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MAJOR ARTICLE

Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae*

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Background. Ceftazidime-avibactam (CAZ-AVI) has been approved in Europe for the treatment of complicated intra-abdominal and urinary tract infections, as well as hospital-acquired pneumonia, and for gram-negative infections with limited treatment options. CAZ-AVI displays in vitro activity against *Klebsiella pneumoniae* carbapenemase (KPC) enzyme producers, but clinical trial data on its efficacy in this setting are lacking.

Methods. We retrospectively reviewed 138 cases of infections caused by KPC-producing *K. pneumoniae* (KPC-Kp) in adults who received CAZ-AVI in compassionate-use programs in Italy. Case features and outcomes were analyzed, and survival was then specifically explored in the large subcohort whose infections were bacteremic.

Results. The 138 patients started CAZ-AVI salvage therapy after a first-line treatment (median, 7 days) with other antimicrobials. CAZ-AVI was administered with at least 1 other active antibiotic in 109 (78.9%) cases. Thirty days after infection onset, 47 (34.1%) of the 138 patients had died. Thirty-day mortality among the 104 patients with bacteremic KPC-Kp infections was significantly lower than that of a matched cohort whose KPC-Kp bacteremia had been treated with drugs other than CAZ-AVI (36.5% vs 55.8%, $P = .005$). Multivariate analysis of the 208 cases of KPC-Kp bacteremia identified septic shock, neutropenia, Charlson comorbidity index ≥3, and recent mechanical ventilation as independent predictors of mortality, whereas receipt of CAZ-AVI was the sole independent predictor of survival.

Conclusions. CAZ-AVI appears to be a promising drug for treatment of severe KPC-Kp infections, especially those involving bacteremia.

Keywords. ceftazidime-avibactam; carbapenemases; KPC-producing *Klebsiella pneumoniae*.

The fixed-dose antimicrobial combination ceftazidime-avibactam (CAZ-AVI) consists of a third-generation cephalosporin and a novel synthetic β-lactamase inhibitor, approved in 2015 by the US Food and Drug Administration for the treatment of complicated intra-abdominal infections and complicated urinary infections [1]. In 2016, it received marketing authorization by the European Medicines Agency for the same indications, as well as for hospital-acquired pneumonia (including ventilator-associated infections), and more generally, for aerobic gram-negative infections in adults with limited treatment options [2].

Infections falling within the latter category are increasingly being attributed to carbapenem-resistant Enterobacteriaceae (CRE), which are being reported with growing frequency in Italy and many other countries of the world, and the vast majority are caused by isolates producing the *Klebsiella pneumoniae* carbapenemase

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(KPC) [3–15]. CAZ-AVI represents a potentially powerful tool for managing these infections in light of its demonstrated in vitro activity against CRE isolates that produce KPC enzymes (as well as extended-spectrum β-lactamases, AmpC β-lactamases, and oxacillinases) [16]. However, there is a paucity of clinical evidence on the efficacy of CAZ-AVI in humans with CRE infections. In the phase 2 and 3 clinical trials conducted to support its marketing authorization in Europe and the United States [17–21], CAZ-AVI was tested against carbapenems, which, prior to 2015, were considered the "best available therapy" for infections caused by ceftazidime-resistant Enterobacteriaceae. As a result, individuals whose infections were caused by carbapenem-resistant isolates were excluded from enrollment in these trials. CAZ-AVI's performance in this setting has, however, been assessed in retrospective studies of patients whose CRE infections were treated with the drug, although in these studies a relatively limited number of patients was considered [22–25]. Size-related limitations are in particular a feature of the 2 cohort studies in which the efficacy and safety of CAZ-AVI therapy for CRE infections was compared with that of alternative antimicrobial regimens [26, 27].

To address this knowledge gap, we conducted a retrospective multicenter study of 138 Italian patients with documented KPC-producing *K. pneumoniae* (KPC-Kp) infections, all of whom received CAZ-AVI as salvage therapy. Our aims were to document the clinical features and outcomes of these cases and to specifically explore outcomes and predictors of mortality in patients with KPC-Kp bacteremia.

METHODS

Study Design

We conducted a retrospective observational study of inpatients in 17 Italian hospitals who were treated for KPC-Kp infections between 1 April 2016 and 31 December 2017. The study protocol was approved by the Research Ethics Committee of the coordinating center (Fondazione Policlinico Universitario – Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Agostino Gemelli," Catholic University of the Sacred Heart, Rome), and the informed consent requirement was waived because of the study's retrospective, noninterventional nature.

CAZ-AVI was not available for routine clinical use in Italy during the study period. The patients making up the cohort had therefore received CAZ-AVI salvage therapy within the bounds of compassionate-use programs administered by the drug's manufacturers (AstraZeneca and, later, Pfizer). Neither company had any other type of involvement in the study.

Cases were eligible for inclusion in the cohort if the patient (1) was ≥18 years old; (2) had had a culture-confirmed KPC-Kp infection; and (3) had received ≥72 hours of CAZ-AVI salvage therapy (with or without other antimicrobials). CAZ-AVI was administered intravenously at a dose of at 2.5 g every 8 hours, with dosage adjustments for renal impairment, as recommended by the manufacturers.

