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

Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study

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Summary: We retrospectively analyzed observational data on the use and outcomes of CAZ-AVI therapy for infections caused by KPC-Kp in 22 hospitals in Italy. CAZ-AVI appears to be an important drug for treatment of serious KPC-Kp infections, even when used alone.

ABSTRACT

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

Methods. We retrospectively analyzed observational data on the use and outcomes of CAZ-AVI therapy for infections caused by KPC-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 vs. CAZ-AVI monotherapy.

Results. The cohort comprised 577 adults with bloodstream infections (BSIs) (n=391) or non-bacteremic infections (nBSIs) involving mainly the urinary tract, lower respiratory tract, intra-abdominal structures. All received treatment with CAZ-AVI alone (n=165) or with one or more other active antimicrobials (n=412). The all-cause mortality rate 30 days after infection onset was 25% (146/577). There was no statistically significant difference in mortality between patients managed with CAZ-AVI alone and those treated with combination regimens (26.1% vs. 25.0%, P=0.79). In multivariate analysis, mortality was positively associated with the presence at infection onset of septic shock (P=0.002), neutropenia (P <0.001), or an INCREMENT score $\geq$8 (P=0.01); with LRTI (P=0.04); and with CAZ-AVI dose adjustment for renal function (P=0.01). Mortality was negatively associated

with CAZ-AVI administration by prolonged infusion (P=0.006). 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 the potential survival benefits of prolonging CAZ-AVI infusions to 3 hours or more.

Keywords: ceftazidime-avibactam; carbapenemases; KPC-producing Klebsiella pneumoniae

INTRODUCTION

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 associated with strikingly high mortality rates [1-5].

Ceftazidime-avibactam (CAZ-AVI) combines the third-generation cephalosporin, ceftazidime, with avibactam, a novel synthetic beta-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 post-marketing use and outcomes of CAZ-AVI therapy for infections caused by KPC-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 enrolment

The study involved retrospective analysis of observational data on inpatients in 22 Italian hospitals (academic and non-academic) 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 enrolment

met all of the following criteria: 1) age ≥18 years at hospital admission; 2) culture-documented monomicrobial KPC-Kp infection; and 3) ≥ 72 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 co-morbidity 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, i.e., 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 CPE score (*low* [<8 points]) vs. *high* [≥8 points]) [14-16] and the presence or absence of septic shock (i.e., sepsis associated with organ dysfunction and persistent hypotension despite volume replacement) [17]. Infections were considered *hospital-acquired* if the index culture was collected > 48 h 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 one or more other sites). KPC-Kp infections were considered *non-BSIs* (nBSIs) if 1) the causative isolate had been recovered from cultures of urine, intra-abdominal wounds, sputum, bronchoalveolar lavage fluid, or other non-blood 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).

CAZ-AVI treatment and outcomes

CAZ-AVI 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-h period. In some cases, however, the recommended dosage was given by prolonged infusion (lasting $\geq$ 3 h). CAZ-AVI treatment regimens classified as *combination therapy* included at least one 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 outpatients 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 (SD) or medians and interquartile ranges (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 non-normally distributed continuous variables, respectively. Categorical variables were evaluated with the chi-square or two-tailed Fisher exact test.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all associations that emerged. Two-tailed tests were used to determine statistical significance reflected by a *P* value of <0.05. Multivariate logistic regression analysis was used to identify independent risk factors for 30-day mortality. Variables emerging from univariate analysis with *P* values of <0.1 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 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.

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 h 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 one out of four was identified during an ICU stay. Over two thirds of the infections (n=391, 67.8%) were BSIs. The 186 nonBSIs (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 ≥ 8 (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. At treatment outset, all isolates displayed in vitro susceptibility to CAZ-AVI with MICs range 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 one out of four 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]. CAZ-AVI was started within 48 h 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 >3, and 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%) of those with LRTIs, 1 (2.9%) of those with IAIs, and 1 (4.8%) of those with other non-BSIs), 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 ≥ 16 µg/mL. 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). Sixty-three (15%) of the 420 patients considered cured (42 with BSIs, 8 with LRTI, 7 with IAI, 5 with cUTIs, and one 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 ≥ 16 µg/mL, and the new infection was treated with colistin + fosfomycin. No statistically significant relationship was observed between relapse and the use of CAZ-AVI monotherapy- vs. 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), those with LRTIs (37.3%, 22/59), and 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=0.79) 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 vs. 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 CAZ-AVI.

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 Charlson comorbidity index >3, and to have an indwelling CVC, 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 a 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 health care-associated (rather than hospital-acquired); classified as "low-mortality" based on the INCREMENT score <8; and treated with CAZ-AVI administered by prolonged rather than standard infusion.

