Clinical Infectious Diseases

MAJOR ARTICLE

Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase–Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

Mario Tumbarello,[1,2,3] Francesca Raffaelli,[1] Maddalena Giannella,[4] Elisabetta Mantengoli,[5] Alessandra Mularoni,[6] Mario Venditti,[7] Francesco Giuseppe De Rosa,[8] Loredana Sarmati,[9] Matteo Bassetti,[10,11] Gaetano Brindicci,[12] Marianna Rossi,[13] Roberto Luzzati,[14] Paolo Antonio Grossi,[15] Alberto Corona,[16] Alessandro Capone,[17] Marco Falcone,[18] Cristina Mussini,[19] Enrico Maria Trecarichi,[20], Antonio Cascio,[21] Elena Guffanti,[22] Alessandro Russo,[23] Gennaro De Pascale,[24] Carlo Tascini,[25] Ivan Gentile,[26] Angela Raffaella Losito,[1] Linda Bussini,[4] Giampaolo Corti,[5,27] Giancarlo Ceccarelli,[7] Silvia Corcione,[8,28] Mirko Compagno,[29] Daniele Roberto Giacobbe,[10,11] Annalisa Saracino,[12] Massimo Fantoni,[1,2] Spinello Antinori,[30] Maddalena Peghin,[31] Paolo Bonfanti,[13,32] Alessandra Oliva,[7] Andrea De Gasperi,[22] Giusy Tiseo,[18] Cristina Rovelli,[15] Marianna Meschiari,[33] Nour Shbaklo,[8] Teresa Spanu,[1,34] Roberto Cauda,[1,2] and Pierluigi Viale[4]

[1]Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy; [2]Dipartimento di Sicurezza e Bioetica, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Medical Biotechnologies, University of Siena, Siena, Italy; [4]Department of Medical and Surgical Sciences, University of Bologna, IRCCS Pol. S. Orsola Bologna, Italy; [5]SOD Malattie Infettive e Tropicali Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [6]ISMETT-IRCCS Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy; [7]Dipartimento di Sanità Pubblica e Malattie Infettive, Università Sapienza, Rome, Italy; [8]Department of Medical Sciences, University of Turin, Turin, Italy; [9]Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Rome, Italy; [10]Infectious Diseases Unit, Ospedale Policlinico San Martino–IRCCS, Genova, Italy; [11]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; [12]Operative Unit of Infectious Diseases, Hospital-University Polyclinic of Bari, Bari, Italy; [13]UOC Malattie Infettive, Ospedale San Gerardo, Genoa, Italy; [14]Infectious Diseases Unit, University Hospital of Trieste, Trieste, Italy; [15]Clinica di Malattie Infettive e Tropicali, Università degli Studi dell'Insubria–ASST-Sette Laghi, Varese, Italy; [16]SC Anestesia e Rianimazione, ASST Fatebenefratelli Sacco, Polo Universitario, Milan, Italy; [17]Infezioni Sistemiche ed Immunodepresso, National Institute for Infectious Disease L Spallanzani, Rome, Italy; [18]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [19]Clinica delle Malattie Infettive, Università di Modena e Reggio Emilia, Modena, Italy; [20]Department of Medical and Surgical Sciences, Infectious and Tropical Disease Unit, Magna Graecia University of Catanzaro, Catanzaro, Italy; [21]Infectious and Tropical Diseases Unit– Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G D'Alessandro," University of Palermo, Palermo, Italy; [22]Anestesia Rianimazione 2, ASST GOM Niguarda, Milan, Italy; [23]Internal Medicine Unit, Policlinico Casilino, Rome, Italy; [24]Dipartimento di Scienza dell'Emergenza, Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy; [25]Malattie Infettive ad Indirizzo neurologico Ospedale Cotugno, Naples, Italy; [26]Dipartimento di Medicina Clinica e Chirurgia–Sezione di Malattie Infettive, Università di Napoli "Federico II," Naples, Italy; [27]Dipartimento Medicina Sperimentale e Clinica Università di Firenze, Florence, Italy; [28]Tufts University School of Medicine, Boston, MA, USA; [29]Clinical Infectious Diseases, Tor Vergata University, Rome, Italy; [30]Dipartimento di Scienze Biomediche e Cliniche L Sacco Università degli Studi di Milano Polo Universitario, Milan, Italy; [31]Clinica Malattie Infettive, Dipartimento di Area Medica Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy; [32]Dipartimento di Medicina e Chirurgia, Università Milano Bicocca, Milan, Italy; [33]Clinica delle Malattie Infettive, Azienda Ospedaliero Universitaria Policlinico di Modena, Modena, Italy; and [34]Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy

Background. A growing body of observational evidence supports the value of ceftazidime-avibactam (CAZ-AVI) in managing infections caused by carbapenem-resistant Enterobacteriaceae.

Methods. We retrospectively analyzed observational data on use and outcomes of CAZ-AVI therapy for infections caused by Klebsiella pneumoniae carbapenemase–producing *K. pneumoniae* (KPC-Kp) strains. Multivariate regression analysis was used to identify variables independently associated with 30-day mortality. Results were adjusted for propensity score for receipt of CAZ-AVI combination regimens versus CAZ-AVI monotherapy.

Results. The cohort comprised 577 adults with bloodstream infections (n = 391) or nonbacteremic infections involving mainly the urinary tract, lower respiratory tract, and intra-abdominal structures. All received treatment with CAZ-AVI alone (n = 165) or with ≥1 other active antimicrobials (n = 412). The all-cause mortality rate 30 days after infection onset was 25% (146/577). There was no significant difference in mortality between patients managed with CAZ-AVI alone and those treated with combination regimens (26.1% vs 25.0%, $P = .79$). In multivariate analysis, mortality was positively associated with presence at infection onset of septic shock ($P = .002$), neutropenia ($P < .001$), or an INCREMENT score ≥8 ($P = .01$); with lower respiratory tract infection (LRTI) ($P = .04$); and with CAZ-AVI dose adjustment for renal function ($P = .01$). Mortality was negatively associated with CAZ-AVI administration by prolonged infusion ($P = .006$). All associations remained significant after propensity score adjustment.

Conclusions. CAZ-AVI is an important option for treating serious KPC-Kp infections, even when used alone. Further study is needed to explore the drug's seemingly more limited efficacy in LRTIs and potential survival benefits of prolonging CAZ-AVI infusions to ≥3 hours.

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

Received 2 December 2020; editorial decision 16 February 2021; published online 22 February 2021.

Correspondence: M. Tumbarello, Università Cattolica del Sacro Cuore,, Largo Francesco Vito 1, 00168 Rome, Italy (mario.tumbarello@unicatt.it; mariotumb@gmail.com).

Clinical Infectious Diseases® 2021;73(9):1664–76

DOI: 10.1093/cid/ciab176

The last decade has witnessed a progressive worldwide spread of carbapenem-resistant Enterobacteriaceae (CRE), which is proving to be a formidable challenge to global health and associated with strikingly high mortality rates [1–5].

Ceftazidime-avibactam (CAZ-AVI) combines the third-generation cephalosporin, ceftazidime, with avibactam, a

novel synthetic B-lactamase inhibitor capable of inhibiting both KPC (Amber Class A) and OXA-48 (Amber Class D) carbapenemases. Limited information on the management of CRE infections with CAZ-AVI is currently available from published clinical trials. In contrast, however, a growing body of evidence supporting this agent's value in this setting is emerging from observational studies. With a few exceptions [6, 7], most studies indicate that CAZ-AVI treatment of CRE infections has consistently been associated with substantially lower mortality rates than previously used drug regimens [8–12]. Most of these studies, however, have been conducted in fairly small patient cohorts.

In an attempt to expand and fortify the evidence base for efforts aimed at optimizing the use of this new agent, we retrospectively analyzed a large body of observational data on the postmarketing use and outcomes of CAZ-AVI therapy for infections caused by *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* (KPC-Kp) strains in Italy, where these organisms are responsible for the vast majority of CRE infections.