Descriptive statistics were computed to summarize the characteristics (demographic, clinical, and epidemiological) of the infections, their treatment, and their outcomes (ie, 30-day mortality). Infections were classified as KPC-Kp bacteremia if (1) blood cultures were positive for a KPC-Kp strain (with or without KPC-Kp–positive cultures from 1 or more other sites), and (2) there were clinical signs of the systemic inflammatory response syndrome. Nonbacteremic KPC-Kp infections were defined by (1) documented recovery of a KPC-Kp isolate from cultures of nonblood samples (eg, intra-abdominal wounds, urine, sputum, bronchoalveolar lavage fluid); (2) no blood culture positivity for KPC-Kp during the index hospitalization; and (3) clinical signs of infection. Treatment regimens containing CAZ-AVI were classified as combination therapy if they included at least 1 other antimicrobial (administered for ≥72 hours) displaying activity against the KPC-KP isolate. Relapse was defined as the onset, during the index hospitalization, of a second microbiologically documented KPC-Kp infection in a patient whose original infection had been classified as a clinical cure (with or without microbiological confirmation).

Our secondary aim was to assess the efficacy of CAZ-AVI specifically in patients with KPC-Kp bacteremia. To this end, we analyzed case characteristics and outcomes in the subcohort of patients whose CAZ-AVI–treated KPC-Kp infections were bacteremic (cases), as defined above. Findings were compared with those on a matched cohort of patients whose bacteremic KPC-Kp infections had been managed in the participating centers receiving ≥72 hours of salvage therapy regimens that did not include CAZ-AVI (controls). Case-control matching was based on (1) the number of days (± 1 day) from bacteremia onset to the initiation of salvage therapy and (2) Pitt bacteremia scores (± 1 point) [28]. We also analyzed data on survivor and nonsurvivor subgroups in the combined group of bacteremia patients (cases plus controls) to identify predictors of 30-day mortality.

Definitions

The following terms were defined prior to data analysis:

- Hospital admission was the date the patient was admitted to the study facility.
- Infection onset was the collection date of the index culture (ie, the first culture that yielded the study isolate).
- Septic shock was sepsis associated with organ dysfunction and persistent hypotension despite volume replacement [29].
- Clinical failure was persistence of signs and symptoms from baseline to the end of antibiotic therapy.
- Microbiological failure was persistence of positive cultures (evaluated only in patients with repeated cultures available).
- Salvage therapy was antibiotic therapy administered after clinical and/or microbiological failure of a first-line treatment regimen or when it had not been possible to continue the previous therapy because of the onset of severe side effects (eg, acute renal failure or allergic reactions).

- High-risk bacteremic infections were those with unidentified sources or identified sources other than urinary tract or biliary tract infections.

Microbiology

Isolates were identified with the Vitek 2 system (bioMérieux, Marcy l'Etoile, France) or matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI Biotyper, Bruker Daltonics GmbH, Leipzig, Germany, or Vitek-MS, bioMérieux). Each hospital conducted antibiotic susceptibility testing according to its own protocols, in most cases using the Vitek 2 system (bioMérieux) or the Sensititre broth microdilution method (Trek Diagnostic Systems, Cleveland, Ohio). CAZ-AVI susceptibility was tested by disk diffusion or broth microdilution. Results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. Phenotypic detection of carbapenemase types was performed according to EUCAST guidelines [30]. Genotypic detection of carbapenemases was performed for a subset of isolates by using the eazyplex SuperBug CRE assay (Amplex Diagnostics GmbH, Germany) or the Xpert Carba-R assay (Cepheid, Italy).

Statistical Analysis

Results are expressed as mean ± standard deviation or median and interquartile range (IQR) (continuous variables) or as percentages of the group from which they were derived (categorical variables). The Student *t* test and Mann-Whitney *U* test were used to compare normally and nonnormally distributed continuous variables, respectively. Categorical variables were evaluated with the χ^2 or the Fisher exact test. Odds ratios and 95% confidence intervals were calculated for all associations that emerged. Two-tailed tests were used to determine statistical significance; a *P* value of <.05 was considered significant. Multivariate logistic regression analysis was used to identify independent risk factors for 30-day mortality. Variables emerging from univariate analysis with *P* values of <.1 were included in the multivariate model in a backward stepwise manner. A propensity score for receiving therapy with CAZ-AVI was added to the model. The propensity score was calculated using a nonparsimonious multivariate logistic regression model in which the outcome variable was the treatment with CAZ-AVI. The Kaplan-Meier method was used for survival analysis. All statistical analyses were performed with the Intercooled Stata program, version 11.