In the multivariate analysis (**Table 6**), 30-day mortality was independently associated with septic shock at infection onset, neutropenia, INCREMENT score ≥8, 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, post-marketing CAZ-AVI therapy for KPC-Kp infections (BSI and nBSI). 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.

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. showed that CAZ-AVI reaches adequate concentrations in the airway epithelial lining fluid [27]. 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 (e.g., 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 two 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 VAPs, 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 multi-drug 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.

One of our most interesting findings regarded the administration of CAZ-AVI via prolonged infusion (lasting 3 hours or more), which emerged as an independent predictor of 30-day survival. Beta-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 vs. 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 intra-abdominal infections, as recently suggested by other researchers [15].

Crass et al. 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 h of therapy as a means for improving outcomes [36]. 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. (10%) [26] probably reflects, at least in part, the type of infections they considered (i.e., 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.

NOTES

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Conflict of interest.

MT has been scientific advisor/consultant for Angelini, Menarini, MSD, Nordic Pharma, Shionogi, and Roche, and speaker/chairman at accredited educational courses funded by unrestricted grants from Astellas, Gilead, MSD, and Pfeizer. MT reports grants from Menarini, outside the submitted work. MV has been scientific advisor/consultant for Angelini, Menarini, MSD, Nordic Pharma, Pfizer and speaker/chairman at accredited educational courses funded by unrestricted grants from Gilead, MSD, Correvio, Angelini, Thermo Fisher, Menarini and Pfizer. FDR has been scientific advisor/consultant/speaker for Pfizer, MSD, Angelini, Nordic Pharma, Shionogi, Correvio, Basilea, Avir Pharma, BioTest, ThermoFisher. FDR reports grants from Angelini, Pfizer, Shionogi, Correvio, and ThermoFisher, outside the submitted work. MB 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. PAG reports personal fees from Merck, Sharp & Dohme, Biotest, Angelini, Nordic Pharma, Vertex, Gilead, Astellas. M. Falcone received speaker honoraria or research grant from MSD, Pfizer, Shionogi, Angelini, Nordic Pharma, Menarini Farmaceutica. CT has received research grants, and/or been a consultant and/or received a fee for speaking from bioMérieux, Zambon, Basilea, Merck, Nordic Pharma, Angelini, Thermo Fisher, Biotest, Pfizer, Astra Zeneca, Shionogi, Hikma, Avir Pharma, Biotest. PV has received honoraria from Pfizer, MSD, Shionogi for participating in accredited educational activities and from Pfizer, Shionogi, Gilead for coordinating or attending research projects. All other authors declare no conflict of interest.

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Table 1. Characteristics of patients with CAZ-AVI-treated monomicrobial KPC-Kp infections.

	All infections (n=577)	BSIs (n=391)	All nBSIs (n=186)	P value (BSI vs nBSI)	nBSI types n=186)			
bbbVariable					cUTIs (n=71)	LRTIs (n=59)	IAIs (n=35)	Others (n= 21)
Patient variables								
Males	386 (66.9)	277 (70.8)	109 (58.6)	**0.003**	35 (49.3)	42 (71.2)	21 (60)	11 (52.4)
Age - median (IQR)	66 (56-76)	65 (56-75)	66 (56-78)	0.57	65 (56-75)	63 (56-77)	63 (48-76)	67 (59-75)
Comorbidities								
COPD	87 (15.1)	61 (15.6)	26 (13.9)	0.61	7 (9.9)	11 (18.6)	3 (8.6)	5 (23.8)
Cardiovascular disease	265 (45.9)	179 (45.8)	86 (46.2)	0.92	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)	**0.005**	23 (32.4)	19 (32.2)	3 (8.6)	5 (23.8)
Solid tumor	121 (20.97)	86 (21.99)	35 (18.82)	0.38	19 (26.8)	8 (13.6)	8 (22.9)	0
Hematologic malignancy	46 (7.97)	40 (10.23)	6 (3.2)	**0.004**	4 (5.6)	2 (3.4)	0	0
Liver disease	51 (8.8)	38 (9.7)	13 (6.9)	0.28	3 (4.2)	3 (5.1)	6 (17.1)	1 (4.8)
Immunodeficiency	45 (7.8)	32 (8.2)	13 (6.9)	0.62	4 (5.6)	4 (6.8)	4 (11.4)	1 (4.8)
Solid organ transplantation	86 (14.9)	65 (16.6)	21 (11.3)	0.09	8 (11.3)	7 (11.9)	4 (11.4)	2 (9.5)
Chronic renal failure	156 (27.1)	100 (25.6)	56 (30.1)	0.25	29 (40.8)	8 (13.6)	11 (31.4)	8 (38.1)
Diabetes mellitus	130 (22.5)	79 (20.2)	51 (27.4)	0.05	22 (30.9)	14 (23.7)	8 (22.9)	7 (33.3)
Neutropenia	22 (3.8)	22 (5.6)	0	**0.001**	0	0	0	0
Charlson Comorbidity Index ≥	489 (84.7)	337 (86.2)	152 (81.7)	0.16	64 (90.1)	48 (81.4)	24 (68.6)	16 (76.2)

