Ceftazidime-avibactam in combination with *in vitro* non-susceptible antimicrobials versus ceftazidime-avibactam in monotherapy in critically ill patients with carbapenem-resistant *Klebsiella pneumoniae* infection

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Research

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Abstract

Background: There is no clinical study investigating if using CAZ-AVI combination schemes with an *in vitro* non-susceptible antimicrobial could be superior to CAZ-AVI monotherapy against CRKP clinically.

Methods: We performed a retrospective, cohort study at two tertiary hospitals in China for patients with CRKP infection who treated by CAZ-AVI at least 72 hours. A Cox-proportional hazards regression model was set up to evaluate covariates which potentially affected 30-day mortality.

Results: Sixty-two patients were eligible in our study, 41 (66.1%) received CZA-AVI combination therapy and 21 (33.9%) received CZA-AVI monotherapy. The overall 30-day mortality was 33.9% (21 patients): 24.4% (10/41) and 47.6% (11/21), *P*=0.028, in combination and monotherapy groups, respectively. Combination therapy was significantly associated with lower 30-day mortality (HR 0.167, 95%CI 0.060-0.465, *P*=0.001), while higher APACHE II score, use of vasoactive drug and comorbidity of organ transplantation were considered as factors on increasing mortality. The propensity score showed no significant alteration with other variables after adding it into the final model. In the subgroup analysis, the protective effect revealed when combination with carbapenems, tigecycline or fosfomycin were applied, and in the following subgroups of patients: with sepsis, with CrCl > 50 mL/min, stayed in ICU ≤30 days or underwent mechanical ventilation.

Conclusions: CAZ-AVI combination with another in vitro non-susceptible antimicrobial, especially carbapenems, fosfomycin and tigecycline, could significantly decrease 30-day mortality rate for critically ill patients with CRKP infection. Further investigation should be carried out to confirm this conclusion and find out the autofit antimicrobials in CAZ-AVI combination schemes.

Introduction

As an urgent medical crisis, antimicrobial resistance has become one of biggest worldwide threats to public health in the last few decades mainly due to inappropriate use of antibiotics. The emergence of carbapenem-resistant gram-negative pathogens, especially carbapenem-resistant *Klebsiella pneumoniae* (CRKP), pose a tough clinical therapeutic challenge since carbapenems have been regarded as highly effective antimicrobial agents to treat a series of severe multidrug-resistant bacterial infections[1, 2]. CRKP infection is endemic in China with high probability of occurrence and prevalence, which indicated that improving CRKP infection control and treatment levels was urgent and essential in nationwide medical institutions[3].

When it comes to treatment of CRKP, combination therapy is considered as the prior choice for CRKP infection treatment because of its contribution to lower mortality rates, instead of monotherapy. Unfortunately, there are only few available antimicrobial agents for clinical use. Tigecycline, fosfomycin, aztreonam, polymyxins and aminoglycosides are the mainstays of CRKP treatments. In some cases, high-dose and prolonged-infusion of carbapenems or double-carbapenems therapy could also be applied as therapeutic options. It is urgent to develop other effective drugs against CRKP infection[4, 5]. New

antibiotics like plazomicin, eravacycline, meropenem-vaborbacatam and ceftazidime-avibactam (CAZ-AVI) have been proved as great complements for CRKP infection treatment[6].

CAZ-AVI, a novel combination of cephalosporin and β-lactamase inhibitor, was first approved for treatment of complicated intra-abdominal infections and complicated urinary tract infections by U.S. Food and Drug Administration in February 2015[7]. In China, CAZ-AVI has been of great concern for its confirmed clinical efficacy against CRKP infection by inhibiting the activities of extended-spectrum β-lactamase (ESBL), AmpC-producing β-lactamase, *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 carbapenemase since its initial marketing in September 2019 [8–11].

It is acknowledged that selection of anti-CRKP agents depends on infectious severity, patients' clinical information, and most importantly, *in vitro* susceptibility result[6]. In view of therapeutic difficulty, clinicians usually tend to prescribe CAZ-AVI in combination with another susceptible (if any) antimicrobial agent for eradicating CRKP. Although several *in vitro* studies have proved that using CAZ-AVI in combination with an extra anti-CRKP agent was synergistic against CRKP[12, 13], no differences in mortality and microbiological cure rates were observed for patients receiving CAZ combination therapy or CAZ monotherapy in both studies of Onorato L *et al*.[14] and Fiore M *et al*.[15]. What's more, there is also no clinical study investigating if using CAZ-AVI combination schemes with an *in vitro* non-susceptible antimicrobial drug could have a better clinical effectiveness than CAZ-AVI monotherapy for treating CRKP infection.

Therefore, this study primarily aimed to find out if CAZ-AVI in combination with an *in vitro* non-susceptible antibiotic is superior to CAZ-AVI monotherapy against CRKP infection in critical ill patients based on addressing potential indication bias.