RESULTS

Characteristics and Outcomes of the Study Cohort

Clinical and Microbiological Characteristics

As shown in Figure 1, during the study period, 154 patients in the participating centers received CAZ-AVI salvage therapy for an infection caused by carbapenem-resistant gram-negative bacteria, and in 97% of the cases (n = 149), the organism was a KPC-Kp. Eleven of the 149 KPC-Kp infections were excluded from the study because the case failed to meet 1 or more inclusion criteria. The cohort thus consisted of 138 adults with KPC-Kp infections who received CAZ-AVI salvage therapy. Three-quarters of the KPC-Kp infections (n = 104 [75.4%]) were bacteremic, and most of these (n = 64 [61.5%]) were classified as high-risk. The 34 nonbacteremic infections involved (in order of decreasing frequency) the lower respiratory tract, intra-abdominal structures, the urinary tract, or other sites.

Table 1 summarizes the demographic and clinical characteristics of the study cohort and its bacteremic and nonbacteremic subgroups. Patients ranged in age from 23 to 88 years, and more than two-thirds were male (68.1%). Most infections (122/138 [88.4%]) were hospital-acquired. More than 40% (60/138 [43.5%]) were diagnosed on a medical ward, and one-third (46/138 [33.3%]) were identified while the patient was in an ICU.

All 138 KPC-Kp isolates were resistant to penicillins, extended-spectrum cephalosporins, ertapenem, and ciprofloxacin, and most (129/138 [93.5%]) had meropenem minimum inhibitory concentrations (MICs) of ≥16 mg/L. At the outset of salvage therapy, all isolates displayed in vitro susceptibility to CAZ-AVI; some were also susceptible to gentamicin (41%), fosfomycin (39%), tigecycline (32%), colistin (27%), or amikacin (16%).

Salvage Treatment Regimens and Outcomes

As shown in Table 1, all 138 patients received CAZ-AVI therapy for a median duration of 14 days (IQR, 4–41 days); in most cases (109/138 [78.9%]), the CAZ-AVI was administered with at least 1 other active antibacterial agent (gentamicin in 31.2% [34/109], tigecycline in 14.7% [16/109], colistin in 20.2% [22/109], fosfomycin in 9.2% [10/109], and other drugs in 5.5% [6/109]). In addition, 21 of 109 (19.3%) patients received carbapenems.

The overall 30-day mortality rate was 34.1% (47/138). The highest rate (36.5% [38/104]) was recorded in the patients with bacteremic KPC-Kp infections; the lowest (16.7% [1/6]) was observed in those with urinary tract infections (Figure 1). Three of the patients who died (2.2% of the entire cohort) (2 with bacteremia, 1 with pneumonia) had persistently positive cultures after starting CAZ-AVI treatment, and their isolates eventually developed in vitro resistance to the drug. Two of the 3 were treated with CAZ-AVI monotherapy, and 1 of the 2 received chronic renal replacement therapy. During the index hospitalization, 12 of the 138 (8.7%) patients (10 with bacteremia, 1 with a urinary tract infection, 1 with pneumonia) experienced KPC-Kp infection relapses after CAZ-AVI treatment was discontinued (median interval, 23 days). In all 12 cases, the KPC-Kp isolates remained susceptible to CAZ-AVI, and clinical and/or microbiological cures were achieved after retreatment with CAZ-AVI plus gentamicin.