METHODS

Study design and cohort enrollment

The study involved a retrospective analysis of observational data on inpatients in 22 Italian hospitals (academic and nonacademic) who received CAZ-AVI for KPC-Kp infections between 1 June 2018 and 31 January 2020. The protocol was approved by the Research Ethics Committee of the Coordinating Center. Patients eligible for study cohort enrollment met all of the following criteria: (1) age 18 years or older at hospital admission, (2) culture-documented monomicrobial KPC-Kp infection, and (3) 72 or more hours of treatment with CAZ-AVI, alone or with other antimicrobials with in vitro activity against the KPC-Kp isolate. Coordinators at each participating center reviewed enrolled patients' electronic medical records for the entire index hospitalization and extracted data on the patients' demographic and comorbidity profiles; epidemiological, clinical, and microbiological features of the infections; characteristics of the antimicrobial treatment regimens; and case outcomes. Study data were securely recorded on standardized forms and sent to the Coordinating Center for analysis.

Patient and Infection Profiles

The impact of comorbidities present at infection onset (collection date of the index culture; ie, first culture yielding the study isolate) was assessed in terms of individual conditions and Charlson comorbidity index [13]. Illness severity at infection onset was classified on the basis of the estimated mortality risk as reflected by the INCREMENT carbapenemase producing Enterobacteriaceae (CPE) score (low [<8 points]) vs high [≥8 points]) [14–16] and the presence or absence of septic shock (ie, sepsis associated with organ dysfunction and persistent hypotension despite volume replacement) [17]. Infections were considered hospital acquired if the index culture was collected more than 48 hours after hospital admission. Diagnosis of bloodstream infections (BSIs) was supported by blood-culture positivity for a KPC-Kp strain (with or without KPC-Kp–positive cultures from ≥1 other sites). KPC-Kp infections were considered nonbacteremic infections (nBSIs) if (1) the causative isolate had been recovered from cultures of urine, intra-abdominal wounds, sputum, bronchoalveolar lavage fluid, or other nonblood specimens; (2) there were no KPC-Kp–positive blood cultures during the index hospitalization; and (3) the patient presented clinical and/or radiological signs of infection. Cases that failed to meet these criteria and/or were treated with a definitive antibiotic regimen inconsistent with the isolate's antimicrobial susceptibility testing profile were classified as colonization and excluded from the analysis.

Protocols for source control (central line or urinary catheter removal, abscess drainage, wound debridement, potential infected devices removal) as well as for execution of control cultures were followed in all participating hospitals.

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 broth microdilution method (BMD). All isolates were tested for susceptibility to CAZ-AVI, meropenem, and colistin using the BMD. For some isolates, we also obtained minimum inhibitory concentrations (MICs) for fosfomycin (agar dilution method) and tigecycline (BMD) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [18]. Susceptibility findings were interpreted in accordance with EUCAST clinical breakpoints. All isolates were screened phenotypically for carbapenemase production according to EUCAST guidelines [19]. Detection of carbapenemases was performed by using the NG-Test CARBA 5 (NG Biotech, Guipry, France) or the RESIST-3 O.O.K. K-SeT (Coris BioConcept, Gembloux, Belgium) immunochromatographic assays, or the Eazyplex SuperBug CRE assay (Amplex Diagnostics GmbH, Germany) or the Xpert Carba-R assay (Cepheid, Buccinasco, Italy).

Ceftazidime-Avibactam Treatment and Outcomes

Ceftazidime-avibactam was administered intravenously at a standard dose of 2.5 g every 8 hours, with dosage adjustments for renal impairment, as recommended by the manufacturers

[20]. In most cases, each dose was infused over a 2-hour period. In some cases, however, the recommended dosage was given by prolonged infusion (lasting ≥3 hours). The CAZ-AVI treatment regimens classified as combination therapy included at least 1 other antimicrobial (administered for ≥72 hours) with in vitro activity against the patient's KPC-Kp isolate. Data were collected for the duration of the index hospitalization. The primary outcome was all-cause mortality 30 days after infection onset. Secondary outcomes included the development of in vitro CAZ-AVI resistance, adverse reactions, and infection relapse.

Patients discharged before 30 days after infection onset were followed up through the consultation of available outpatient medical records or with a phone call.

Infection relapse was defined as the onset of a second microbiologically documented KPC-Kp infection in a patient whose original infection had been classified as a clinical cure defined as clinical response to treatment with resolution of symptoms/signs of the infection upon discontinuation of CAZ-AVI.

Statistical Analysis

Results are expressed as means ± standard deviations or medians and interquartile ranges (IQRs) (continuous variables) or as percentages of the group from which they were derived (categorical variables). The Student's *t* test and Mann-Whitney *U* test were used to compare normally and non–normally distributed continuous variables, respectively. Categorical variables were evaluated with the chi-square or 2-tailed Fisher's exact test. Odds ratios and 95% confidence intervals were calculated for all associations that emerged. Two-tailed tests were used to determine statistical significance reflected by a *P* value of less than .05. Multivariate logistic regression analysis was used to identify independent risk factors for 30-day mortality. Variables emerging from univariate analysis with *P* values of less than .1 were included in the multivariate model in a backward stepwise manner. A propensity score reflecting the likelihood of receiving combination rather than monotherapy was included in the model to balance baseline covariates predictive of treatment and to control for confounding. The score was calculated using a bivariate logistic regression model in which receipt of combination therapy was the outcome variable. The Kaplan-Meier method was used for survival analysis. All statistical analyses were performed with the Intercooled Stata program, version 11 (StataCorp, College Station, TX).

RESULTS

Clinical and Microbiological Characteristics of KPC-Kp Infections

As summarized in Figure 1 and Table 1, the cohort analyzed comprised 577 adults with KPC-Kp infections who received at least 72 hours of CAZ-AVI therapy. Patients ranged in age from 21 to 91 years, and two-thirds were male (66.9%). Most infections (491/577, 85.1%) were hospital acquired. Almost half (280/577, 48.5%) were diagnosed on a medical ward, and approximately 1 out of 4 was identified during an intensive care unit (ICU) stay. Over two-thirds of the infections (n = 391, 67.8%) were BSIs. The 186 nBSIs included (in order of decreasing frequency) complicated urinary tract infections (cUTIs), lower respiratory tract infections (LRTIs), intra-abdominal infections (IAIs), and infections involving other sites. Non-BSIs (in particular, LRTIs and IAIs) were significantly more likely to carry a high mortality risk, reflected by INCREMENT scores of 8 or higher ($P < .01$). All KPC-Kp isolates displayed in vitro resistance to penicillins, extended-spectrum cephalosporins, ertapenem, and ciprofloxacin, and most (524/577, 91%) had meropenem MICs of 16 mg/L or greater. At treatment outset, all isolates displayed in vitro susceptibility to CAZ-AVI with MICs ranging from 1 to 8 μg/mL. Most were also susceptible to colistin (434/577, 75%), fosfomycin (97/138, 70%), tigecycline (312/401, 78%), gentamicin (375/577, 65%), and/or amikacin (345/577, 60%), and 1 out of 4 was susceptible to trimethoprim/sulfamethoxazole (144/577, 25%).

Treatment Regimens and Outcomes

As shown in Table 2, the median duration of CAZ-AVI therapy was 12 days (IQR, 8–16 days). Ceftazidime-avibactam was started within 48 hours of infection onset in over half of all cases (311, 53.9%), most of which were bacteremic ($P < .001$). Prolonged infusion was used in fewer than half of all cases (246/577 patients, 42.6%). Dosage adjustments for impaired renal function were more common in patients with nBSIs ($P < .001$). Over 70% of all infections were managed with combination regimens, which generally consisted of CAZ-AVI plus 1 other active drug (usually fosfomycin, tigecycline, gentamicin, or meropenem). As shown in Table 3, use of combination regimens was unrelated to infection-severity parameters, but it was significantly more frequent on surgical wards and in patients with Charlson comorbidity indexes greater than 3 and in those with LRTIs ($P < .01$ for both). Combination regimens were associated with longer treatment and more frequent use of prolonged infusion of CAZ-AVI ($P < .001$ for both).

Outcomes observed during the index hospitalization are shown in Table 2. In 20 patients (3.5% of the entire cohort), including 14 (3.6%) with BSIs, 4 (6.8%) with LRTIs, 1 (2.9%) with IAI, and 1 (4.8%) with other nBSIs, despite an adequate source control in 15 patients with a known source of infection, KPC-Kp culture positivity persisted after CAZ-AVI was started, and the isolates eventually developed in vitro resistance to the drug with MICs of 16 μg/mL or greater. At that point (after 6–10 days of CAZ-AVI therapy), the infections were managed with combinations of colistin and tigecycline (n = 14) or gentamicin + fosfomycin (n = 6).