Methods

Study design and participants

We conducted a retrospective, cohort study at two tertiary hospitals in Shanghai, China. This study was approved by Institutional Review Board from Huashan and Ruijin hospital and performed by the ethical standards of the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. All data in this study were extracted from the electronic medical record information system in each hospital.

All participators with aged ≥ 18 years admitted intensive care unit (ICU) from January 2019 to December 2020, who suffered from documented CRKP infections (according to microbiological culture tests) with susceptibility testing results and received at least one dose of CAZ-AVI infusion for treatment were included in our cohort. Patients were excluded when they met any one of following exclusion criteria: (1) patients received previous CAZ-AVI treatment before current study beginning; (2) patients received CAZ-AVI treatment duration < 72 hours or died within this period; (3) a CAZ-AVI-resistant pathogen was isolated from patients; (4) patients received CAZ-AVI accompanied with a second *in vitro* susceptible agent as

combination therapy, according to the susceptibility testing result; and (5) patients with any missing data. If patients underwent more than one treatment with CAZ-AVI, only the first course was taken into consideration in our study.

CAZ-AVI dosing regimen

CAZ-AVI treatment duration was at the discretion of clinicians. A fixed dose of 2.5 g CAZ-AVI was administered every 8 hours with 2-hour infusion time. Dose adjustment was applied for patients with moderate or severe renal impairment, namely creatinine clearance (CrCl) ≤ 50 mL/min. Dose adjustment details were all listed in Table 1. Patients who underwent any mode of continuous renal replacement therapy (CRRT) received a usual dosage regimen with 2.5 g q8h (infusion time ≥ 2 h) because of limited clinical evidence[16].

Table 1
CAZ-AVI dose adjustment for patients with moderate or severe renal impairment

CrCl (ml/min)	Dose	Dosing Interval	Infusion time
31 ~ 50	1.25 g	every 8 hours	≥ 2 hours
16 ~ 30	0.94 g	every 12 hours	≥ 2 hours
6 ~ 15	0.94 g	every 24 hours	≥ 2 hours
≤ 5	0.94 g	every 48 hours	≥ 2 hours

Study objectives, definitions and variables

The primary outcome of our study was 30-day mortality. Combination therapy was considered as prescribing a non-susceptible anti-CRKP agent accompanied with CAZ-AVI within 48 hours of starting CAZ-AVI treatment and maintaining therapeutic duration of at least 72 hours.

Variables which were possibly associated with 30-day mortality included age; sex; weight; site of infection (defined in accordance with Centers for Disease Control and Prevention (CDC) criteria[17]); sepsis when starting CAZ-AVI therapy (identified by Sequential Organ Failure Assessment (SOFA) score of 2 points and more[18]); polymicrobial infections; Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at the onset of CAZ-AVI therapy[19]; CrCl (calculated by Cockcroft-Gault formula[20]) at the beginning of CAZ-AVI therapy; CRRT within duration of CAZ-AVI therapy; length of ICU stay before starting CAZ-AVI therapy; concomitant use of vasoactive drugs and mechanical ventilation with the initiation of CAZ-AVI therapy; Charlson comorbidity index (CCI) score[21] and comorbidities; time to start CAZ-AVI therapy and CAZ-AVI treatment duration.

Microbiology

All pathogens' isolation and antimicrobial susceptibility test (except CAZ-AVI) were carried out by Vitek 2 Compact system (bioMérieux, Inc). Susceptibility of CAZ-AVI was determined by disk-diffusion method

(Kirby-Bauer Method). The diameter of inhibition zone for CAZ-AVI ≥ 21mm and ≤ 20mm represented susceptible and resistant, respectively. Clinical and Laboratory Standards Institute (CLSI) criteria 2019 was performed as the evaluation standard of breakpoints to interpret all antibiotics susceptibility testing result.

Statistical analysis

All statistical analyses were performed by SPSS (version 26.0, Chicago, IL, USA).

Each variable was assessed by bivariate analysis about 30-day mortality. Shapiro-Wilk test was carried out to verifying the normality of distribution about variables separately. The chi-square test or Fisher's exact test were applied for analyzing categorical variables as well as calculating *P*-value, while the Student's t-test or Mann-Whitney U test were implemented to analyze continuous variables and calculate *P*-value. Any Variable with a *P*-value ≤ 0.20 would be selected to execute a forward stepwise selection for building a Cox-proportional hazards regression model. Covariates with *P*-values ≤ 0.10 were remained in the model.

For the sake of adjusting for confounding by indication, comparison of variables between Combination therapy and monotherapy was performed at first. Variables with *P*-values ≤ 0.20 were included in the Cox-proportional hazards regression model for 30-day mortality, while only those with *P*-values ≤ 0.10 would be maintained in this model. Moreover, a propensity score was calculated by the logistic regression model covered the aforementioned variables with *P*-values ≤ 0.10 and examined in the final model.

The proportional hazard assumption was assessed graphically by the plot of log[-log(survival)] versus log(time). Collinearity between covariates was checked as well. Tests for interactions were not conducted. All tests were two-tailed, and *P*-values ≤ 0.05 were considered as statistically significant.