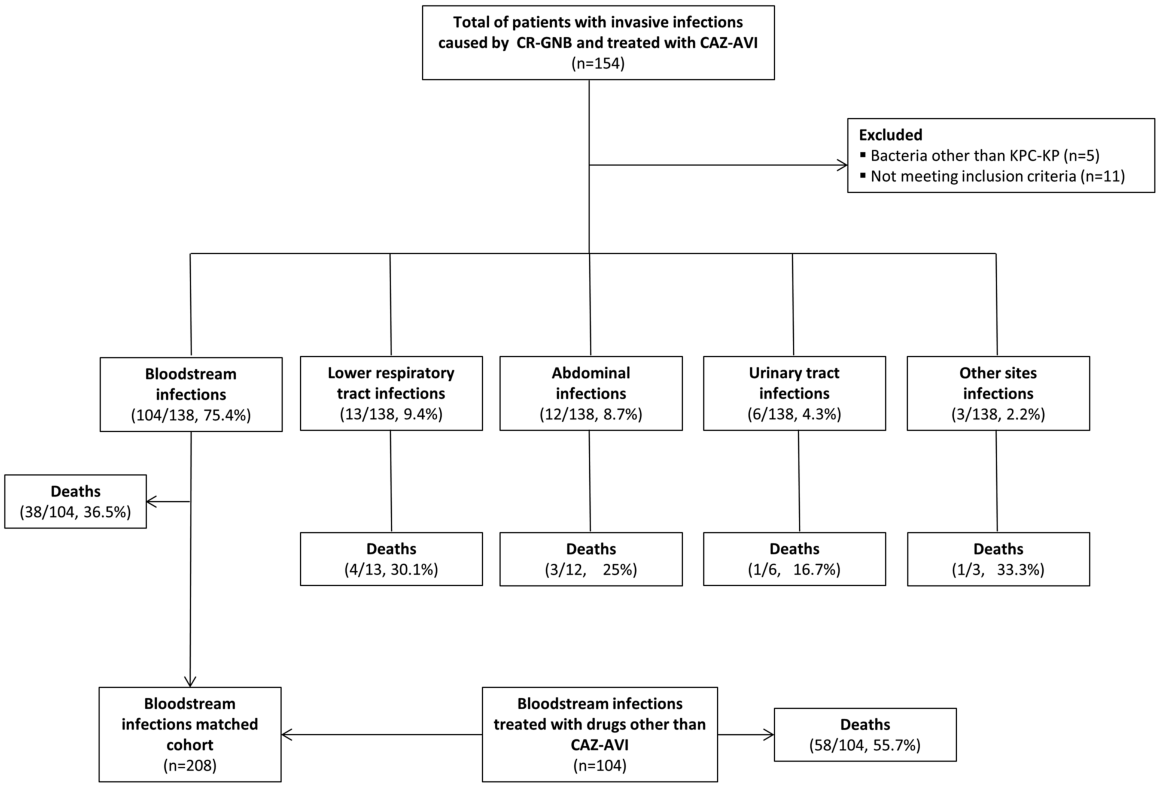

Figure 1. Flowchart of patients' inclusion process. Abbreviations: CAZ-AVI, ceftazidime-avibactam; CR-GNB, carbapenem-resistant Gram-negative bacteria; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*.

Outcomes and Predictors of Mortality in Patients With KPC-Kp Bacteremia Treated With CAZ-AVI Versus Other Regimens

Table 2 shows the demographic and clinical characteristics of the 104 patients with KPC-Kp bacteremia treated with CAZ-AVI salvage therapy (cases) and those of the matched cohort whose KPC-Kp bloodstream infections (BSIs) were managed with second-line regimens containing drugs other than CAZ-AVI (controls). Thirty-day survival rates of CAZ-AVI treated bacteremic patients according to concomitant drugs used as combination therapy or to CAZ-AVI monotherapy is reported in Figure 2, whereas antibiotic salvage regimens that received control patients are shown in Supplementary Table 1.

The 30-day mortality rate among KPC-Kp bacteremia patients who received CAZ-AVI was significantly lower than that of controls (36.5% vs 55.8%, $P = .005$) (Table 2). Among patients managed with single-drug salvage treatment regimens, those who received CAZ-AVI displayed significantly lower 30-day mortality than those treated with alternative single-drug regimens (9/22 [40.9%] vs 21/27 [77.8%], $P = .008$). A similar difference was observed in patients managed with combination regimens (29/82 [35.4%], in those who received CAZ-AVI vs 37/77 [48.1%], in the control group), although it was not statistically significant ($P = .10$).

The results of the univariate and multivariate analyses of risk factors for 30-day mortality in the 208 patients with KPC-Kp BSIs are shown in Tables 3 and 4, respectively. In the multivariate analysis, septic shock at the start of salvage therapy, neutropenia, Charlson comorbidity index ≥3, and recent mechanical ventilation emerged as independent predictors of mortality, whereas treatment with CAZ-AVI (with or without other active drugs) was the only variable independently associated with survival. After adjustment for the propensity score in the logistic regression model evaluating risk factors for mortality, all the variables remained in the model without significant differences (Table 4). Survival curve analysis confirmed the reduced mortality risk associated with CAZ-AVI treatment ($P < .001$), even after adjustment for septic shock at the start of salvage therapy (Figure 3).

DISCUSSION

The past decade has witnessed a global increase in the prevalence of CRE infections, particularly those caused by *K. pneumoniae*. CRE infections (especially those characterized by bacteremia) are associated with high morbidity and mortality [3], and the options for their treatment are very limited. Clinical trial data on the management of these infections are lacking. However,

Table 1. Characteristics of Patients With Ceftazidime-Avibactam–treated *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Infections