The remaining 557 patients remained on CAZ-AVI until they were clinically cured (n = 420) or died (n = 137).

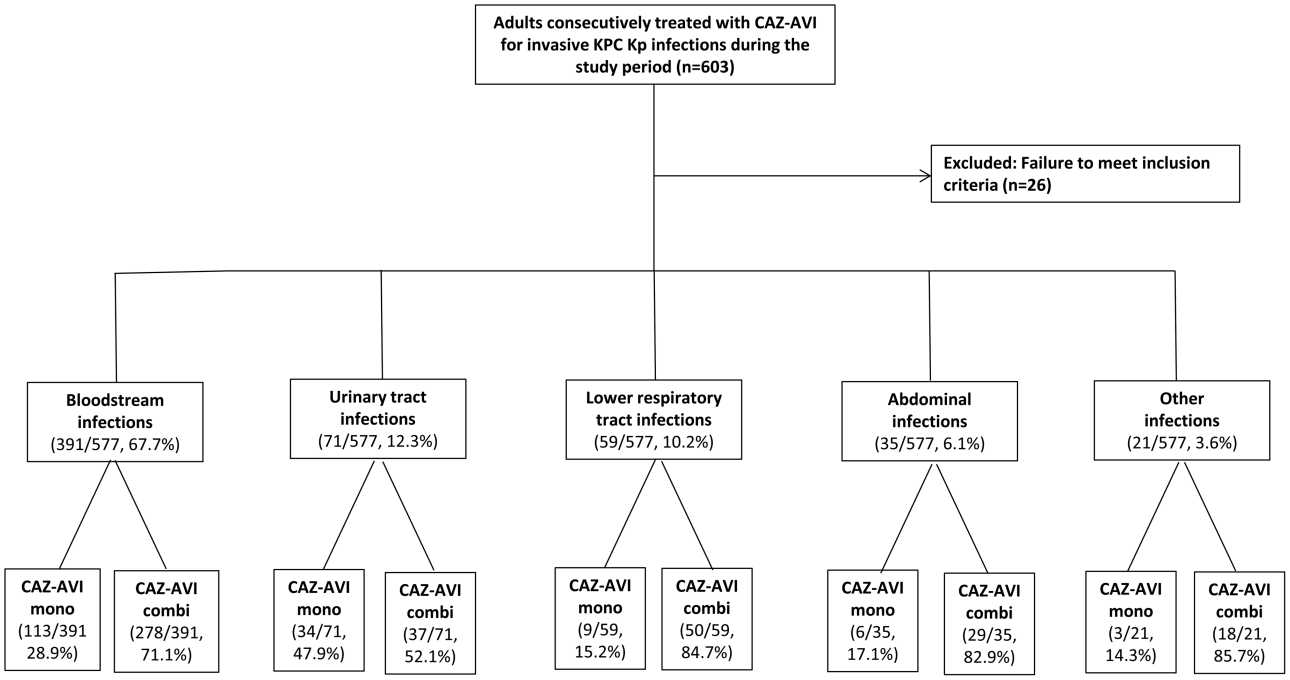

Figure 1. Flowchart showing cohort enrollment. Abbreviations: CAZ-AVI, ceftazidime-avibactam; combi, combination regimen; KPC Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; mono, monotherapy.

Sixty-three (15%) of the 420 patients considered cured (42 with BSIs, 8 with LRTI, 7 with IAI, 5 with cUTIs, and 1 with another type of nBSI) experienced clinical relapses 11–26 days after CAZ-AVI was discontinued (median, 20 days). In 61 of these 63 cases, the KPC-Kp isolate recovered during the relapse displayed persistent in vitro susceptibility to CAZ-AVI, and microbiological and/or clinical cures were achieved after re-treatment with CAZ-AVI plus fosfomycin or CAZ-AVI plus gentamicin. In the remaining 2 relapses, the KPC-Kp strain had become resistant with MICs of 16 µg/mL or greater, and the new infection was treated with colistin + fosfomycin. No statistically significant relationship was observed between relapse and the use of CAZ-AVI monotherapy versus combination regimens (Table 3) or CAZ-AVI infusion times (Table 4). Adverse reactions were observed in 20 (3.4%) of the patients (rash in 9, diarrhea in 5, nausea and vomiting in 4, hypokalemia in 2).

Thirty days after infection onset, 25.3% (146/577) of the patients had died (Table 2), but well over half of the survivors (247/431, 57.3%) had already been discharged. The highest 30-day mortality rates were recorded among the patients who developed CAZ-AVI resistance during treatment (45%, 9/20), in those with LRTIs (37.3%, 22/59), and in those with BSIs (26.3%, 103/391). There was no statistically significant difference in mortality between patients managed with CAZ-AVI alone and those treated with combination regimens at the level of the whole cohort (Table 3) (43/165 [26.1%] vs 103/412 [25.0%]; $P = .79$) or within subgroups defined by infection types (Figure 2). Among patients treated with combination regimens, 30-day survival rates did not differ significantly with the partner drugs used (data not shown). Statistically significant differences were observed between 30-day survival rates at the level of the whole cohort and in patient subgroups receiving CAZ-AVI via prolonged versus standard infusion (Table 4 and Figure 3). Renal adjustment of the CAZ-AVI dose significantly decreased survival only in patients with LRTIs or IAIs (Figure 4).

Predictors of Mortality in Patients With KPC-Kp Infections Treated With Ceftazidime-Avibactam

In the univariate analysis (Table 5), patients who died within 30 days of infection onset tended to be older, to have a hospital-acquired infection, to have pre-existing cardiovascular and cerebrovascular disease and/or neutropenia, to have a Charlson comorbidity index greater than 3, and to have an indwelling central venous catheter, bladder catheter, nasogastric tube, or surgical drain at infection onset. Their infections were more frequently diagnosed in an ICU and were more likely to be an LRTI or BSI (particularly those with a high INCREMENT score). Mortality was also associated with septic shock at infection onset and with CAZ-AVI dose adjustments for renal function during treatment. Patients who survived tended to have been diagnosed on medical wards. Their infections were more likely to be healthcare associated (rather than hospital acquired), classified as "low mortality" based on the INCREMENT score less than 8, and treated with CAZ-AVI administered by prolonged rather than standard infusion.