Results

From January 2019 to December 2020, a total of 62 eligible patients were included in our study eventually (Fig. 1). Among these 62 patients, their mean age was 60.9 ± 17.1 years and their mean weight was 66.3 ± 13.5 kg. Forty-seven (75.8%) patients were male. As for the primary infection site, twenty-five patients (40.3%) were identified as respiratory infection, as well as 9 for bloodstream infection (14.5%), 12 for abdominal infection (19.4%), 11 for urinary tract infection (17.7%) and 5 for other infections (8.1%). In addition, 40 patients (64.5%) and 12 (19.4%) patients suffered from sepsis and polymicrobial infection, respectively. The APACHE II score at the onset of CAZ-AVI therapy was 17.5 (Interquartile Range [IQR], 14.8–20).

According to the CAZ-AVI dosing regimen, 12 patients (19.4%) received dose adjustment when starting CAZ-AVI therapy due to their lower CrCl level without CRRT treatment. The median average CAZ-AVI treatment duration was 14 days (IQR, 10–14).

The overall 30-day mortality was 33.9% (21 patients) and the median time of death was 14 days (IQR, 9.5–22.5). There were 41 (66.1%) patients received CZA-AVI combination therapy as well as 21 (33.9%) with CZA-AVI monotherapy. Dosing regimens of combined antimicrobial agents were described in Table 2. The 30-day mortality for patients in combination therapy and monotherapy groups were 24.4% (10/41) and 47.6% (11/21), *P* = 0.028, respectively. The mortality rates for patients receiving combination therapy and monotherapy were 9.3/1000 patient days and 24.9/1000 patient days, *P* = 0.014 (Log Rank, Fig. 2), respectively.

Table 2
Concomitant antimicrobial agents in CAZ-AVI combination therapy scheme

Antimicrobial agents	**n = 41**	**Dose regimen**	**30-day mortality n = 10 (24.4%)**
Meropenem	11 (26.8)	1 for 500 mg qd 1 for 500 mg q12 1 for 1000 mg q12h 8 for 1000 mg q8h	3 (27.3)
Imipenem	3 (7.3)	2 for 1000 mg q8h 1 for 1000 mg q6h	1 (33.3)
Tigecycline[a]	9 (22.0)	9 for 50 mg q12h	3 (33.3)
Amikacin	10 (24.4)	1 for 600 mg qd 3 for 800 mg qd 4 for 1000 mg qd 1 for 1200 mg qd 1 for 1400 mg qd	1 (10)
Fosfomycin	6 (14.6)	2 for 4 g q8h 4 for 4 g q6h	2 (33.3)
Aztreonam	2 (4.9)	2 for 2 g q8h	0
[a]All 9 patients were given first dose tigecycline 100 mg as loading dose.			

Table 3 displayed the details of patient characteristics in combination and monotherapy group. Age (*P* = 0.079), respiratory infection (*P* = 0.166), sepsis (*P* = 0.169), length of ICU stay before starting CAZ-AVI therapy (*P* = 0.059) and CCI score (*P* = 0.090) were chosen for stepwise variables selection in the Cox-proportional hazards regression model and creation of the propensity score.

Table 3
Characteristics of patients receiving CAZ-AVI combination and monotherapy antimicrobial treatment

Variable[a]	Combination (n = 41)	Monotherapy (n = 21)	*P*-value
Age, years	58.2 ± 18.4	66.2 ± 13.2	0.079
Sex (male)	33 (80.5)	14 (66.7)	0.229
Weight, kg	67.8 ± 14.2	63.2 ± 11.6	0.207
Primary site of infection	7 (17.1)	2 (9.5)	0.705
Primary bloodstream infection	14 (34.1)	11 (52.4)	0.166
Respiratory infection	9 (22.0)	3 (14.3)	0.735
Abdominal infection	7 (17.1)	4 (19.0)	1.000
Urinary tract infection	4 (9.8)	1 (4.8)	0.654
Other infections			
Sepsis	24 (58.5)	16 (76.2)	0.169
Polymicrobial infection	9 (22.0)	3 (14.3)	0.735
APACHE II score (CAZ-AVI onset)	18 (14-20.5)	17 (16–19)	0.846
CrCl, mL/min	76.7 (42.5-133.6)	97.5 (60.0-131.9)	0.409
CRRT	4 (9.8)	2 (9.5)	1.000
Length of ICU stay before starting CAZ-AVI therapy, days	17 (8–31)	32 (9.5–58.5)	0.059
Vasoactive drug	24 (58.5)	13 (61.9)	0.798
Mechanical ventilation	26 (63.4)	13 (61.9)	0.907

Variable[a]	Combination (n = 41)	Monotherapy (n = 21)	*P*-value
Comorbidities	10 (24.4)	6 (28.6)	0.722
Cardiovascular disease	18 (43.9)	8 (38.1)	0.661
Respiratory Disease	7 (17.1)	4 (19.0)	1.000
Central Nervous system disease	4 (9.8)	2 (9.5)	1.000
Autoimmune disease	13 (31.7)	7 (33.3)	0.897
Liver disease	11 (26.8)	4 (19.0)	0.498
Renal insufficiency	8 (19.5)	7 (33.3)	0.229
Diabetes	6 (14.6)	4 (19.0)	0.722
Organ transplantation	13 (31.7)	7 (33.3)	0.897
Neoplasia			
CCI score	4 (3–5)	4 (3.5-6)	0.090
CAZ-AVI treatment duration, days	14 (12–14)	14 (10–14)	0.299
All data are exhibited as number (%), mean ± SD or median (P_{25}-P_{75}).			

