ranged from 0.0% in Norway, Sweden, Finland, and Estonia to 62.3% in Greece (16).

Treatment options for carbapenem-resistant organisms are limited; they include primarily colistin, aminoglycosides, tigecycline (for CRE only), fosfomycin, and double-carbapenem therapy. A recent systematic review by Falagas et al. of 20 nonrandomized studies compared mortality following different antibiotic regimens for CRE infections (17). Mortality was variously defined as 28- or 30-day mortality, in-hospital mortality, infection-related mortality, or unspecified. Mortality associated with the most common treatment regimens was up to 57% for colistin alone, up to 80% for tigecycline alone, up to 64% for colistin-tigecycline, up to 50% for gentamicin-tigecycline, and up to 67% for combined therapy with colistin and a carbapenem. While colistin has been considered the mainstay of therapy for carbapenem-resistant infections (18), colistin resistance among CRE isolates has increased (19). In our study, 59% of tested isolates were colistin resistant. Although we lack information about the laboratory methods used at each study site, and some methods for colistin susceptibility testing are flawed (with inaccurate results more likely to be false-susceptible than false-resistant) (20), these test results are relevant because they influenced the decision to use CAZ-AVI. The rationale behind double-carbapenem therapy for carbapenem-resistant organisms is that ertapenem, which is more easily hydrolyzed by carbapenemases, saturates these enzymes so that higher concentrations of the second carbapenem are available to treat the infection. Two recent articles summarized the outcomes of 29 patients who received double-carbapenem therapy for infections caused by carbapenem-resistant *K. pneumoniae*; clinical success was achieved in 16 cases (55%) (21, 22).

In our study, 73.7% of patients with infections caused by CRE or CRPa who received salvage therapy with CAZ-AVI experienced clinical and/or microbiological cure, and all-cause in-hospital mortality was 39.5%. Among those cured were patients with infections at difficult-to-treat sites, such as endocarditis and osteomyelitis, for which CAZ-AVI has not been studied. Mortality among patients with bacteremia was 42%. In previous studies, all-cause mortality from CRE bacteremia ranged from 19% (among patients given combination therapy that included a carbapenem) to 94% (23–28). In our study, microbiological cure was a predictor of survival: 79% of patients with negative cultures at the end of treatment survived until discharge. Among the 21% of patients who achieved microbiological cure but did not survive, mortality was attributed to other, non-infection-related causes. The delayed onset of CAZ-AVI treatment was associated with worse clinical and microbiological outcomes. Minimizing CAZ-AVI use in order to prevent the emergence of resistance is critical; however, waiting to exhaust all other (and potentially more toxic) treatment options before resorting to CAZ-AVI may reduce a patient's likelihood of being cured.

We found that having an infection caused by an OXA-48-producing pathogen, as opposed to a KPC-producing pathogen, was a predictor of mortality; the association did not reach statistical significance ($P = 0.07$), likely because of the small sample size.

OXA-48 does not hydrolyze ceftazidime efficiently and does not usually cause ceftazidime resistance. However, most OXA-48-producing isolates are resistant to ceftazidime due to coproduction of ESBL enzymes (29). Because ESBLs are well inhibited by avibactam and OXA-48 is partly inhibited by avibactam (30), the higher mortality observed in patients infected with OXA-48 producers is unexpected and intriguing. We do not have further details on the strains that can shed light on this finding, and further studies are warranted.

Shields et al. recently published a single-center case series of 37 patients with CRE infections treated with CAZ-AVI for at least 3 days (31). In contrast to our study, in which 95% of patients received CAZ-AVI as salvage therapy, CAZ-AVI was the first drug used to treat CRE infections in Shields' study. CAZ-AVI was administered as monotherapy in 70% of patients. Fifty-nine percent of patients experienced clinical success, defined as survival without recurrence at 30 days, clinical improvement, and negative cultures within 7 days of the start of treatment. Thirty-day all-cause mortality was 24%. Because of differences in how outcomes were defined, the results of Shields' study and ours are not directly comparable. Notably, three patients in Shields' study developed CAZ-AVI resistance following 10 to 19 days of treatment. A study of KPC-producing *Enterobacteriaceae* demonstrated the *in vitro* selection of CAZ-AVI-resistant mutants, primarily via alterations to the bla_{KPC} Ω loop (32). In our study, when CAZ-AVI susceptibility testing was repeated in 1 of 2 patients with relapse of infection and 3 of 4 patients with documented microbiological failure, no resistance was detected.

We found two additional clinical studies of CAZ-AVI treatment for carbapenem-resistant infections. The first was a case report of a 64-year-old woman who received compassionate-use CAZ-AVI for bacteremia caused by KPC-producing *K. pneumoniae* that did not respond to colistin and dual-carbapenem therapy. She was treated successfully with CAZ-AVI and ertapenem (22). The second was a case series of three patients (aged 72 to 89 years) with CRE bacteremia that had not responded to previous antibiotics. All three achieved clinical and microbiological cure following monotherapy with CAZ-AVI (33).