Variable	All Infections (N = 138)	Bacteremic Infections (n = 104)	Nonbacteremic Infections (n = 34)	*P* Value
Patient variables				
Male sex	94 (68.1)	68 (65.4)	26 (76.5)	.23
Age, y, median (IQR)	60 (25–79)	61 (27–79)	57 (25–79)	.31
Comorbidities				
COPD	12 (8.7)	10 (9.6)	2 (5.9)	.50
Cardiovascular disease	51 (36.9)	43 (41.4)	8 (23.5)	.06
Cerebrovascular disease or dementia	15 (10.9)	8 (7.7)	7 (20.6)	.03
Solid tumor	27 (19.6)	19 (18.3)	8 (23.5)	.50
Hematologic malignancy	19 (13.7)	15 (14.4)	4 (11.7)	.69
Liver disease	25 (18.1)	19 (18.3)	6 (17.6)	.93
SOT	35 (25.4)	28 (26.9)	7 (20.6)	.46
Chronic renal failure	35 (25.4)	27 (25.9)	8 (23.5)	.77
Diabetes mellitus	22 (15.9)	20 (19.2)	2 (5.9)	.06
Neutropenia	15 (10.9)	13 (12.5)	2 (5.9)	.28
Charlson comorbidity index ≥3	47 (34.1)	38 (36.5)	9 (26.5)	.28
Ward submitting index culture				
Medical (all)	60 (43.5)	42 (40.4)	18 (52.9)	.20
Hematology	9 (6.5)	6 (5.7)	3 (8.8)	.53
Surgical (all)	32 (23.2)	23 (22.1)	9 (26.5)	.60
Transplantation	7 (5.1)	5 (4.8)	2 (5.9)	.80
ICU	46 (33.3)	39 (37.5)	7 (20.6)	.07
Preinfection healthcare interventions				
Surgery[a]	60 (43.5)	41 (39.4)	19 (55.9)	.09
Dialysis[a]	15 (10.9)	14 (13.5)	1 (2.9)	.08
Endoscopy[b]	21 (15.2)	17 (16.3)	4 (11.7)	.52
Mechanical ventilation[b]	43 (31.2)	24 (23.1)	9 (26.5)	.49
Indwelling invasive devices				
Central venous catheter	108 (78.3)	79 (75.9)	29 (85.3)	.25
Bladder catheter	100 (72.5)	74 (71.2)	26 (76.5)	.55
Nasogastric tube[b]	56 (40.6)	42 (40.4)	14 (41.2)	.93
Surgical drain[b]	45 (32.6)	35 (33.6)	10 (29.4)	.65
Infection variables				
Polymicrobial	12 (8.7%)	2 (1.9)	10 (29.4)	<.001
Healthcare-associated	16 (11.6)	10 (9.6)	6 (17.6)	.20
Hospital-acquired	122 (88.4)	94 (90.4)	28 (82.3)	.20
Septic shock[c]	43 (31.2)	34 (32.7)	9 (26.5)	.49
Treatment variables				
Antibiotic regimens prior to CAZ-AVI salvage therapy				
Colistin plus tigecycline	31 (22.5)	23 (22.1)	8 (23.5)	.86
Colistin plus tigecycline plus meropenem	28 (20.3)	24 (23.1)	4 (11.7)	.15
Double carbapenem	18 (13.1)	15 (14.4)	3 (8.8)	.40
Fosfomycin plus tigecycline	16 (11.6)	11 (10.6)	5 (14.7)	.51
Colistin	12 (8.7)	7 (6.7)	5 (14.7)	.15
Colistin plus meropenem	8 (5.7)	5 (4.8)	3 (8.8)	.38
Gentamicin plus tigecycline	8 (5.7)	4 (3.8)	4 (11.7)	.08
Other	13 (9.4)	15 (14.4)	2 (5.9)	.18
Days before CAZ-AVI treatment, median (IQR)	7 (3–10)	7 (3–9)	7 (4–10)	.23
CAZ-AVI combined with	109 (78.9)	82 (78.8)	27 (79.4)	.94
Noncarbapenem drugs[d]	88/109 (80.7)	63/82 (76.8)	25/27 (92.6)	.07
Carbapenems[d]	21/109 (19.3)	19/82 (23.17)	2/27 (7.4)	.07
Days of CAV-AVI treatment, median (IQR)	14 (4–41)	14 (3–28)	15 (6–55)	.18
Outcomes				
30-d mortality	47 (34.1)	38 (36.5)	9 (26.5)	.28
Infection relapse[e]	12 (8.7)	10 (9.6)	2 (5.9)	.50

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

Abbreviations: CAZ-AVI, ceftazidime-avibactam; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; SOT, solid organ transplantation.

[a]During the 30 days preceding infection onset.

[b]During the 72 hours preceding infection onset.

[c]Present when CAZ-AVI treatment was started.

[d]Carbapenem-containing regimens included imipenem OR meropenem with or without ertapenem.

[e]Diagnosed during the index hospitalization after clinical cure of the original infection.

Table 2. Characteristics of Patient Groups[a] Whose *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremic Infections Were Treated with Ceftazidime-Avibactam–containing Salvage Regimens (Cases) or Alternative Salvage Regimens (Controls)

Characteristic	Cases (n = 104)	Controls (n = 104)	*P* Value
Patient variables			
Male sex	68 (65.4)	67 (64.4)	.88
Age, y, median (IQR)	60 (27–79)	72 (53–85)	<.001
Comorbidities			
COPD	10 (9.6)	11 (10.6)	.82
Cardiovascular disease	43 (41.3)	59 (56.7)	.02
Cerebrovascular disease or dementia	8 (7.7)	15 (14.4)	.12
Solid tumor	19 (18.3)	15 (14.4)	.45
Hematologic malignancy	15 (14.4)	16 (15.4)	.84
Liver disease	19 (18.3)	10 (9.6)	.07
Solid organ transplant recipient	28 (26.9)	14 (13.5)	.01
Chronic renal failure	27 (25.9)	30 (28.8)	.64
Diabetes	20 (19.2)	28 (26.9)	.18
Neutropenia	13 (12.5)	14 (13.5)	.84
Charlson comorbidity index ≥3	38 (36.5)	28 (26.9)	.14
Ward submitting index culture			
Medical (all)	42 (40.4)	55 (52.8)	.07
Hematology	6 (5.8)	13 (12.5)	.09
Surgical (all)	23 (22.1)	20 (19.2)	.61
Organ transplants	5 (4.8)	2 (1.9)	.25
ICU	39 (37.5)	27 (25.9)	.07
Infection variables			
Healthcare-associated	10 (9.6)	11 (10.6)	.81
Hospital-acquired	94 (90.4)	91 (87.5)	.51
High-risk BSI[b]	64 (61.5)	74 (71.2)	.14
Colistin-resistant KPC-Kp isolate	84 (80.7)	89 (85.6)	.85
Clinical status[c]			
Septic shock	34 (32.7)	28 (26.9)	.36
Pitt score, median (IQR)	4 (0–7)	4 (0–8)	.34
Salvage therapy variables			
Days before salvage therapy, median (IQR)	7 (3–9)	7 (3–8)	.36
Monotherapy	22 (21.2)	27 (25.9)	.41
Combination therapy	82 (78.8)	77 (74.3)	.41
Outcomes			
30-d mortality	38 (36.5)	58 (55.8)	.005
Infection relapse[d]	10 (9.6)	9 (8.6)	.81