Table 4 showed us the bivariate analysis results for 30-day mortality. Other infections (P = 0.157), polymicrobial infection (P = 0.195), APACHE II score at the onset of CAZ-AVI therapy (P = 0.032), CrCl (P = 0.076), vasoactive drug (P < 0.001), mechanical ventilation (P = 0.008), cardiovascular disease (P = 0.028), respiratory disease (P = 0.082), liver disease (P = 0.111), organ transplantation (P < 0.001), neoplasia (P = 0.111) and combination therapy (P = 0.028) were also included in Cox regression model for stepwise variables selection.

Table 4
Potential risk factors for 30-day mortality in patients treated with CAZ-AVI

Variable[a]	30-day Mortality		*P*-value
	Survival (n = 41)	Death (n = 21)	
Age, years	57.9 ± 17.2	66.7 ± 15.8	0.055
Sex (male)	31 (75.6)	16 (76.2)	0.960
Weight, kg	66.2 ± 13.8	66.4 ± 13.1	0.949
Primary site of infection	7 (17.1)	2 (9.5)	0.705
Primary bloodstream infection	13 (31.7)	12 (57.1)	0.053
Respiratory infection	7 (17.1)	5 (23.8)	0.520
Abdominal infection	9 (22.0)	2 (9.5)	0.305
Urinary tract infection	5 (12.2)	0	0.157
Other infections			
Sepsis	22 (53.7)	18 (85.7)	0.014
Polymicrobial infection	10 (24.4)	2 (9.5)	0.195
APACHE II score (CAZ-AVI onset)	16 (14-19.5)	18 (17–21)	0.032
CrCl, mL/min	100.2 (55.3–142.0)	61.4 (33.8-108.7)	0.076
CRRT	3 (7.3)	3 (14.3)	0.398
Length of ICU stay before starting CAZ-AVI therapy, days	21 (7.5–33.5)	23 (13-51.5)	0.198
Vasoactive drug	17 (41.5)	20 (95.2)	< 0.001
Mechanical ventilation	21 (51.2)	18 (85.7)	0.008

Variable[a]	30-day Mortality		*P*-value
	Survival (n = 41)	Death (n = 21)	
Comorbidities	7 (17.1)	9 (42.9)	0.028
Cardiovascular disease	14 (34.1)	12 (57.1)	0.082
Respiratory disease	8 (19.5)	3 (14.3)	0.735
Central Nervous system disease	5 (12.2)	1 (4.8)	0.654
Autoimmune disease	16 (39.0)	4 (19.0)	0.111
Liver disease	9 (22.0)	6 (28.6)	0.565
Renal insufficiency	9 (22.0)	6 (28.6)	0.565
Diabetes	1 (2.4)	9 (42.9)	< 0.001
Organ transplantation	16 (39.0)	4 (19.0)	0.111
Neoplasia			
CCI score	4 (3–5)	4 (3.5-5)	0.311
Combination therapy	31 (75.6)	10 (47.6)	0.028
CAZ-AVI treatment duration, days	14 (12–14)	14 (9.5–18)	0.704
All data are exhibited as number (%), mean ± SD or median (P_{25}-P_{75}).			

Multivariate analysis results were listed detailedly in Table 5. Combination therapy was significantly associated with lower 30-day mortality (HR 0.167, 95%CI 0.060–0.465, $P = 0.001$), while higher APACHE II score at the onset of CAZ-AVI therapy, use of vasoactive drug and comorbidity of organ transplantation were considered as the factors on increasing 30-day mortality. Moreover, the propensity score showed no significant alteration with the results of other variables in the Cox regression model.

Table 5

Cox-proportional hazards regression model for 30-day mortality[a]

Variable[b]	HR	95% CI	*P*-value
Combination therapy	0.167	0.060–0.465	0.001
APACHE II score (CAZ-AVI onset)	1.180	1.027–1.356	0.019
Vasoactive drug	14.732	1.881-115.407	0.010
Organ transplantation	3.817	1.475–9.881	0.006

[a] *A propensity score for prescribing combination therapy included age, respiratory infection, sepsis, length of ICU stay before starting CAZ-AVI therapy and CCI score in a logistic regression model using a Likelihood Ratio (LR) forward stepwise method (Hosmer-Lemeshow goodness-of-fit test: χ^2-square = 7.478; P = 0.486). The propensity score that was included in the final Cox-proportional hazards regression model showed no significant alteration with the results of other variables (P = 0.926).*