Pre-infection healthcare interventions								
Previous hospital admission	372 (64.5)	251 (64.2)	121 (65.1)	0.84	51 (71.8)	29 (49.1)	27 (77.1)	14 (66.7)
Surgery [a]	231 (40.1)	143 (36.6)	88 (47.3)	0.01	24 (33.8)	22 (37.3)	26 (74.3)	16 (76.2)
Dialysis [a]	50 (8.7)	29 (7.4)	21 (11.3)	0.12	4 (5.6)	5 (8.5)	9 (25.7)	3 (14.3)
Endoscopy [b]	42 (7.3)	27 (6.9)	15 (8.1)	0.62	4 (5.6)	4 (6.8)	6 (17.1)	1 (4.8)
Mechanical ventilation [b]	162 (28.1)	108 (27.6)	54 (29.1)	0.72	11 (15.5)	32 (54.2)	8 (22.8)	3 (14.3)
Indwelling devices								
Central venous catheter [b]	387 (67.1)	279 (71.4)	108 (58.1)	0.001	22 (30.9)	47 (79.7)	26 (74.3)	13 (61.9)
Bladder catheter [b]	371 (64.3)	248 (63.4)	123 (66.1)	0.53	44 (61.9)	44 (74.6)	25 (71.4)	10 (47.6)
Nasogastric tube [b]	144 (24.9)	95 (24.3)	49 (26.3)	0.59	8 (11.3)	22 (37.3)	15 (42.9)	4 (19.1)
Surgical drain [b]	145 (25.1)	89 (22.7)	56 (30.1)	0.06	14 (19.7)	11 (18.6)	28 (80)	3 (14.3)
Infection characteristics								
Hospital-acquired	491 (85.1)	332 (84.9)	159 (85.5)	0.86	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)	0.01	12 (16.9)	27 (45.8)	25 (71.4)	7 (33.3)
Septic shock	100 (17.3)	70 (17.9)	30 (16.1)	0.59	3 (4.2)	15 (25.4)	12 (34.3)	0
Ward submitting index culture								
Medical	280 (48.5)	183 (46.8)	97 (52.1)	0.23	52 (73.2)	23 (38.9)	11 (31.4)	11 (52.4)
Surgical	107 (18.5)	74 (18.9)	33 (17.7)	0.73	10 (14.1)	4 (6.8)	12 (34.3)	7 (33.3)

ICU	137 (23.7)	96 (24.5)	41 (22.1)	0.51	4 (5.6)	27 (45.7)	9 (25.7)	1 (4.8)

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; nBSI, non-bacteremic infection;

Unless otherwise stated, data are expressed as numbers (%).

[a] During the 30 days preceding infection onset.

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

[c] At infection onset

Table 2. CAZ-AVI 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)	0.59	9 (7-14)	12 (9-15)	14 (10-27)	15 (12-21)
Started empirically	93 (16.1)	66 (16.9)	27 (14.5)	0.47	7 (9.9)	15 (25.4)	3 (8.6)	2 (9.5)
Started within 48 h of infection onset	311 (53.9)	240 (61.4)	71 (38.2)	<0.001	23 (32.4)	28 (47.5)	13 (37.1)	7 (33.3)
Monotherapy regimens	165 (28.6)	113 (28.9)	52 (27.9)	0.81	34 (47.9)	9 (15.2)	6 (17.1)	3 (14.3)
Combination regimens with:	412 (71.4)	278 (71.1)	134 (72.1)	0.81	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)	0.59	31 (43.7)	43 (72.8)	29 (82.9)	17 (80.9)
Fosfomycin	92 (15.9)	55 (14.1)	37 (19.9)	0.07	13 (18.3)	14 (23.7)	6 (17.1)	4 (19.1)
Tigecycline	80 (13.9)	49 (12.5)	31 (16.7)	0.18	4 (5.6)	8 (13.6)	12 (34.3)	7 (33.3)
Gentamicin	68 (11.8)	51 (13.1)	17 (9.1)	0.17	6 (8.4)	6 (10.2)	3 (8.6)	2 (9.5)
Meropenem	69 (11.9)	57 (14.6)	12 (6.4)	0.005	1 (1.4)	6 (10.2)	2 (5.7)	3 (14.3)
Colistin	29 (5.1)	19 (4.9)	10 (5.4)	0.79	2 (2.8)	5 (8.5)	2 (5.7)	1 (4.8)
Amikacin	25 (4.3)	20 (5.1)	5 (2.7)	0.18	3 (4.2)	1 (1.7)	1 (2.9)	0
Others	18 (3.1)	10 (2.6)	8 (4.3)	0.26	2 (2.8)	4 (6.8)	2 (5.7)	0
≥2 active antimicrobials	31 (5.4)	17 (4.3)	14 (7.5)	0.11	6 (8.4)	7 (11.9)	0	1 (4.8)