In our case series, there were six adverse events that were attributed to CAZ-AVI, three of which were severe. One patient who received CAZ-AVI in combination with two other antibiotics developed *C. difficile* infection during treatment. Like nearly all antibiotics, CAZ-AVI alters the normal flora of the colon, predisposing patients to *C. difficile* infection, as has been shown in healthy volunteers given CAZ-AVI (34). The risk of *C. difficile* infection following CAZ-AVI treatment appears to be low: only three of 1,204 (0.2%) patients treated with CAZ-AVI in three phase III clinical trials developed *C. difficile* infection (9–11). There were two neurological adverse events in our case series: convulsions and disorientation with progression to stupor. While it is not clear if these events were related to CAZ-AVI use or to other factors, the neurotoxic effects of cephalosporins are described mostly in the elderly and in patients with renal impairment or prior neurologic disease (35). Both patients in our study who developed neurotoxicity were aged 70 years or over, with normal renal function.

The main limitation of this study, as with any case series, is the lack of a concurrent control group; comparison is to the published experience summarized above. Comparison to a concurrent control group is problematic because of the potential for selection bias, confounding by indication, and confounding by time to treatment. A second limitation is that the experience with CAZ-AVI in the context of compassionate use may not be generalizable to the population of patients who may be candidates for CAZ-AVI treatment. Patients in compassionate-use programs often have severe acute illness or comorbidities that make them ineligible for clinical trials, increasing their risk of adverse outcomes (36). On the other hand, a sample of such patients may be biased toward clinical success: physicians may be more likely to request compassionate-use drugs for patients with a favorable underlying diagnosis, and immortal time bias may be present, as patients need to survive long enough for the drug to arrive. A third limitation is that two-thirds of patients received CAZ-AVI concurrently with other antibiotics with *in vitro* activity against their pathogen. In these patients, it is difficult to

ascertain whether the clinical success was associated with CAZ-AVI, the concurrent antibiotic, or the combination of both. However, when we compared patients who received CAZ-AVI monotherapy to those who were given additional antibiotics, the proportions cured were similar; thus, we believe CAZ-AVI had a major role in the cure. Finally, the small sample size may have precluded us from identifying significant predictors of clinical cure, microbiological cure, and mortality.

In summary, we have presented a case series of patients treated with CAZ-AVI for carbapenem-resistant infections on a compassionate-use basis. The majority of patients had life-threatening infections, some in difficult-to-cure sites, and 95% of them had failed previous antibiotic treatments. Three-quarters of the patients experienced clinical and/or microbiological cure following CAZ-AVI treatment. CAZ-AVI shows promising clinical results for infections for which treatment options are extremely limited.

MATERIALS AND METHODS

Data collection. When data for this paper were collected, CAZ-AVI was not approved for use in the European Union. Upon our request, AstraZeneca (a codeveloper of CAZ-AVI) contacted physicians to whom they had provided compassionate-access CAZ-AVI to treat carbapenem-resistant infections and invited them to participate in the study. AstraZeneca had no further involvement. Twenty-five physicians agreed to participate and were sent case report forms. To be eligible for inclusion, patients must have received at least one dose of CAZ-AVI in the context of compassionate use. Data collected included patient demographic characteristics, comorbidities and McCabe score (37), a description of the infection treated by CAZ-AVI (including an antibiogram), treatment with other antibiotics before or concurrently with CAZ-AVI, reasons for using CAZ-AVI, details of CAZ-AVI treatment, adverse events, the clinical and microbiological response, and relapse of infection.

Microbiological methods. Each hospital conducted antibiotic susceptibility testing according to its own protocols. We report susceptibility as it was interpreted by the local laboratories. All sites tested for susceptibility to CAZ-AVI by disk diffusion; results were interpreted according to the breakpoints set by the FDA (14). Plasma concentrations of ceftazidime and avibactam were not assessed during the course of treatment.

Statistical methods. The main outcome variables were clinical response at the end of treatment, microbiological response at the end of treatment, and all-cause in-hospital mortality. Clinical response was classified as cure, partial improvement, or treatment failure resulting in death and was analyzed as cure versus partial improvement or treatment failure. Microbiological response was classified as a negative culture, positive culture, or culture not repeated and was analyzed as documented cure (negative culture) versus positive culture or culture not repeated. Patient characteristics measured as continuous variables were summarized by median and interquartile range; categorical variables were summarized as proportions. The McCabe score was treated as a dichotomous variable, with a score of >1 indicating underlying disease with death expected within 5 years. Patient characteristics were compared by outcome using the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Analyses were performed using Stata version 13 (Stata Corporation, College Station, TX).

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