[b] *Age, sepsis, respiratory infection, length of ICU stay before starting CAZ-AVI therapy, CCI score in* Table 1 *and other infections, polymicrobial infection, CrCl, mechanical ventilation, cardiovascular disease, respiratory Disease, liver disease, neoplasia in* Table 2 *were all checked but excluded finally in the Cox-proportional hazards regression model because the P-value > 0.10 for each aforementioned variable.*

[c] *HR = Hazard ratio.*

[d] *CI= confidence interval.*

Subgroup Analysis

CAZ-AVI combination therapy could be conductive to lower 30-day mortality when patients received carbapenems, tigecycline and fosfomycin as another concomitant agent, compared with CAZ-AVI monotherapy. Furthermore, combination therapy was a protective factor in the subgroup of patients with sepsis or CrCl > 50 mL/min. Patients stayed in ICU ≤ 30 days or underwent mechanical ventilation when starting CAZ-AVI therapy were also benefited from CAZ-AVI combination therapy for decreased mortality as well (Table 6).

Table 6
Hazard ratio of CAZ-AVI combination therapy and 30-day mortality according in the subgroup analysis.

Subgroup[a]	n	HR[b]	95% CI[c]	*P*-value
Combination with carbapenem[d]	35	0.222	0.053–0.938	0.041
Combination with tigecycline	30	0.220	0.052–0.936	0.040
Combination with fosfomycin	27	0.101	0.016–0.638	0.015
Sepsis	40	0.136	0.039–0.474	0.002
CrCl > 50mL/min	45	0.219	0.065–0.741	0.015
ICU stay before starting CAZ-AVI therapy ≤ 30d	41	0.139	0.036–0.542	0.004
Mechanical ventilation	39	0.214	0.066–0.686	0.010

[a] *Adjusted for APACHE II score (CAZ-AVI onset), vasoactive drug and organ transplantation.*

[b] *HR = Hazard ratio.*

[c] *CI= confidence interval.*

[d] *Eleven patients received meropenem and three patients received imipenem.*

Discussion

As the first novel antibiotics coming to market against CRKP, CZA-AVI was highly concerned by clinicians and pharmacists. Although the rapid developing resistance of CAZ-AVI was reported in some cases by several studies[22–25], it was still considered as a first-line anti-CRKP agent due to its superiority to the current polymyxin-based therapy in both efficacy and safety[26, 27]. However, it was remained unclear if CAZ-AVI should be used as monotherapy or in combination with other agents in the article from Jason *et al*.[28] Therefore, we performed a study to made the comparison with CAZ-AVI combination therapy and CAZ-AVI monotherapy for the patients with CRKP infections for the first time.

In our study, we found that CAZ-AVI in combination with another *in vitro* non-susceptible antimicrobial could significantly lower the 30-day mortality for the patients with CRKP infection. Taking developing resistance of few therapeutic drugs against CRKP into consideration, this was a highly inspired conclusion because the CAZ-AVI combination therapy did not depend on the susceptibility of other antimicrobials revealed and sufficient clinical efficacy at the same time.

Furthermore, carbapenems, tigecycline and fosfomycin were recognized as the effective concomitant agents to decrease 30-day mortality by subgroup analysis. This indicated that CAZ-AVI in combination

with fosfomycin could be a potential therapeutic scheme to treat CRKP infection, which was consistent with the conclusion in Ojdana *et al.*'s *in vitro* study that CAZ-AVI combined with fosfomycin could enhance antibacterial activity against carbapenemase-producing *Klebsiella pneumoniae*[13].

As another combined drugs with CZA-AVI, tigecycline was proved clinically effective on patients with CRKP infection in our study, while unsatisfactory results were described by Ojdana *et al.*[13] and Gaibani *et al.*[29] that only 5% and 8% isolates of carbapenemase-producing *Klebsiella pneumoniae* were received synergistic effect of these two agents, respectively. Nevertheless, these two aforesaid studies were both *in vitro* and lack of clinical isolates to verify credibility of their conclusions. Besides, a clinical case had been reported that CZA-AVI plus tigecycline successfully cured a 61-year old man with intra-abdominal carbapenemase-producing *Klebsiella pneumoniae* infection[30]. We still believed that CAZ-AVI plus tigecycline might be another meaningful therapeutic combination against CRKP based upon the above reasons.

We also found that carbapenems (meropenem and imipenem) played a crucial role in combination therapy with CZA-AVI as a protective factor on 30-day mortality. Ertapenem was not included in our study since it was only applied to dual carbapenem treatment as an anti-CRKP combination partner[31]. Gaibani *et al.*'s study[29] suggested that the combination of CAZ-AVI and imipenem could be a therapeutic option against CRKP. Mikhail *et al.* evaluated the synergistic activity of CZA-AVI and other antimicrobials. Their data revealed that the use of CZA-AVI in combination with meropenem had potential synergy to treat Multidrug-Resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*[12]. Although this treatment scheme was rare in clinical practice because CZA-AVI and carbapenems were both β-lactam antibiotics, it might be similarly resultful in consideration of enhancing efficacy about double carbapenem therapy as a rescue strategy for the treatment of CRKP[32–34]. Further investigation should be carried out to find out possible mechanisms of increasing anti-CRKP activity between CZA-AVI with carbapenems and which carbapenem was the optimum choice in clinical practice, as well as the appropriate dose regimen.