Dose adjusted for renal function	94 (16.3)	39 (9.9)	55 (29.6)	<0.001	29 (40.8)	11 (18.6)	9 (25.7)	6 (28.6)
Prolonged infusion	246 (42.6)	162 (41.4)	84 (45.2)	0.39	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)	0.40	13 (18.3)	22 (37.3)	7 (20.0)	1 (4.8)
Infection relapse [b]	63 (10.9)	42 (10.7)	21 (11.3)	0.84	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)	0.83	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	0.33	0	0	0	0
Adverse reactions	20 (3.4)	13 (3.3)	7 (3.8)	0.79	1 (1.4)	3 (5.1)	2 (5.7)	1 (4.8)

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; nBSI, non-bacteremic infection;

Unless otherwise stated, data are expressed as numbers (%).

[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

Table 3. Patient subgroups treated with CAZ-AVI monotherapy vs. CAZ-AVI combination therapy

	Combination therapy (n=412)	Monotherapy (n=165)	*P* value
Patient variables			
Males	276 (66.9)	110 (66.7)	0.94
Age - *median (IQR)*	66 (56-75)	65 (57-78)	0.42
Comorbidities			
COPD	61 (14.8)	26 (15.7)	0.77
Cardiovascular disease	181 (43.9)	84 (50.9)	0.13
Cerebrovascular disease or dementia	81 (19.7)	35 (21.2)	0.67
Solid tumor	82 (19.9)	39 (23.6)	0.32
Hematologic malignancy	38 (9.2)	8 (4.8)	0.07
Liver disease	40 (9.7)	11 (6.7)	0.24
Immunodeficiency	38 (9.2)	7 (4.2)	0.04
Solid organ transplant recipient	64 (15.5)	22 (13.3)	0.50
Chronic renal failure	97 (23.5)	59 (35.8)	0.003
Dialysis	38 (9.2)	12 (7.2)	0.45
Diabetes	100 (24.2)	30 (18.2)	0.11
Neutropenia	16 (3.8)	6 (3.6)	0.89
Charlson Comorbidity Index ≥ 3	339 (82.3)	150 (90.9)	0.009
Ward submitting index culture			
Medical	185 (44.9)	95 (57.6)	0.006
Surgical	87 (21.1)	20 (12.1)	0.01
ICU	103 (25.0)	34 (20.6)	0.26
Infection variables			
Hospital-acquired	357 (86.7)	134 (81.2)	0.09
Bacteremic infections	278 (67.5)	113 (68.5)	0.81
Primary site of bacteremia:			
Urinary tract	53 (12.8)	46 (27.9)	<0.001
Lower respiratory tract	60 (14.5)	26 (15.7)	0.71
Surgical wound	36 (8.7)	8 (4.8)	0.11

Central venous catheter	38 (9.2)	13 (7.9)	0.60
Biliary tract	21 (5.1)	2 (1.2)	0.03
Other	5 (1.2)	6 (3.6)	0.05
Unknown	65 (15.8)	12 (7.3)	0.006
Non-bacteremic infections	134 (32.5)	52 (31.5)	0.81
Lower respiratory tract	50 (12.1)	9 (5.4)	0.01
Intra-abdominal	29 (7.1)	6 (3.6)	0.12
Urinary tract	37 (8.9)	34 (20.6)	<0.001
Other	18 (4.4)	3 (1.8)	0.14
Illness severity [a]			
INCREMENT Score ≥ 8	131 (31.8)	49 (29.7)	0.62
Septic shock	68 (16.5)	32 (19.4)	0.41
CAZ-AVI therapy variables			
Days of therapy - *median (IQR)*	13 (9-17)	10 (7-13)	<0.001
Started within 48 hours of onset	214 (51.9)	97 (58.7)	0.14
Prolonged infusion	193 (46.8)	53 (32.1)	0.001
Dose adjusted for renal function	62 (15.1)	32 (19.4)	0.20
Outcomes [b]			
30-day all-cause mortality	103 (25.0)	43 (26.1)	0.79
Infection relapse [c]	50 (12.1)	13 (7.9)	0.14
Development of resistance	14 (3.4)	6 (3.6)	0.89
Adverse reactions	15 (3.6)	5 (3.0)	0.70

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range.