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

Variable	All Infections (n = 577)	BSIs (n = 391)	All nBSIs (n = 186)	*P* Value (BSI vs nBSI)	nBSI Types (n = 186)			
					cUTIs (n = 71)	LRTIs (n = 59)	IAIs (n = 35)	Others (n = 21)
Patient variables								
Males	386 (66.9)	277 (70.8)	109 (58.6)	.003	35 (49.3)	42 (71.2)	21 (60)	11 (52.4)
Age, median (IQR), years	66 (56–76)	65 (56–75)	66 (56–78)	.57	65 (56–75)	63 (56–77)	63 (48–76)	67 (59–75)
Comorbidities								
COPD	87 (15.1)	61 (15.6)	26 (13.9)	.61	7 (9.9)	11 (18.6)	3 (8.6)	5 (23.8)
Cardiovascular disease	265 (45.9)	179 (45.8)	86 (46.2)	.92	38 (53.5)	25 (42.4)	10 (28.6)	13 (61.9)
Cerebrovascular disease or dementia	116 (20.1)	66 (16.9)	50 (26.9)	.005	23 (32.4)	19 (32.2)	3 (8.6)	5 (23.8)
Solid tumor	121 (20.97)	86 (21.99)	35 (18.82)	.38	19 (26.8)	8 (13.6)	8 (22.9)	0
Hematologic malignancy	46 (7.97)	40 (10.23)	6 (3.2)	.004	4 (5.6)	2 (3.4)	0	0
Liver disease	51 (8.8)	38 (9.7)	13 (6.9)	.28	3 (4.2)	3 (5.1)	6 (17.1)	1 (4.8)
Immunodeficiency	45 (7.8)	32 (8.2)	13 (6.9)	.62	4 (5.6)	4 (6.8)	4 (11.4)	1 (4.8)
Solid-organ transplantation	86 (14.9)	65 (16.6)	21 (11.3)	.09	8 (11.3)	7 (11.9)	4 (11.4)	2 (9.5)
Chronic renal failure	156 (27.1)	100 (25.6)	56 (30.1)	.25	29 (40.8)	8 (13.6)	11 (31.4)	8 (38.1)
Diabetes mellitus	130 (22.5)	79 (20.2)	51 (27.4)	.05	22 (30.9)	14 (23.7)	8 (22.9)	7 (33.3)
Neutropenia	22 (3.8)	22 (5.6)	0	.001	0	0	0	0
Charlson comorbidity index ≥3	489 (84.7)	337 (86.2)	152 (81.7)	.16	64 (90.1)	48 (81.4)	24 (68.6)	16 (76.2)
Preinfection healthcare interventions								
Previous hospital admission	372 (64.5)	251 (64.2)	121 (65.1)	.84	51 (71.8)	29 (49.1)	27 (77.1)	14 (66.7)
Surgery[a]	231 (40.1)	143 (36.6)	88 (47.3)	.01	24 (33.8)	22 (37.3)	26 (74.3)	16 (76.2)
Dialysis[a]	50 (8.7)	29 (7.4)	21 (11.3)	.12	4 (5.6)	5 (8.5)	9 (25.7)	3 (14.3)
Endoscopy[b]	42 (7.3)	27 (6.9)	15 (8.1)	.62	4 (5.6)	4 (6.8)	6 (17.1)	1 (4.8)
Mechanical ventilation[b]	162 (28.1)	108 (27.6)	54 (29.1)	.72	11 (15.5)	32 (54.2)	8 (22.8)	3 (14.3)
Indwelling devices[b]								
Central venous catheter	387 (67.1)	279 (71.4)	108 (58.1)	.001	22 (30.9)	47 (79.7)	26 (74.3)	13 (61.9)
Bladder catheter	371 (64.3)	248 (63.4)	123 (66.1)	.53	44 (61.9)	44 (74.6)	25 (71.4)	10 (47.6)
Nasogastric tube	144 (24.9)	95 (24.3)	49 (26.3)	.59	8 (11.3)	22 (37.3)	15 (42.9)	4 (19.1)
Surgical drain	145 (25.1)	89 (22.7)	56 (30.1)	.06	14 (19.7)	11 (18.6)	28 (80)	3 (14.3)
Infection characteristics								
Hospital-acquired	491 (85.1)	332 (84.9)	159 (85.5)	.86	51 (71.8)	56 (94.9)	34 (97.1)	18 (85.7)
Severity of illness[c]								
INCREMENT score ≥8	180 (31.2)	109 (27.8)	71 (38.1)	.01	12 (16.9)	27 (45.8)	25 (71.4)	7 (33.3)
Septic shock	100 (17.3)	70 (17.9)	30 (16.1)	.59	3 (4.2)	15 (25.4)	12 (34.3)	0
Ward submitting index culture								
Medical	280 (48.5)	183 (46.8)	97 (52.1)	.23	52 (73.2)	23 (38.9)	11 (31.4)	11 (52.4)
Surgical	107 (18.5)	74 (18.9)	33 (17.7)	.73	10 (14.1)	4 (6.8)	12 (34.3)	7 (33.3)
ICU	137 (23.7)	96 (24.5)	41 (22.1)	.51	4 (5.6)	27 (45.7)	9 (25.7)	1 (4.8)

Unless otherwise stated, data are expressed as n (%). Abbreviations: BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; cUTI, complicated urinary tract infection; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; LRTI, lower respiratory tract infection; nBSI, nonbacteremic infection.

[a]During the 30 days preceding infection onset.

[b]At any time during the 120 hours preceding infection onset.

[c]At infection onset.

In the multivariate analysis (Table 6), 30-day mortality was independently associated with septic shock at infection onset, neutropenia, an INCREMENT score of 8 or higher, LRTI, and CAZ-AVI dose adjustment for renal function. Administration of CAZ-AVI by prolonged infusion was a negative predictor of mortality. All predictors remained significant when the logistic regression analysis was repeated after adjustment for the propensity score for receipt of combination therapy.

DISCUSSION

Ours is the largest study published to date on real-life, postmarketing CAZ-AVI therapy for KPC-Kp infections (BSIs and nBSIs). As in all retrospective studies, the results may have been influenced by unrecognized variables with potential effects on outcome. In addition, despite the size of our cohort, an observational study cannot be a substitute for a clinical trial. Therefore, our findings and conclusions cannot provide a solid basis for recommendations for practice in clinical settings.

Table 2. Ceftazidime-Avibactam Treatment Features and Outcomes

Variable	All Infections (n = 577)	BSIs (n = 391)	All nBSIs (n = 186)	*P* Value (BSIs vs nBSIs)	nBSI Types (n = 186)			
					cUTIs (n = 71)	LRTIs (n = 59)	IAIs (n = 35)	Others (n = 21)
CAZ-AVI treatment variables								
Days of treatment, median (IQR)	12 (8–16)	12 (9–16)	12 (8–16)	.59	9 (7–14)	12 (9–15)	14 (10–27)	15 (12–21)
Started empirically	93 (16.1)	66 (16.9)	27 (14.5)	.47	7 (9.9)	15 (25.4)	3 (8.6)	2 (9.5)
Started within 48 hours of infection onset	311 (53.9)	240 (61.4)	71 (38.2)	<.001	23 (32.4)	28 (47.5)	13 (37.1)	7 (33.3)
Monotherapy regimens	165 (28.6)	113 (28.9)	52 (27.9)	.81	34 (47.9)	9 (15.2)	6 (17.1)	3 (14.3)
Combination regimens with:	412 (71.4)	278 (71.1)	134 (72.1)	.81	37 (52.1)	50 (84.7)	29 (82.9)	18 (85.7)
1 other active antimicrobial:	381 (66.1)	261 (66.7)	120 (64.5)	.59	31 (43.7)	43 (72.8)	29 (82.9)	17 (80.9)
Fosfomycin	92 (15.9)	55 (14.1)	37 (19.9)	.07	13 (18.3)	14 (23.7)	6 (17.1)	4 (19.1)
Tigecycline	80 (13.9)	49 (12.5)	31 (16.7)	.18	4 (5.6)	8 (13.6)	12 (34.3)	7 (33.3)
Gentamicin	68 (11.8)	51 (13.1)	17 (9.1)	.17	6 (8.4)	6 (10.2)	3 (8.6)	2 (9.5)
Meropenem	69 (11.9)	57 (14.6)	12 (6.4)	.005	1 (1.4)	6 (10.2)	2 (5.7)	3 (14.3)
Colistin	29 (5.1)	19 (4.9)	10 (5.4)	.79	2 (2.8)	5 (8.5)	2 (5.7)	1 (4.8)
Amikacin	25 (4.3)	20 (5.1)	5 (2.7)	.18	3 (4.2)	1 (1.7)	1 (2.9)	0
Others	18 (3.1)	10 (2.6)	8 (4.3)	.26	2 (2.8)	4 (6.8)	2 (5.7)	0
≥2 Active antimicrobials	31 (5.4)	17 (4.3)	14 (7.5)	.11	6 (8.4)	7 (11.9)	0	1 (4.8)
Dose adjusted for renal function	94 (16.3)	39 (9.9)	55 (29.6)	<.001	29 (40.8)	11 (18.6)	9 (25.7)	6 (28.6)
Prolonged infusion	246 (42.6)	162 (41.4)	84 (45.2)	.39	26 (36.6)	32 (54.2)	17 (48.6)	9 (42.8)
Outcomes[a]								
30-Day all-cause mortality	146 (25.3)	103 (26.3)	43 (23.1)	.40	13 (18.3)	22 (37.3)	7 (20.0)	1 (4.8)
Infection relapse[b]	63 (10.9)	42 (10.7)	21 (11.3)	.84	5 (7.1)	8 (13.6)	7 (20.0)	1 (4.8)
Development of in vitro CAZ-AVI resistance during treatment	20 (3.5)	14 (3.6)	6 (3.2)	.83	0	4 (6.8)	1 (2.9)	1 (4.8)
Development of in vitro CAZ-AVI resistance on infection relapse	2 (0.3)	2 (0.5)	0	.33	0	0	0	0
Adverse reactions	20 (3.4)	13 (3.3)	7 (3.8)	.79	1 (1.4)	3 (5.1)	2 (5.7)	1 (4.8)

Unless otherwise stated, data are expressed as n (%). Abbreviations: BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; cUTI, complicated urinary tract infection; IAI, intra-abdominal infection; IQR, interquartile range; LRTI, lower respiratory tract infection; nBSI, nonbacteremic infection.