What's more, we could not neglect two other kinds of anti-CRKP agents, namely aztreonam and polymyxins (polymyxin B and colistin). Combination of CAZ-AVI and aztreonam had been already reported as a promising treatment option against carbapenemase-producing pathogens, especially metallo-beta-lactamase-producing gram-negative bacteria[35–38]. Polymyxins (polymyxin B and colistin) were addressed as the last resort antibiotics to treat CRKP infection before CAZ-AVI coming into clinical practice[1, 39–41]. However, combination with CAZ-AVI and polymyxins was not found in any clinical studies. In our study, aztreonam and polymyxins were not evaluated as *in vitro* non-susceptible antibiotics with CAZ-AVI because aztreonam resistance was only emerged in 5 patients who received CAZ-AVI less than 72 hours and no isolate was found resistant to polymyxin B and colistin in our study. These two agents should be included in our further studies.

In the current study, CZA-AVI combination therapy was also beneficial to patients with sepsis or receiving mechanical ventilation, which implied us that combination therapy was reasonable for treating critical ill

patients with CRKP infection, especially for patients stayed in ICU less than 30 days when starting using CZA-AVI. Combination therapy also showed protective effect on mortality for patients with CrCl > 50 mL/min, who received non-adjusted dose of CAZ-AVI during treatment duration. It might be concluded that higher dose of CAZ-AVI could effectively lower mortality. However, current CAZ-AVI dosage regimen had been verified by population pharmacokinetic models that high probability of target attainment (> 95%) was observed in patients with various CrCl levels, except for patients with CrCl between 8 to 15 mL/min, according to the research from Das *et al*[42]. Hence, we maintained that the lower mortality could not simply attribute to using non-adjusted dose of CAZ-AVI. Renal insufficiency should be considered as a rational factor on poor outcome for critically ill patients[43].

We had tried our best to control the potential for confounding bias by indication in this study. We used a multivariate model to evaluate all possibly associated variables with combination therapy by forward stepwise selection and include the propensity scores which creating by these same variables. Although Age, sepsis, respiratory infection, length of ICU stay before starting CAZ-AVI therapy, CCI score were included for evaluation in the multivariate model, none of these variables were remained in the final model. In addition, the propensity score was included without any significant alteration with other variables in the final Cox-proportional hazards regression model. Consequently, we thought that indication bias could barely affect our study results.

The current study still had some limitations. Firstly, it was a retrospective cohort study with a small sample size. Well-design prospective studies or randomized control trials with more participators should be designed for further investigation. Secondly, carbapenemase detection tests like Carba NP (CNP) test or modified carbapenem inactivation method (mCIM), were not performed to in our study due to lack of necessary devices and reagents in clinical laboratory. Last but not the least, only dual agents' combination was evaluated in our study, triple or more drugs combination schemes should be applied in our future study.

Conclusions

In conclusion, our study showed that CZA-AVI in combination with another *in vitro* non-susceptible antimicrobial, especially carbapenems, fosfomycin and tigecycline, could significantly lower the mortality risk in critically ill patients with CRKP infection. Further well-designed prospective studies should be performed to verify if CZA-AVI combination therapy could be beneficial to all patients suffering CRKP infection and find out the optimum CZA-AVI combining scheme.

Abbreviations

CRKP: carbapenem-resistant *Klebsiella pneumoniae*; CAZ-AVI: ceftazidime-avibactam; ESBL: extended-spectrum β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; ICU: intensive care unit; CrCl: creatinine clearance; CRRT: continuous renal replacement therapy; CDC: Centers for Disease Control and Prevention; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health

Evaluation II; CCI: Charlson comorbidity index; CLSI: Clinical and Laboratory Standards Institute; IQR: Interquartile Range; CNP: Carba NP mCIM: modified carbapenem inactivation method.

Declarations

Ethics approval and informed consent to participate

This study was approved by Huashan and Ruijin Hospital Institutional Review Board and has been performed in accordance with the ethical standards laid down in “Declaration of Helsinki 1964” and its later amendments or comparable ethical standards. Written informed consent was obtained from individual or guardian participants.

Consent to publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Conflicts of interest

All authors declared no conflict of interest in this study or the findings specified in this paper.

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Authors’ contributions

GZ, JH, LZ, ZY and XB conceived and designed this study. GZ, JZ, BW, JC, LW, KH and YZ collected the information in the case, and contributed to the acquisition, analysis, and interpretation of the data. GZ, JZ, BW, LZ and JH wrote and revised the manuscript. All authors read and approved the final manuscript.