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

Abbreviations: BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*.

[a]Cohorts were matched for days before salvage therapy (± 1 day) and Pitt bacteremia scores (± 1 point) at the start of salvage therapy.

[b]BSI whose source was unidentified or located in structures other than the urinary or biliary tract.

[c]As assessed at the start of salvage therapy.

[d]Diagnosed during the index hospitalization after clinical cure of the original infection.

findings from observational studies have supported the use of combination regimens that include drugs displaying in vitro activity against the *K. pneumoniae* isolates (eg, aminoglycosides, colistin, fosfomycin, and/or tigecycline) and/or drugs to which *K. pneumoniae* isolates are in vitro resistant (ie, carbapenems), at least in patients with severe infections [12, 31–34]. Furthermore, the prevalence of resistance to 1 or more of the few drugs considered active against carbapenem-resistant *K. pneumoniae* isolates is increasing. Worrisome rates of colistin resistance have recently been reported, especially among KPC-Kp isolates, and data from the European Antimicrobial Resistance Surveillance System for 2016 revealed resistance to this drug in 10%–25% of carbapenem-resistant *K. pneumoniae* isolates in at least 4 southern European countries, including Italy [15, 35, 36]. Against this unsettling backdrop, CAZ-AVI emerges as a potentially powerful addition to clinicians' antibacterial armamentarium, particularly in hospitals such as those taking part in this study, where KPC-Kp infections are endemic.

The cohort we analyzed is the largest sample of patients with CAZ-AVI–treated KPC-Kp infections analyzed to date. As such,

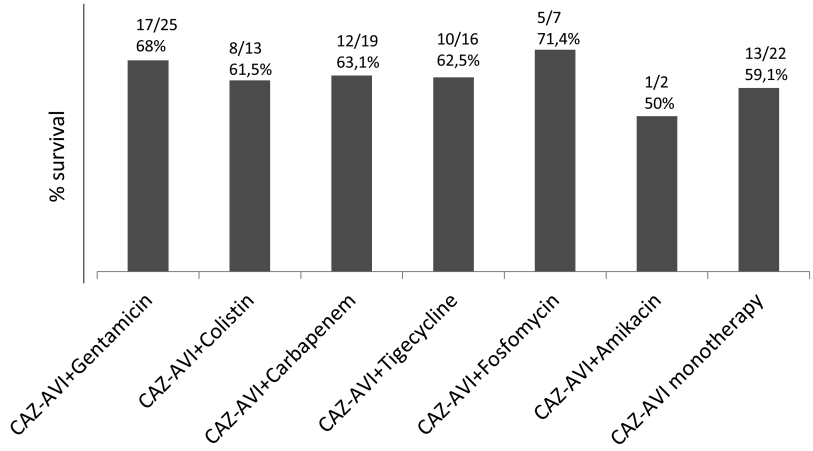

Figure 2. Thirty-day survival rates of ceftazidime-avibactam (CAZ-AVI)–treated bacteremic patients according to concomitant drugs used as combination therapy or to CAZ-AVI monotherapy.

even with the well-known limitations of a retrospective study, it can provide valuable insights into the clinical role of this drug. It is also important to recall, however, that our data reflect CAZ-AVI's performance within the confines of compassionate-use/expanded-access programs, which means that the drug was started only after other antibacterial treatment regimens had failed or could be not continued. In patients with severe gram-negative infections, delayed initiation of active treatment has been associated with poorer outcomes [12, 37]. Therefore, survival in our cohort might reasonably be expected to be worse than those recorded in settings where CAZ-AVI could be started promptly after infection onset. Instead, the 30-day mortality rate we observed (34.1%) is identical to that reported in patients whose CRE infections were treated with CAZ-AVI as the first-line antibiotic regimen [23]. It is also in line with the all-cause in-hospital mortality rate of 39.5% reported in other patients who were managed with CAZ-AVI salvage therapy [22], even though the delay in starting CAZ-AVI in that study was almost twice as long as that in our cohort (median, 13 vs 7 days from infection onset).