Unless otherwise stated, data are expressed as numbers (%).

[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

Table 4. Patient subgroups treated with CAZ-AVI prolonged infusion vs. CAZ-AVI standard infusion

	Prolonged infusion (n=246)	Standard infusion (n=331)	*P* value
Patient variables			
Males	167 (67.9)	219 (66.2)	0.66
Age - *median (IQR)*	66 (57-76)	66 (55-76)	0.58
Comorbidities			
COPD	40 (16.3)	47 (14.2)	0.49
Cardiovascular disease	114 (46.3)	151 (45.69)	0.86
Cerebrovascular disease or dementia	49 (19.9)	67 (20.2)	0.92
Solid tumor	58 (23.6)	63 (19.1)	0.18
Hematologic malignancy	20 (8.1)	26 (7.8)	0.90
Liver disease	29 (11.8)	22 (6.6)	0.03
Immunodeficiency	13 (5.2)	32 (9.7)	0.05
Solid organ transplant recipient	35 (14.2)	51 (15.4)	0.69
Chronic renal failure	55 (22.6)	101 (30.5)	0.03
Dialysis	23 (9.3)	27 (8.1)	0.61
Diabetes	58 (23.6)	72 (21.7)	0.60
Neutropenia	9 (3.6)	13 (3.9)	0.86
Charlson Comorbidity Index ≥ 3	216 (87.8)	273 (82.8)	0.07
Ward submitting index culture			
Medical	110 (44.7)	170 (51.4)	0.11
Surgical	37 (15.1)	70 (21.1)	0.06
ICU	77 (31.3)	60 (18.1)	<0.001
Infection variables			
Hospital-acquired	214 (86.9)	277 (83.7)	0.27
Bacteremic infections	162 (65.8)	229 (69.2)	0.39
Primary site of bacteremia:			
Urinary tract	21 (8.5)	78 (23.6)	<0.001
Lower respiratory tract	43 (17.5)	43 (12.9)	0.13
Surgical wound	16 (6.5)	28 (8.5)	0.38

Central venous catheter	27 (10.9)	24 (7.3)	0.12
Biliary tract	12 (4.9)	11 (3.3)	0.34
Other	3 (1.2)	8 (2.4)	0.29
Unknown	40 (16.3)	37 (11.2)	0.07
Non-bacteremic infections	84 (34.1)	102 (30.8)	0.39
Lower respiratory tract	32 (13.1)	27 (8.2)	0.05
Intra-abdominal	17 (6.9)	18 (5.4)	0.46
Urinary tract	26 (10.6)	45 (13.6)	0.27
Other	9 (3.7)	12 (3.7)	0.98
Illness severity [a]			
INCREMENT Score $\geq$ 8	89 (36.2)	91 (27.5)	0.02
Septic shock	46 (18.7)	54 (16.3)	0.45
CAZ-AVI therapy variables			
Days of therapy - *median (IQR)*	12 (8-16)	12 (8.5-23.5)	0.60
Started within 48 hours of onset	131 (53.2)	180 (54.4)	0.79
Combination therapy	193 (78.5)	219 (66.2)	0.001
Dose adjusted for renal function	47 (19.1)	47 (14.2)	0.11
Outcomes [b]			
30-day all-cause mortality	51 (20.7)	95 (28.7)	0.03
Infection relapse [c]	25 (10.2)	38 (11.9)	0.61
Development of resistance	7 (2.8)	13 (3.9)	0.48
Adverse reactions	9 (3.7)	11 (3.3)	0.83

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range.

Unless otherwise stated, data are expressed as numbers (%).