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References

1. Doi Y: **Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019, **69**(Suppl 7):S565-s575.
2. Karam G, Chastre J, Wilcox MH, Vincent JL: **Antibiotic strategies in the era of multidrug resistance**. *Critical care (London, England)* 2016, **20**(1):136.
3. Zhang Y, Wang Q, Yin Y, Chen H, Jin L, Gu B, Xie L, Yang C, Ma X, Li H *et al*: **Epidemiology of Carbapenem-Resistant Enterobacteriaceae Infections: Report from the China CRE Network**. *Antimicrobial agents and chemotherapy* 2018, **62**(2).
4. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL: **Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections**. *Open forum infectious diseases* 2015, **2**(2):ofv050.
5. Trecarichi EM, Tumbarello M: **Therapeutic options for carbapenem-resistant Enterobacteriaceae infections**. *Virulence* 2017, **8**(4):470-484.
6. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR: **Infections Caused by Carbapenem-Resistant Enterobacteriaceae: An Update on Therapeutic Options**. *Frontiers in microbiology* 2019, **10**:80.
7. Kaye KS, Pogue JM: **Infections Caused by Resistant Gram-Negative Bacteria: Epidemiology and Management**. *Pharmacotherapy* 2015, **35**(10):949-962.
8. Shirley M: **Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections**. *Drugs* 2018, **78**(6):675-692.
9. Zhanel GG, Lawson CD, Adam H, Schweizer F, Zelenitsky S, Lagacé-Wiens PR, Denisuik A, Rubinstein E, Gin AS, Hoban DJ *et al*: **Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination**. *Drugs* 2013, **73**(2):159-177.
10. Zasowski EJ, Rybak JM, Rybak MJ: **The β-Lactams Strike Back: Ceftazidime-Avibactam**. *Pharmacotherapy* 2015, **35**(8):755-770.
11. Kuang H, Zhong C, Wang Y, Ye H, Ao K, Zong Z, Lv X: **Clinical characteristics and outcomes of patients with multidrug-resistant Gram-negative bacterial infections treated with ceftazidime/avibactam**. *Journal of global antimicrobial resistance* 2020, **23**:404-407.

12. Mikhail S, Singh NB, Kebriaei R, Rice SA, Stamper KC, Castanheira M, Rybak MJ: **Evaluation of the Synergy of Ceftazidime-Avibactam in Combination with Meropenem, Amikacin, Aztreonam, Colistin, or Fosfomycin against Well-Characterized Multidrug-Resistant Klebsiella pneumoniae and Pseudomonas aeruginosa**. *Antimicrobial agents and chemotherapy* 2019, **63**(8).
13. Ojdana D, Gutowska A, Sacha P, Majewski P, Wieczorek P, Tryniszewska E: **Activity of Ceftazidime-Avibactam Alone and in Combination with Ertapenem, Fosfomycin, and Tigecycline Against Carbapenemase-Producing Klebsiella pneumoniae**. *Microbial drug resistance (Larchmont, NY)* 2019, **25**(9):1357-1364.
14. 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**. *International journal of antimicrobial agents* 2019, **54**(6):735-740.
15. Fiore M, Alfieri A, Di Franco S, Pace MC, Simeon V, Ingoglia G, Cortegiani A: **Ceftazidime-Avibactam Combination Therapy Compared to Ceftazidime-Avibactam Monotherapy for the Treatment of Severe Infections Due to Carbapenem-Resistant Pathogens: A Systematic Review and Network Meta-Analysis**. *Antibiotics (Basel, Switzerland)* 2020, **9**(7).
16. Li L, Li X, Xia Y, Chu Y, Zhong H, Li J, Liang P, Bu Y, Zhao R, Liao Y *et al*: **Recommendation of Antimicrobial Dosing Optimization During Continuous Renal Replacement Therapy**. *Frontiers in pharmacology* 2020, **11**:786.
17. Horan TC, Andrus M, Dudeck MA: **CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting**. *American journal of infection control* 2008, **36**(5):309-332.
18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *Jama* 2016, **315**(8):801-810.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system**. *Critical care medicine* 1985, **13**(10):818-829.
20. Cockcroft DW, Gault MH: **Prediction of creatinine clearance from serum creatinine**. *Nephron* 1976, **16**(1):31-41.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation**. *Journal of chronic diseases* 1987, **40**(5):373-383.
22. Wang Y, Wang J, Wang R, Cai Y: **Resistance to ceftazidime-avibactam and underlying mechanisms**. *Journal of global antimicrobial resistance* 2020, **22**:18-27.
23. Göttig S, Frank D, Mungo E, Nolte A, Hogardt M, Besier S, Wichelhaus TA: **Emergence of ceftazidime/avibactam resistance in KPC-3-producing Klebsiella pneumoniae in vivo**. *The Journal of antimicrobial chemotherapy* 2019, **74**(11):3211-3216.
24. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, Press EG, Kreiswirth BN, Clancy CJ, Nguyen MH: **Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among**

Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016, **63**(12):1615-1618.