[a]Assessed during the index hospitalization.

[b]Diagnosed microbiologically during the index hospitalization after the original infection had been classified as microbiologically and/or clinically cured.

Despite these limitations, our findings provide an important confirmation of the drug's previously reported efficacy as first-line [8–10] or salvage [6, 11] treatment of these infections: the overall 30-day mortality rate of 25.3% is significantly lower than rates achieved with earlier non–CAZ-AVI-based drug regimens. Moreover, in line with the findings of trials conducted for marketing authorization [21–25], CAZ-AVI therapy was associated with a low rate of adverse reactions, which required drug discontinuation in only few cases.

Interestingly, mortality was significantly higher among patients with LRTIs than in those with other types of infections, including BSIs. In previous studies, clinical success rates in CAZ-AVI–treated patients with pneumonia were also lower than those observed in patients with bacteremia [26]. The drug's pharmacokinetic properties could play a role in its relatively poor performance in cases of CRE pneumonia, although Dimelow et al [27] showed that CAZ-AVI reaches adequate concentrations in the airway epithelial lining fluid. The fact that the highest mortality rate in our cohort emerged in patients with LRTIs might well reflect, at least in part, the severity of these infections in our cohort (eg, the percentage of LRTI patients with INCREMENT scores of ≥8 was appreciably higher than that of the bacteremic subgroup).

Prior to the introduction of CAZ-AVI, combinations of 2 or more active antimicrobials were widely deemed to be superior to single-drug regimens in the treatment of CRE infections, particularly those associated with septic shock or a high mortality score [3, 14, 28–30]. In our cohort, however, even in these severe cases, no significant survival benefit was observed when CAZ-AVI was administered with another active agent. Combination regimens were associated with appreciably better survival in some patients (those with LRTI, especially ventilator-associated pneumonia, and the limited number of patients with IAIs), but none of these differences was statistically significant. These findings are consistent with those of a recent meta-analysis, which revealed similar rates of microbiologic eradication and mortality rates in patients whose CRE infections were treated with CAZ-AVI alone or with other active drugs [31]. Given the potential toxicity of certain multidrug regimens used and the hazards associated with the unnecessary use of antibiotics in general, the fact that CAZ-AVI is frequently effective when given as monotherapy should not be overlooked.

Table 3. Patient Subgroups Treated With Ceftazidime-Avibactam (CAZ-AVI) Monotherapy Versus CAZ-AVI Combination Therapy

	Combination Therapy (n = 412)	Monotherapy (n = 165)	*P* Value
Patient variables			
Males	276 (66.9)	110 (66.7)	.94
Age, median (IQR), years	66 (56–75)	65 (57–78)	.42
Comorbidities			
COPD	61 (14.8)	26 (15.7)	.77
Cardiovascular disease	181 (43.9)	84 (50.9)	.13
Cerebrovascular disease or dementia	81 (19.7)	35 (21.2)	.67
Solid tumor	82 (19.9)	39 (23.6)	.32
Hematologic malignancy	38 (9.2)	8 (4.8)	.07
Liver disease	40 (9.7)	11 (6.7)	.24
Immunodeficiency	38 (9.2)	7 (4.2)	.04
Solid-organ transplant recipient	64 (15.5)	22 (13.3)	.50
Chronic renal failure	97 (23.5)	59 (35.8)	.003
Dialysis	38 (9.2)	12 (7.2)	.45
Diabetes	100 (24.2)	30 (18.2)	.11
Neutropenia	16 (3.8)	6 (3.6)	.89
Charlson comorbidity index ≥3	339 (82.3)	150 (90.9)	.009
Ward submitting index culture			
Medical	185 (44.9)	95 (57.6)	.006
Surgical	87 (21.1)	20 (12.1)	.01
ICU	103 (25.0)	34 (20.6)	.26
Infection variables			
Hospital-acquired	357 (86.7)	134 (81.2)	.09
Bacteremic infections	278 (67.5)	113 (68.5)	.81
Primary site of bacteremia			
Urinary tract	53 (12.8)	46 (27.9)	<.001
Lower respiratory tract	60 (14.5)	26 (15.7)	.71
Surgical wound	36 (8.7)	8 (4.8)	.11
Central venous catheter	38 (9.2)	13 (7.9)	.60
Biliary tract	21 (5.1)	2 (1.2)	.03
Other	5 (1.2)	6 (3.6)	.05
Unknown	65 (15.8)	12 (7.3)	.006
Nonbacteremic infections	134 (32.5)	52 (31.5)	.81
Lower respiratory tract	50 (12.1)	9 (5.4)	.01
Intra-abdominal	29 (7.1)	6 (3.6)	.12
Urinary tract	37 (8.9)	34 (20.6)	<.001
Other	18 (4.4)	3 (1.8)	.14
Illness severity[a]			
INCREMENT score ≥8	131 (31.8)	49 (29.7)	.62
Septic shock	68 (16.5)	32 (19.4)	.41
CAZ-AVI therapy variables			
Days of therapy, median (IQR)	13 (9–17)	10 (7–13)	<.001
Started within 48 hours of onset	214 (51.9)	97 (58.7)	.14
Prolonged infusion	193 (46.8)	53 (32.1)	.001
Dose adjusted for renal function	62 (15.1)	32 (19.4)	.20
Outcomes[b]			
30-Day all-cause mortality	103 (25.0)	43 (26.1)	.79
Infection relapse[c]	50 (12.1)	13 (7.9)	.14
Development of resistance	14 (3.4)	6 (3.6)	.89
Adverse reactions	15 (3.6)	5 (3.0)	.70

Unless otherwise stated, data are expressed as n (%). Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range.

[a]At infection onset.

[b]Assessed during the index hospitalization.

[c]Diagnosed microbiologically during the index hospitalization after microbiological and/or clinical cure of the original infection.