[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

Table 5. Univariate analysis of factors associated with 30-day mortality

Variable	No. (%) of patients		*P* value	OR (95% CI)
	Non-survivors n=146 (25.3)	Survivors n=431 (74.7)		
Patient variables				
Male	96 (65.7)	290 (67.3)	0.73	0.93 (0.62-1.42)
Age - *median (IQR)*	70 (59-79)	64 (54-74)	<0.001	-
Comorbidities				
COPD	28 (19.2)	59 (13.7)	0.11	1.49 (0.87-2.51)
Cardiovascular disease	79 (54.1)	186 (43.2)	0.02	1.55 (1.04-2.31)
Cerebrovascular disease or dementia	39 (26.7)	77 (17.8)	0.02	1.67 (1.04-2.66)
Solid tumor	23 (15.7)	98 (22.7)	0.07	0.67 (0.37-1.06)
Hematologic malignancy	20 (13.7)	26 (6.1)	0.003	2.47 (1.26-4.77)
Liver disease	17 (11.6)	34 (7.9)	0.17	1.54 (0.78-2.94)
Immunodeficiency	11 (7.5)	34 (7.9)	0.89	0.95 (.42-1.99)
Solid organ transplantation	19 (13.1)	67 (15.5)	0.46	0.81 (0.44-1.43)
Chronic renal failure	37 (25.3)	119 (27.6)	0.59	0.89 (0.56-1.39)
Diabetes	38 (26.1)	92 (21.3)	0.17	0.63 (0.30-1.28)
Neutropenia	14 (9.6)	8 (1.9)	<0.001	5.61 (2.13-15.73)
Charlson Comorbidity Index ≥ 3	139 (95.2)	350 (81.2)	<0.001	4.59 (2.05-12.06)
Ward submitting index culture				
Medical	60 (41.1)	220 (51.0)	0.03	0.67 (0.45-0.99)
Surgical	24 (16.4)	83 (19.3)	0.45	0.82 (0.47-1.38)
ICU	48 (32.8)	89 (20.6)	0.02	1.88 (1.21-2.90)
Pre-infection healthcare interventions				
Surgery[a]	56 (38.4)	175 (40.6)	0.63	0.91 (0.61-1.36)
Dialysis[a]	16 (10.9)	34 (7.9)	0.25	1.44 (0.71-2.77)
Endoscopy[b]	9 (6.2)	33 (7.7)	0.55	0.79 (0.32-1.74)
Mechanical ventilation[b]	49 (33.6)	113 (26.2)	0.09	1.42 (0.92-2.17)
Indwelling devices				
Central venous catheter [b]	112 (76.7)	275 (63.8)	0.04	1.86 (1.19-2.96)
Bladder catheter [b]	111 (76.1)	260 (60.3)	<0.001	2.08 (1.34-3.29)
Nasogastric tube [b]	59 (40.4)	85 (19.7)	<0.001	2.76 (1.79-4.22)
Surgical drain [b]	47 (32.2)	98 (22.7)	0.02	1.61 (1.04-2.48)
Infection characteristics				

Hospital-acquired	133 (91.1)	358 (83.1)	0.02	2.08 (1.10-4.24)
BSIs	103 (70.5)	288 (66.8)	0.40	1.19 (0.78-1.83)
nBSIs	43 (29.4)	143 (33.2)	0.40	0.84 (0.54-1.28)
LRTIs	22 (15.1)	37 (8.6)	0.02	1.89 (1.02-3.43)
IAIs	7 (4.8)	28 (6.5)	0.46	0.73 (0.26-1.75)
cUTIs	13 (8.9)	58 (13.5)	0.15	0.63 (0.31-1.21)
Other	1 (0.7)	20 (4.6)	0.02	0.14 (0.03- 0.90)
Disease severity of illness[c]				
INCREMENT score ≥8	75 (51.4)	105 (24.4)	<0.001	3.27 (2.17-4.94)
Septic shock	53 (36.3)	47 (10.9)	<0.001	4.65 (2.88-7.51)
CAZ-AVI treatment variables				
Started empirically	20 (13.7)	73 (16.9)	0.36	0.78 (0.43-1.35)
Started within 48 hours of infection onset	80 (54.8)	231 (53.6)	0.80	1.05 (0.71-1.56)
Monotherapy regimens	43 (29.5)	122 (28.3)	0.79	1.06 (0.68-1.62)
Combination regimens with:	103 (70.5)	309 (71.7)	0.79	0.94 (0.61-1.47)
1 other active drug	98 (67.1)	283 (65.6)	0.74	1.11 (0.70-1.64)
≥2 other active drug	5 (3.4)	26 (6.1)	0.22	0.55 (0.16-1.50)
Dose adjusted for renal function	33 (22.6)	61 (14.1)	0.01	1.77 (1.06-2.90)
Prolonged infusion	51 (34.9)	195 (45.2)	0.03	0.65 (0.43-0.97)
Outcomes [d]				
Infection relapse [e]	21 (14.4)	42 (9.7)	0.12	1.56 (0.84-2.81)
Development of *in vitro* CAZ-AVI resistance	6 (4.1)	14 (3.2)	0.60	1.28 (0.39-3.62)
Adverse reactions	7 (4.8)	13 (3.1)	0.31	1.62 (0.53-4.46)

Abbreviations: BSI, bloodstream infection; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; cUTI, complicated urinary tract infection; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; nBSI, non-bacteremic infection; NA, not applicable; OR, odds ratio.

Data are expressed as numbers (%) unless otherwise stated.