In the 37 CAZ-AVI–treated CRE infections they analyzed, Shields et al reported a rate of recurrences in 5 of 37 cases (13.5%), which is quite similar to our experience in the present study, where infection relapses occurred in 12 of the 138 (8.7%) [23]. Furthermore, 3 of 37 (8.1%) cases reported by Shields et al were associated with acquired in vitro resistance to CAZ-AVI (MICs >8 μg/mL) [23] whereas, in our cohort, this event occurred only in 3 of 138 (2.2%) KPC-Kp isolates. It is important to acknowledge that these differences may reflect the use of CAZ-AVI predominantly in different types of infections (bacteremia in our study and pneumonia in that of Shields et al); Shields et al did not observe resistance in bacteremia, whereas 2 cases of resistance in this study occurred in pneumonia; also, in our cohort, 1 of 3 cases of resistance to CAZ-AVI occurred in a patient with pneumonia, although the total number of cases of pneumonia (13/138) was very low compared to cases of BSI (104/138) in our study [23]. In addition, pneumonia has been recently recognized as risk factor for CAZ-AVI resistance among patients with CRE infections [24].

CAZ-AVI also produced encouraging results in the KPC-Kp BSIs that made up approximately 75% of the cases in our cohort. Comparison of these cases with a matched cohort of KPC-Kp BSIs treated with other second-line antimicrobial regimens revealed significantly lower 30-day mortality in the CAV-AZI–treated patients. Two previous studies have compared the outcomes of first-line CAZ-AVI treatment with those of other antimicrobial regimens in patients with CRE bacteremia [26, 27]. All 109 cases retrospectively analyzed by Shields et al consisted of carbapenem-resistant *K. pneumoniae* BSIs. Although only 13 (11.9%) of these infections were treated with regimens that included CAZ-AVI, the rate of clinical success at 30 days in this small subgroup (85%) significantly exceeded those achieved in the other treatment-defined subgroups ($P = .006$) [26]. This is fully consistent with the striking difference in 30-day survival observed between our BSI cases and controls (Table 2) and with the emergence of CAZ-AVI treatment as the sole independent predictor of clinical success in our multivariable logistic regression model. Our findings are also in line with those of van Duin et al, who prospectively analyzed 137 CRE infections (almost half of which involved bacteremia) treated with colistin-containing vs CAZ-AVI-containing regimens [27]. After 30 days of treatment, better outcomes were found to be more likely in the CAZ-AVI–treated group (adjusted probability, 64%). It should be stressed, however, that the latter group was substantially smaller than the one managed with colistin (38 vs 99), and it included only 15 patients with BSIs.

In conclusion, data on this relatively large multicenter cohort indicate that CAZ-AVI is likely to be an important option for

Table 3. Univariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia (Cases and Controls)

Variable	No. (%) of Patients		*P* Value	OR (95% CI)
	Nonsurvivors (n = 96 [46.2%])	Survivors (n = 112 [53.8%])		
Patient variables				
Male sex	56 (58.3)	79 (70.5)	.06	0.58 (.32–1.08)
Age, y, median (IQR)	67 (30–86)	65 (29–81)	.19	…
Comorbidities				
COPD	11 (11.5)	10 (8.9)	.54	1.32 (.48–3.64)
Cardiovascular disease	47 (48.9)	55 (49.1)	.98	0.99 (.56–1.78)
Cerebrovascular disease or dementia	14 (14.6)	9 (8.1)	.13	1.95 (.74–5.37)
Solid tumor	15 (15.6)	19 (16.9)	.79	0.90 (.40–2.02)
Hematologic malignancy	17 (17.7)	14 (12.5)	.29	1.51 (.65–3.51)
Liver disease	14 (14.6)	15 (13.4)	.80	1.10 (.46–2.61)
Solid organ transplant recipient	18 (18.7)	24 (21.4)	.63	0.85 (.40–1.76)
Chronic renal failure	26 (27.1)	31 (27.6)	.92	0.97 (.50–1.87)
Diabetes	18 (18.7)	30 (26.8)	.17	0.63 (.30–1.28)
Neutropenia	18 (18.7)	9 (8.1)	.02	2.64 (1.05–7.02)
Charlson comorbidity index ≥3	41 (42.7)	25 (22.3)	.001	2.59 (1.36–4.96)
Ward submitting index culture				
Medical (all)	39 (40.6)	58 (51.8)	.10	0.64 (.35–1.14)
Hematology	11 (11.5)	8 (7.1)	.20	1.68 (.58–5.04)
Surgical (all)	14 (14.6)	29 (25.9)	.04	0.48 (.22–1.03)
Transplants	2 (2.1)	5 (4.5)	.34	0.45 (.04–2.87)
ICU	42 (43.7)	24 (21.4)	<.001	2.85 (1.49–5.48)
Pre-BSI healthcare interventions				
Surgery[a]	6 (6.3)	11 (9.8)	.34	0.61 (.18–1.89)
Dialysis[a]	17 (17.7)	9 (8.1)	.001	2.72 (1.07–7.32)
Endoscopy[b]	13 (13.5)	12 (10.7)	.53	1.30 (.51–3.31)
Mechanical ventilation[b]	36 (37.5)	20 (17.8)	.001	2.76 (1.39–5.51)
Indwelling invasive devices				
Central venous catheter	71 (73.9)	68 (60.7)	.04	1.87 (.97–3.48)
Bladder catheter	62 (64.6)	70 (62.5)	.75	1.09 (.59–2.01)
Nasogastric tube[b]	37 (38.5)	30 (26.8)	.07	1.71 (.91–3.21)
Surgical drain[b]	21 (21.9)	27 (24.1)	.70	0.88 (.43–1.77)
Treatments administered[a]				
Corticosteroids	34 (35.4)	25 (22.3)	.04	1.90 (.99–3.68)
Chemotherapy or radiotherapy	16 (16.7)	10 (8.9)	.09	2.04 (.81–5.30)
Infection variables				
Healthcare-associated	10 (10.4)	11 (9.8)	.88	1.06 (.28–2.91)
Hospital-acquired	86 (89.6)	99 (88.4)	.78	1.12 (.43–3.03)
Clinical status[c]				
Septic shock	42 (43.7)	20 (17.8)	<.001	3.58 (1.83–7.09)
Pitt score	4.5 (1–9)	2 (0–8)	<.001	…
Colistin-resistant KPC-Kp isolate	86 (89.6)	87 (77.6)	.02	2.47 (1.06–6.10)
Salvage therapy variables				
CAZ-AVI–including therapy	38 (39.6)	66 (58.9)	.005	0.45 (.25–0.83)
Monotherapy	30 (31.3)	19 (16.9)	.01	2.22 (1.10–4.55)
CAZ-AVI	9 (9.4)	13 (11.6)	.60	0.78 (.28–2.10)
Another agent	21 (21.9)	6 (5.4)	<.001	4.94 (1.80–15.59)
Combination therapy	66 (68.7)	93 (83.1)	.01	0.44 (.21–.91)
Combinations that included CAZ-AVI	29 (30.2)	53 (47.3)	.01	0.48 (.26–.88)
Combinations that did not include CAZ-AVI	37 (38.5)	40 (35.7)	.67	1.12 (.62–2.06)