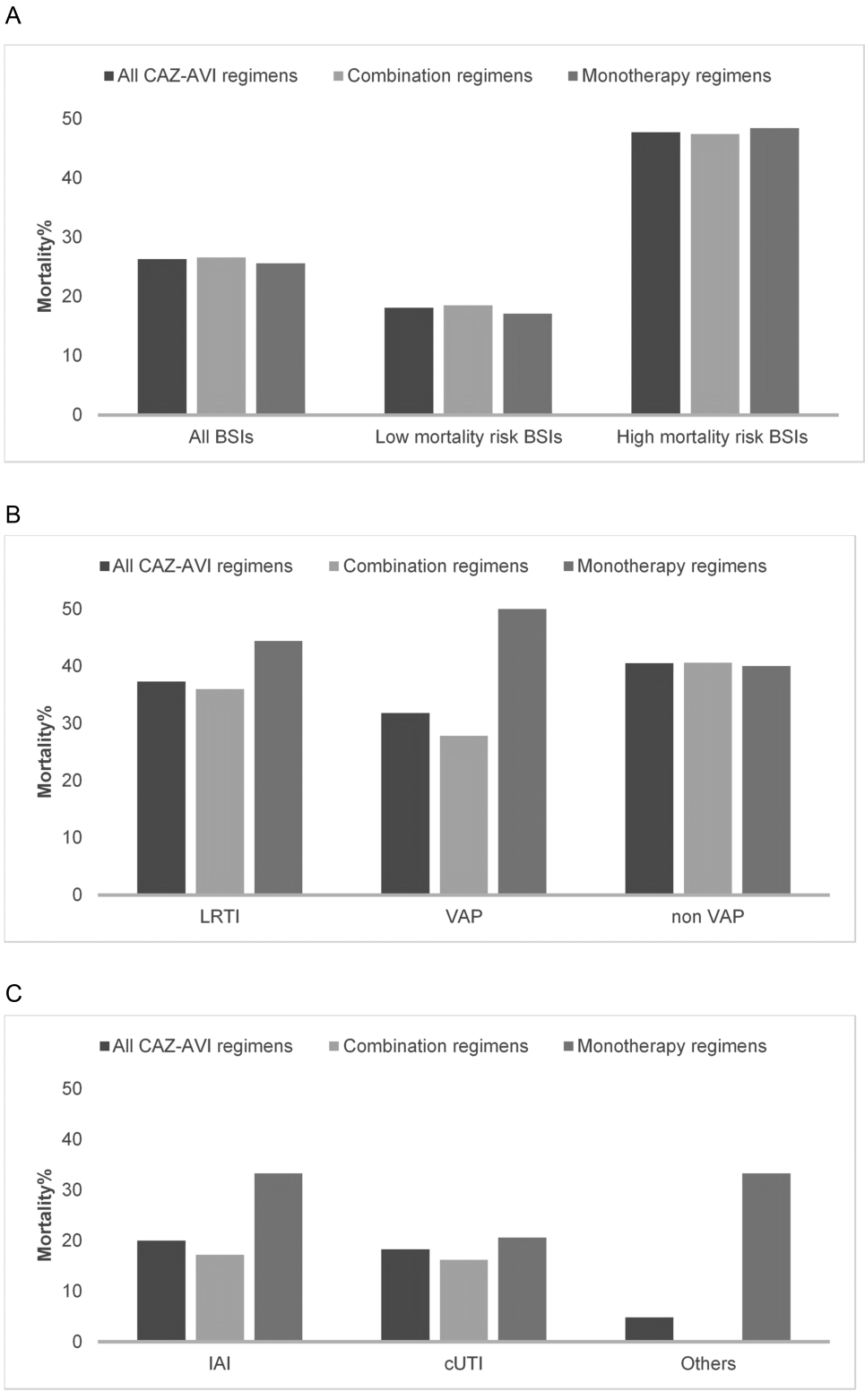

Figure 2. Thirty-day mortality rates in patients receiving CAZ-AVI monotherapy versus CAZ-AVI combination therapy. Results are shown for (*A*) patients with BSIs (n = 391) and subgroups with low (n = 282) versus high (n = 109) mortality risk (INCREMENT scores <8 vs ≥8); (*B*) patients with nBSIs involving the lower respiratory tract (LRTI; n = 59) and subgroups with VAP (n = 22) versus non-VAP (n = 37); (*C*) patients with other types of nBSI, including cUTIs (n = 71), IAIs (n = 35), and infections at other sites (n = 21). No statistically significant differences in mortality were observed between monotherapy and combination regimens in any of the analyses. Abbreviations: BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; cUTI, complicated urinary tract infection; IAI, intra-abdominal infections; LRTI, lower respiratory tract infection; nBSI, nonbacteremic infection; VAP, ventilator-associated pneumonia.

Table 4. Patient Subgroups Treated With Ceftazidime-Avibactam (CAZ-AVI) Prolonged Infusion Versus CAZ-AVI Standard Infusion

	Prolonged Infusion (n = 246)	Standard Infusion (n = 331)	*P* Value
Patient variables			
Males	167 (67.9)	219 (66.2)	.66
Age, median (IQR), years	66 (57–76)	66 (55–76)	.58
Comorbidities			
COPD	40 (16.3)	47 (14.2)	.49
Cardiovascular disease	114 (46.3)	151 (45.69)	.86
Cerebrovascular disease or dementia	49 (19.9)	67 (20.2)	.92
Solid tumor	58 (23.6)	63 (19.1)	.18
Hematologic malignancy	20 (8.1)	26 (7.8)	.90
Liver disease	29 (11.8)	22 (6.6)	.03
Immunodeficiency	13 (5.2)	32 (9.7)	.05
Solid-organ transplant recipient	35 (14.2)	51 (15.4)	.69
Chronic renal failure	55 (22.6)	101 (30.5)	.03
Dialysis	23 (9.3)	27 (8.1)	.61
Diabetes	58 (23.6)	72 (21.7)	.60
Neutropenia	9 (3.6)	13 (3.9)	.86
Charlson comorbidity index ≥3	216 (87.8)	273 (82.8)	.07
Ward submitting index culture			
Medical	110 (44.7)	170 (51.4)	.11
Surgical	37 (15.1)	70 (21.1)	.06
ICU	77 (31.3)	60 (18.1)	<.001
Infection variables			
Hospital-acquired	214 (86.9)	277 (83.7)	.27
Bacteremic infections	162 (65.8)	229 (69.2)	.39
Primary site of bacteremia			
Urinary tract	21 (8.5)	78 (23.6)	<.001
Lower respiratory tract	43 (17.5)	43 (12.9)	.13
Surgical wound	16 (6.5)	28 (8.5)	.38
Central venous catheter	27 (10.9)	24 (7.3)	.12
Biliary tract	12 (4.9)	11 (3.3)	.34
Other	3 (1.2)	8 (2.4)	.29
Unknown	40 (16.3)	37 (11.2)	.07
Nonbacteremic infections	84 (34.1)	102 (30.8)	.39
Lower respiratory tract	32 (13.1)	27 (8.2)	.05
Intra-abdominal	17 (6.9)	18 (5.4)	.46
Urinary tract	26 (10.6)	45 (13.6)	.27
Other	9 (3.7)	12 (3.7)	.98
Illness severity[a]			
INCREMENT score ≥8	89 (36.2)	91 (27.5)	.02
Septic shock	46 (18.7)	54 (16.3)	.45
CAZ-AVI therapy variables			
Days of therapy, median (IQR)	12 (8–16)	12 (8.5–23.5)	.60
Started within 48 hours of onset	131 (53.2)	180 (54.4)	.79
Combination therapy	193 (78.5)	219 (66.2)	.001
Dose adjusted for renal function	47 (19.1)	47 (14.2)	.11
Outcomes[b]			
30-Day all-cause mortality	51 (20.7)	95 (28.7)	.03
Infection relapse[c]	25 (10.2)	38 (11.9)	.61
Development of resistance	7 (2.8)	13 (3.9)	.48
Adverse reactions	9 (3.7)	11 (3.3)	.83

Unless otherwise stated, data are expressed as n (%). Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range.

[a]At infection onset.

[b]Assessed during the index hospitalization.

[c]Diagnosed microbiologically during the index hospitalization after microbiological and/or clinical cure of the original infection.

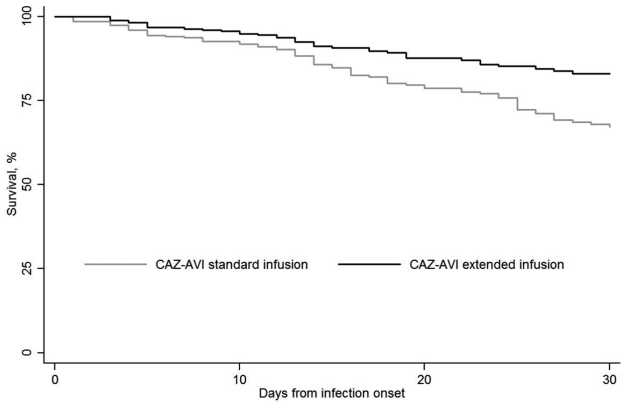

Figure 3. Kaplan-Meyer analysis of the impact of CAZ-AVI infusion times on 30-day survival. Significantly better survival was observed when CAZ-AVI was administered by prolonged infusion (standard dose given over ≥3 hours) versus standard infusion ($P < .001$). Abbreviation: CAZ-AVI, ceftazidime-avibactam.

One of our most interesting findings regarded the administration of CAZ-AVI via prolonged infusion (lasting ≥3 hours), which emerged as an independent predictor of 30-day survival. B-Lactam antibiotics are known to exhibit time-dependent killing [32], and randomized studies conducted in various patient populations have documented significantly better clinical outcomes and survival rates among patients who receive these drugs by prolonged versus standard-duration infusion [33–35]. Thus far, however, data have been lacking on the potential clinical benefits of prolonging CAZ-AVI infusions in patients with infections caused by CRE.

In contrast, our findings highlight the potentially negative impact on outcome of CAZ-AVI dose adjustments for impaired renal function, especially in patients with CRE pneumonia or IAIs, as recently suggested by other researchers [15]. Crass et al [36] recently noted that protocols for renally adjusted dosing of CAZ-AVI (and other antibiotics with wide therapeutic indices) are based largely on data obtained in individuals with stable chronic kidney disease. As such, these dosages may not be appropriate for antibiotic therapies for severe infectious events, which are frequently associated with acute kidney injury that was often transient. In light of these observations, they proposed deferral of dose adjustments within the first 48 hours of therapy as a means for improving outcomes. If dose reductions are deemed necessary, however, renal function should be promptly reassessed and standard dosing restored as soon as possible to diminish the risk of underexposure to the antibiotic.