[a] During the 30 days preceding infection onset.

[b] During the 72 h 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* value	OR (95% CI)	*P* value	OR (95% CI)
INCREMENT score ≥8	0.01	2.06 (1.18-3.59)	0.005	2.23 (1.27-3.91)
Septic shock at infection onset	0.002	2.72 (1.45-5.09)	0.003	2.59 (1.37-4.89)
Neutropenia	<0.001	6.37 (2.42-16.74)	<0.001	6.86 (2.55-18.42)
Lower respiratory tract infection	0.04	1.90 (1.03-3.53)	0.008	2.48 (1.26-4.86)
CAZ-AVI by prolonged infusion	0.003	0.52 (0.34-0.79)	0.006	0.54 (0.34-0.83)
CAZ AVI dose adjustment for renal function	0.001	2.39 (1.42-4.03)	0.01	2.01 (1.15-3.48)

Abbreviations: CI, confidence interval; OR, odds ratio

Figure legends:

Figure 1. Flow chart showing cohort enrolment

Figure 2. Thirty-day mortality rates in patients receiving CAZ-AVI monotherapy vs. CAZ-AVI combination therapy. Results are shown for (A) patients with BSIs (n=391) and subgroups with low (n= 282) vs. high (n= 109) mortality risk (INCREMENT scores <8 vs. ≥8); (B) patients with nonbacteremic infections (nBSIs) involving the lower respiratory tract (LRTI, n= 59) and subgroups with ventilator-associated pneumonia (VAP, n=22) vs. non-VAP (nVAP, n=37); (C) patients with other types of nBSI, including complicated urinary-tract infections (cUTIs, n= 71), intra-abdominal infections (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.

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 h) versus standard infusion ($P < .001$).

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=0.04) or IAI (P =0.03).

Abbreviations: CAZ-AVI, ceftazidime-avibactam; BSI, bloodstream infections; LRTI, lower respiratory tract infections; IAI, intra-abdominal infections; cUTI, complicated urinary tract infections.