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

Abbreviations: BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; OR, odds ratio.

[a]During the 30 days preceding infection onset.

[b]During the 72 hours preceding infection onset.

[c]As assessed when salvage treatment was started.

[d]Double-carbapenem regimens included meropenem and ertapenem.

Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia

	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
Variable	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index ≥3	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia	.01	3.22 (1.25–8.29)	.03	3.36 (1.25–8.75)
Septic shock	.002	2.95 (1.46–5.94)	.003	2.94 (1.46–5.92)
Any regimen that included CAZ-AVI	<.001	0.25 (.13–.51)	.001	0.27 (.13–.57)

Abbreviations: CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; OR, odds ratio.

treating serious KPC-Kp infections, particularly those involving bacteremia. Although the drug was administered in a compassionate-use setting—that is, only after other antimicrobial regimens had failed—its use was associated with clear survival benefits relative to other commonly used regimens. Further work is needed to devise strategies for the optimal use of this important new drug in the treatment of CRE infections.

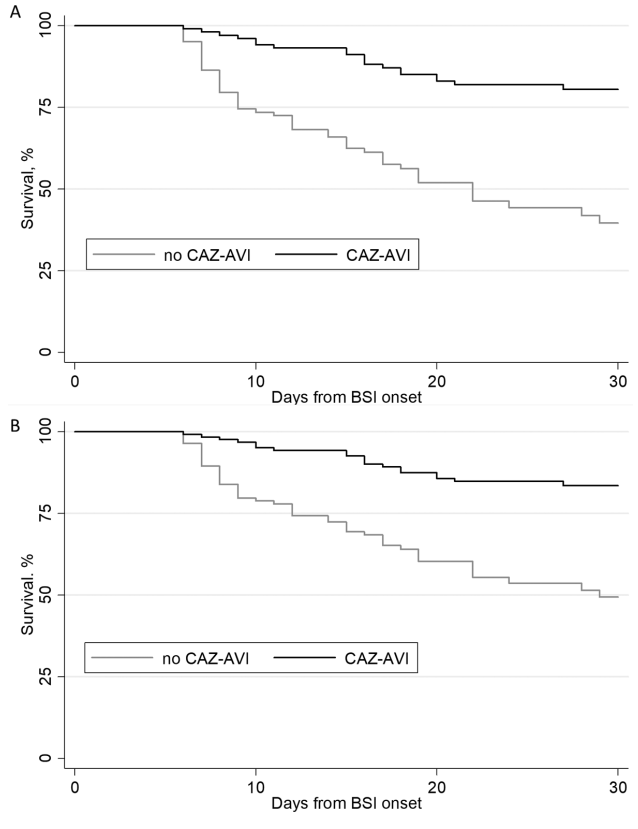

Figure 3. Kaplan-Meier survival analyses in the cohorts with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* bloodstream infections (BSIs). *A,* Survival in patients whose definitive treatment regimens included ceftazidime-avibactam (CAZ-AVI; black curve) was significantly better than that of patients treated with other antimicrobial drug regimens (gray curve) ($P < .001$). *B,* The difference remained significant after adjustment for the presence of septic shock at the start of salvage treatment ($P < .001$).

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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