Various groups have described the emergence during treatment of in vitro and in vivo resistance to CAZ-AVI [9, 11, 37–40]. In our cohort, in vitro resistance developed during therapy in 20 patients (3.5%). Moreover, in 2 of the 63 patients who experienced recurrent infections after an apparent clinical cure, the relapse was caused by a CAZ-AVI–resistant strain. These figures are consistent with those reported in other studies [11, 12, 26]. The appreciably higher resistance rate reported by Shields et al [26] (10%) probably reflects, at least in part, the type of infections they considered (ie, LRTIs in most of the patients vs BSIs in most of those in our cohort).

In conclusion, data on this large multicenter cohort indicate that CAZ-AVI is an important option for treating serious KPC-Kp infections, even when used alone. Further study is needed to explore factors contributing to the drug's seemingly more limited efficacy in LRTIs and the potential survival benefits in this setting of prolonging CAZ-AVI infusions to 3 hours or more.

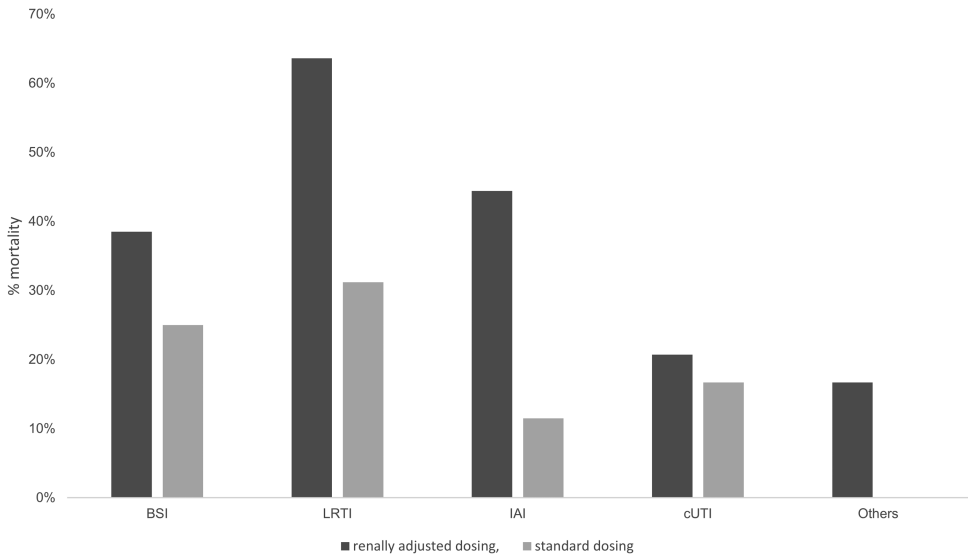

Figure 4. Impact on 30-day mortality rates of renally adjusted CAZ-AVI dosing. Statistically significant effects were observed only in subgroups with LRTI ($P = .04$) or IAI ($P = .03$). Abbreviations: BSI, bloodstream infections; CAZ-AVI, ceftazidime-avibactam; cUTI, complicated urinary tract infections; IAI, intra-abdominal infections; LRTI, lower respiratory tract infections.

Table 5. Univariate Analysis of Factors Associated With 30-Day Mortality

Variable	Nonsurvivors (n = 146; 25.3%)	Survivors (n = 431; 74.7%)	*P* Value	OR (95% CI)
Patient variables				
Males	96 (65.7)	290 (67.3)	.73	.93 (.62–1.42)
Age, median (IQR), years	70 (59–79)	64 (54–74)	<.001	…
Comorbidities				
COPD	28 (19.2)	59 (13.7)	.11	1.49 (.87–2.51)
Cardiovascular disease	79 (54.1)	186 (43.2)	.02	1.55 (1.04–2.31)
Cerebrovascular disease or dementia	39 (26.7)	77 (17.8)	.02	1.67 (1.04–2.66)
Solid tumor	23 (15.7)	98 (22.7)	.07	.67 (.37–1.06)
Hematologic malignancy	20 (13.7)	26 (6.1)	.003	2.47 (1.26–4.77)
Liver disease	17 (11.6)	34 (7.9)	.17	1.54 (.78–2.94)
Immunodeficiency	11 (7.5)	34 (7.9)	.89	.95 (.42-1.99)
Solid-organ transplantation	19 (13.1)	67 (15.5)	.46	.81 (.44–1.43)
Chronic renal failure	37 (25.3)	119 (27.6)	.59	.89 (.56–1.39)
Diabetes	38 (26.1)	92 (21.3)	.17	.63 (.30–1.28)
Neutropenia	14 (9.6)	8 (1.9)	<.001	5.61 (2.13–15.73)
Charlson comorbidity index ≥3	139 (95.2)	350 (81.2)	<.001	4.59 (2.05–12.06)
Ward submitting index culture				
Medical	60 (41.1)	220 (51.0)	.03	.67 (.45–.99)
Surgical	24 (16.4)	83 (19.3)	.45	.82 (.47–1.38)
ICU	48 (32.8)	89 (20.6)	.02	1.88 (1.21–2.90)
Preinfection healthcare interventions				
Surgery[a]	56 (38.4)	175 (40.6)	.63	.91 (.61–1.36)
Dialysis[a]	16 (10.9)	34 (7.9)	.25	1.44 (.71–2.77)
Endoscopy[b]	9 (6.2)	33 (7.7)	.55	.79 (.32–1.74)
Mechanical ventilation[b]	49 (33.6)	113 (26.2)	.09	1.42 (.92–2.17)
Indwelling devices				
Central venous catheter[b]	112 (76.7)	275 (63.8)	.04	1.86 (1.19–2.96)
Bladder catheter[b]	111 (76.1)	260 (60.3)	<.001	2.08 (1.34–3.29)
Nasogastric tube[b]	59 (40.4)	85 (19.7)	<.001	2.76 (1.79–4.22)
Surgical drain[b]	47 (32.2)	98 (22.7)	.02	1.61 (1.04–2.48)
Infection characteristics				
Hospital-acquired	133 (91.1)	358 (83.1)	.02	2.08 (1.10–4.24)
BSIs	103 (70.5)	288 (66.8)	.40	1.19 (.78–1.83)
nBSIs	43 (29.4)	143 (33.2)	.40	.84 (.54–1.28)
LRTIs	22 (15.1)	37 (8.6)	.02	1.89 (1.02–3.43)
IAIs	7 (4.8)	28 (6.5)	.46	.73 (.26–1.75)
cUTIs	13 (8.9)	58 (13.5)	.15	.63 (.31–1.21)
Other	1 (0.7)	20 (4.6)	.02	.14 (.03–.90)
Disease severity of illness[c]				
INCREMENT score ≥8	75 (51.4)	105 (24.4)	<.001	3.27 (2.17–4.94)
Septic shock	53 (36.3)	47 (10.9)	<.001	4.65 (2.88–7.51)
CAZ-AVI treatment variables				
Started empirically	20 (13.7)	73 (16.9)	.36	.78 (.43–1.35)
Started within 48 hours of infection onset	80 (54.8)	231 (53.6)	.80	1.05 (.71–1.56)
Monotherapy regimens	43 (29.5)	122 (28.3)	.79	1.06 (.68–1.62)
Combination regimens with:	103 (70.5)	309 (71.7)	.79	.94 (.61–1.47)
1 other active drug	98 (67.1)	283 (65.6)	.74	1.11 (.70–1.64)
≥2 other active drugs	5 (3.4)	26 (6.1)	.22	.55 (.16–1.50)
Dose adjusted for renal function	33 (22.6)	61 (14.1)	.01	1.77 (1.06–2.90)
Prolonged infusion	51 (34.9)	195 (45.2)	.03	.65 (.43–0.97)
Outcomes[d]				
Infection relapse[e]	21 (14.4)	42 (9.7)	.12	1.56 (.84–2.81)
Development of in vitro CAZ-AVI resistance	6 (4.1)	14 (3.2)	.60	1.28 (.39–3.62)
Adverse reactions	7 (4.8)	13 (3.1)	.31	1.62 (.53–4.46)

Data are expressed as n (%) unless otherwise stated. Abbreviations: BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; COPD, chronic obstructive pulmonary disease; cUTI, complicated urinary tract infection; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; nBSI, nonbacteremic infection; OR, odds ratio.