Figure1

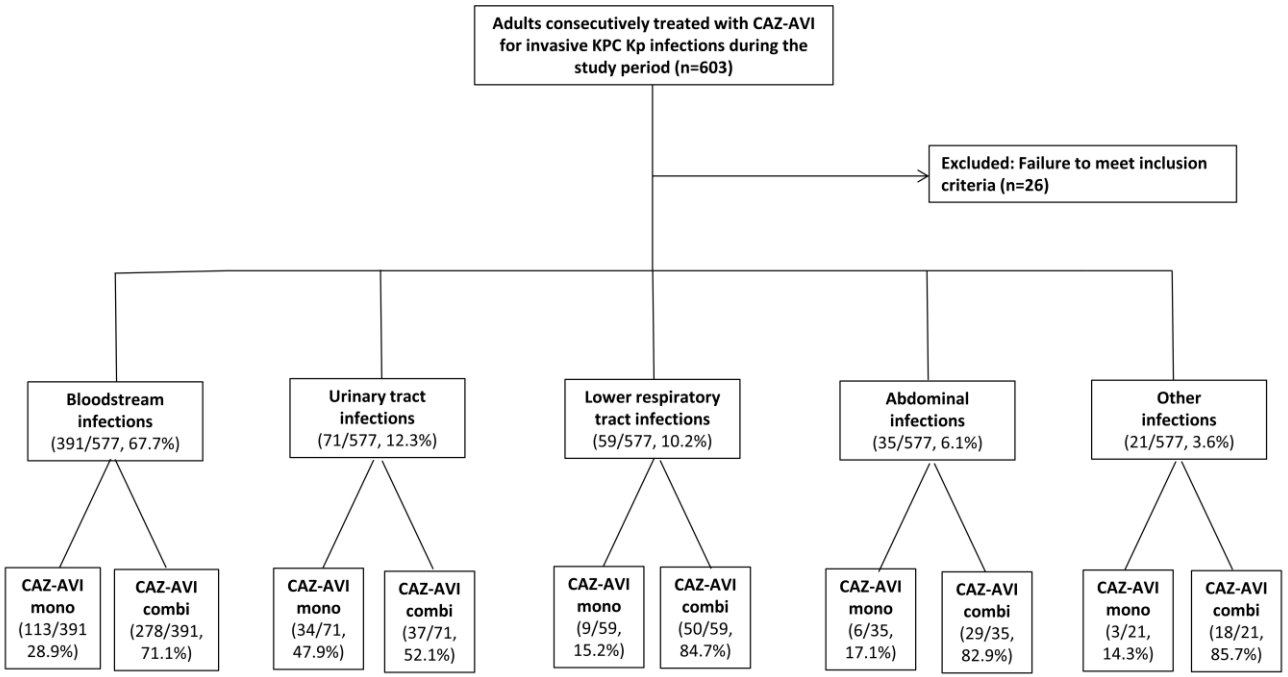

Figure 2

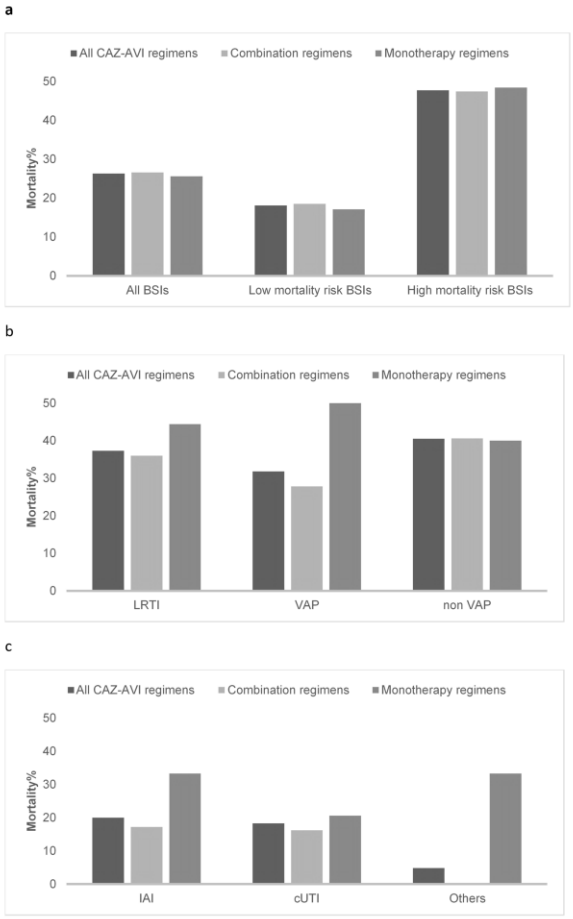

Figure 3

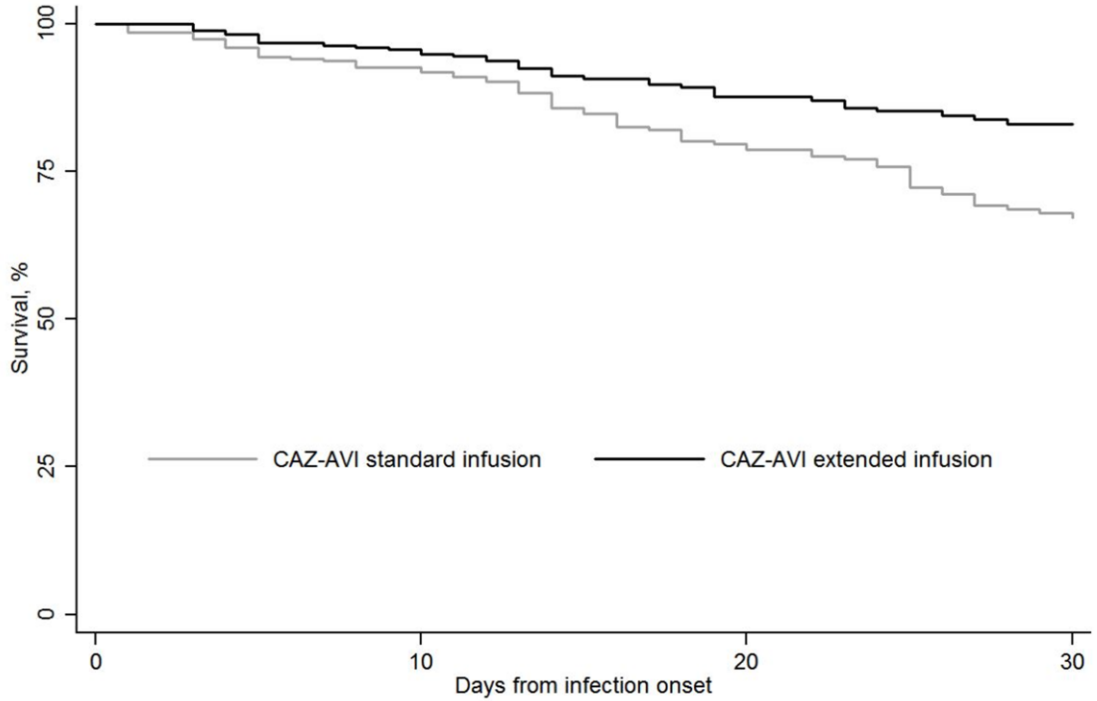

Figure 4