[a]During the 30 days preceding infection onset.

[b]During the 72 hours preceding infection onset.

[c]At infection onset.

[d]Assessed during the index hospitalization.

[e]Diagnosed microbiologically during the index hospitalization after microbiological and/or clinical cure of the original infection.

Table 6. Multivariate Analysis of Factors Associated With 30-Day Mortality

	Adjusted for the Propensity Score Matching for Combination Therapy?			
	No		Yes	
Variables	*P*	OR (95% CI)	*P*	OR (95% CI)
INCREMENT score ≥8	.01	2.06 (1.18–3.59)	.005	2.23 (1.27–3.91)
Septic shock at infection onset	.002	2.72 (1.45–5.09)	.003	2.59 (1.37–4.89)
Neutropenia	<.001	6.37 (2.42–16.74)	<.001	6.86 (2.55–18.42)
Lower respiratory tract infection	.04	1.90 (1.03–3.53)	.008	2.48 (1.26–4.86)
CAZ-AVI by prolonged infusion	.003	.52 (.34–.79)	.006	.54 (.34–.83)
CAZ-AVI dose adjustment for renal function	.001	2.39 (1.42–4.03)	.01	2.01 (1.15–3.48)

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

Notes

Financial support. This work was partially supported by a grant from the Università Cattolica del Sacro Cuore, Rome, Italy (Fondi Ateneo Linea D-1 2019).

Potential conflicts of interest. M. T. has been a scientific advisor/consultant for Angelini, Menarini; Merck, Sharp & Dohme (MSD); Nordic Pharma; Shionogi; and Roche; and a speaker/chairman at accredited educational courses funded by unrestricted grants from Astellas, Gilead, MSD, and Pfizer. M. T. reports grants from Menarini, outside the submitted work. M. V. has been a scientific advisor/consultant for Angelini, Menarini, MSD, Nordic Pharma, and Pfizer and a speaker/chairman at accredited educational courses funded by unrestricted grants from Gilead, MSD, Correvio, Angelini, ThermoFisher, Menarini, and Pfizer. F. G. D. R. has been a scientific advisor/consultant/speaker for Pfizer, MSD, Angelini, Nordic Pharma, Shionogi, Correvio, Basilea, Avir Pharma, BioTest, and ThermoFisher. F. G. D. R. reports grants from Angelini, Pfizer, Shionogi, Correvio, and ThermoFisher, outside the submitted work. M. B. has participated in advisory boards and/or received speaker honoraria or study grants from Angelini, Astellas, Bayer, Basilea, BioMérieux, Cidara, Gilead, Menarini, MSD, Nabriva, Pfizer, Roche, and Shionogi. P. A. G. reports personal fees from MSD, Biotest, Angelini, Nordic Pharma, Vertex, Gilead, and Astellas. M. F. received speaker honoraria or research grants from MSD, Pfizer, Shionogi, Angelini, Nordic Pharma, and Menarini Farmaceutica. C. T. has received research grants and/or been a consultant and/or received a fee for speaking from bioMérieux, Zambon, Basilea, MSD, Nordic Pharma, Angelini, ThermoFisher, Biotest, Pfizer, AstraZeneca, Shionogi, Hikma, Avir Pharma, and Biotest. P. V. has received honoraria from Pfizer, MSD, and Shionogi for participating in accredited educational activities and from Pfizer, Shionogi, and Gilead for coordinating or attending research projects. All other authors report no potential conflicts. 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. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev **2018**; 31:2.
2. Giacobbe DR, Del Bono V, Trecarichi EM, et al.; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Risk factors for bloodstream infections due to colistin-resistant KPC-producing Klebsiella pneumoniae: results from a multicenter case-control-control study. Clin Microbiol Infect **2015**; 21:1106.e1–8.
3. Tumbarello M, Trecarichi EM, De Rosa FG, et al.; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother **2015**; 70:2133–43.
4. Trecarichi EM, Tumbarello M. Therapeutic options for carbapenem-resistant Enterobacteriaceae infections. Virulence **2017**; 8:470–84.
5. Bassetti M, Giacobbe DR, Giamarellou H, et al.; Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing Klebsiella pneumoniae infections. Clin Microbiol Infect **2018**; 24:133–44.
6. Temkin E, Torre-Cisneros J, Beovic B, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother **2017**; 61:2.
7. Alraddadi BM, Saeedi M, Qutub M, Alshukairi A, Hassanien A, Wali G. Efficacy of ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. BMC Infect Dis **2019**; 19:772.
8. 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 **2017**; 61:8.
9. 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.
10. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Real-world experience with ceftazidime-avibactam for multidrug-resistant gram-negative bacterial infections. Open Forum Infect Dis **2019**; 6:ofz522.
11. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Clin Infect Dis **2019**; 68:355–64.
12. Tsolaki V, Mantzarlis K, Mpakalis A, et al. Ceftazidime-avibactam to treat life-threatening infections by carbapenem-resistant pathogens in critically ill mechanically ventilated patients. Antimicrob Agents Chemother. **2020**; 64:e02320-19.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
14. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al.; REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis **2017**; 17:726–34.
15. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Evaluation of the INCREMENT-CPE, Pitt Bacteremia and qPitt scores in patients with carbapenem-resistant Enterobacteriaceae infections treated with ceftazidime-avibactam. Infect Dis Ther **2020**; 9:291–304.
16. Henderson H, Luterbach CL, Cober E, et al. The Pitt Bacteremia score predicts mortality in nonbacteremic infections. Clin Infect Dis **2020**; 70:1826–33.
17. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med **2017**; 43:304–77.
18. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0. **2020**. Available at: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_10.0_Breakpoint_Tables.pdf. Accessed 30 November 2020.
19. European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. Version 2.0. July **2017**. Available at: https://eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_170711.pdf. Accessed 30 November 2020.
20. European Medicines Agency (EMA). European Public Assessment Report (EPAR) for Zavicefta, product information. Last update 20 November 2020.

Available at: https://www.ema.europa.eu/en/documents/product-information/zavicefta-epar-product-information_en.pdf. Accessed 23 November 2020.
21. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis **2018**; 18:285–95.
22. Vazquez JA, González Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin **2012**; 28:1921–31.
23. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. J Antimicrob Chemother **2013**; 68:1183–92.
24. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis **2016**; 62:1380–9.
25. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis **2016**; 63:754–62.
26. Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. 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.
27. Dimelow R, Wright JG, MacPherson M, Newell P, Das S. Population pharmacokinetic modelling of ceftazidime and avibactam in the plasma and epithelial lining fluid of healthy volunteers. Drugs R D **2018**; 18:221–30.
28. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis **2012**; 55:943–50.
29. Giannella M, Trecarichi EM, Giacobbe DR, et al.; Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva (ISGRI-SITA). Effect of combination therapy containing a high-dose carbapenem on mortality in patients with carbapenem-resistant Klebsiella pneumoniae bloodstream infection. Int J Antimicrob Agents **2018**; 51:244–8.
30. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother **2014**; 58:2322–8.
31. Onorato L, Di Caprio G, Signoriello S, Coppola N. Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant gram-negative bacteria: a meta-analysis. Int J Antimicrob Agents **2019**; 54:735–40.
32. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am **2003**; 17:479–501.
33. Chytra I, Stepan M, Benes J, et al. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. Crit Care **2012**; 16:R113.
34. Abdul-Aziz MH, Lipman J, Akova M, et al.; DALI Study Group. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. J Antimicrob Chemother **2016**; 71:196–207.
35. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis **2018**; 18:108–20.
36. Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal dosing of antibiotics: are we jumping the gun? Clin Infect Dis **2019**; 68:1596–602.
37. 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.
38. Shields RK, Chen L, Cheng S, et al. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant Klebsiella pneumoniae infections. Antimicrob Agents Chemother **2017**; 61(3):e02097-16.
39. Livermore DM, Warner M, Jamrozy D, et al. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. Antimicrob Agents Chemother **2015**; 59:5324–30.
40. Haidar G, Clancy CJ, Shields RK, Hao B, Cheng S, Nguyen MH. Mutations in blaKPC-3 that confer ceftazidime-avibactam resistance encode novel KPC-3 variants that function as extended-spectrum β-lactamases. Antimicrob Agents Chemother **2017**; 61:e02534-16.