25. Giddins MJ, Macesic N, Annavajhala MK, Stump S, Khan S, McConville TH, Mehta M, Gomez-Simmonds A, Uhlemann AC: **Successive Emergence of Ceftazidime-Avibactam Resistance through Distinct Genomic Adaptations in bla(KPC-2)-Harboring Klebsiella pneumoniae Sequence Type 307 Isolates**. *Antimicrobial agents and chemotherapy* 2018, **62**(3).
26. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, Doi Y, Kreiswirth BN, Clancy CJ: **Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia**. *Antimicrobial agents and chemotherapy* 2017, **61**(8).
27. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, Watkins RR, Doi Y *et al*: **Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018, **66**(2):163-171.
28. Pogue JM, Bonomo RA, Kaye KS: **Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019, **68**(3):519-524.
29. Gaibani P, Lewis RE, Volpe SL, Giannella M, Campoli C, Landini MP, Viale P, Re MC, Ambretti S: **In vitro interaction of ceftazidime-avibactam in combination with different antimicrobials against KPC-producing Klebsiella pneumoniae clinical isolates**. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2017, **65**:1-3.
30. Guedes M, Duro R, Fonseca T, Abreu I, Rocha-Pereira N: **Carbapenemase-producing Klebsiella pneumoniae intra-abdominal infection successfully treated with ceftazidime/avibactam plus tigecycline**. *IDCases* 2020, **20**:e00745.
31. Fritzenwanker M, Imirzalioglu C, Herold S, Wagenlehner FM, Zimmer KP, Chakraborty T: **Treatment Options for Carbapenem- Resistant Gram-Negative Infections**. *Deutsches Arzteblatt international* 2018, **115**(20-21):345-352.
32. De Pascale G, Martucci G, Montini L, Panarello G, Cutuli SL, Di Carlo D, Di Gravio V, Di Stefano R, Capitanio G, Vallecoccia MS *et al*: **Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing Klebsiella pneumoniae infections: a two-center, matched case-control study**. *Crit Care* 2017, **21**(1):173.
33. Bulik CC, Nicolau DP: **Double-carbapenem therapy for carbapenemase-producing Klebsiella pneumoniae**. *Antimicrobial agents and chemotherapy* 2011, **55**(6):3002-3004.
34. Souli M, Karaiskos I, Masgala A, Galani L, Barmpouti E, Giamarellou H: **Double-carbapenem combination as salvage therapy for untreatable infections by KPC-2-producing Klebsiella pneumoniae**. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2017, **36**(7):1305-1315.

35. Lee M, Abbey T, Biagi M, Wenzler E: **Activity of aztreonam in combination with ceftazidime-avibactam against serine- and metallo-β-lactamase-producing Pseudomonas aeruginosa**. *Diagnostic microbiology and infectious disease* 2021, **99**(1):115227.
36. Avery LM, Nicolau DP: **Assessing the in vitro activity of ceftazidime/avibactam and aztreonam among carbapenemase-producing Enterobacteriaceae: Defining the zone of hope**. *International journal of antimicrobial agents* 2018, **52**(5):688-691.
37. Biagi M, Wu T, Lee M, Patel S, Butler D, Wenzler E: **Searching for the Optimal Treatment for Metallo- and Serine-β-Lactamase Producing Enterobacteriaceae: Aztreonam in Combination with Ceftazidime-avibactam or Meropenem-vaborbactam**. *Antimicrobial agents and chemotherapy* 2019, **63**(12).
38. Pragasam AK, Veeraraghavan B, Shankar BA, Bakthavatchalam YD, Mathuram A, George B, Chacko B, Korula P, Anandan S: **Will ceftazidime/avibactam plus aztreonam be effective for NDM and OXA-48-Like producing organisms: Lessons learnt from In vitro study**. *Indian journal of medical microbiology* 2019, **37**(1):34-41.
39. Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G: **The "Old" and the "New" Antibiotics for MDR Gram-Negative Pathogens: For Whom, When, and How**. *Frontiers in public health* 2019, **7**:151.
40. Liang Q, Huang M, Xu Z: **Early use of polymyxin B reduces the mortality of carbapenem-resistant Klebsiella pneumoniae bloodstream infection**. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases* 2019, **23**(1):60-65.
41. Bandick RG, Mousavi S, Bereswill S, Heimesaat MM: **Review of therapeutic options for infections with carbapenem-resistant Klebsiella pneumoniae**. *European journal of microbiology & immunology* 2020, **10**(3):115-124.
42. Das S, Li J, Riccobene T, Carrothers TJ, Newell P, Melnick D, Critchley IA, Stone GG, Nichols WW: **Dose Selection and Validation for Ceftazidime-Avibactam in Adults with Complicated Intra-abdominal Infections, Complicated Urinary Tract Infections, and Nosocomial Pneumonia**. *Antimicrobial agents and chemotherapy* 2019, **63**(4).
43. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP: **Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes**. *Kidney international* 2002, **62**(3):986-996.

Figures

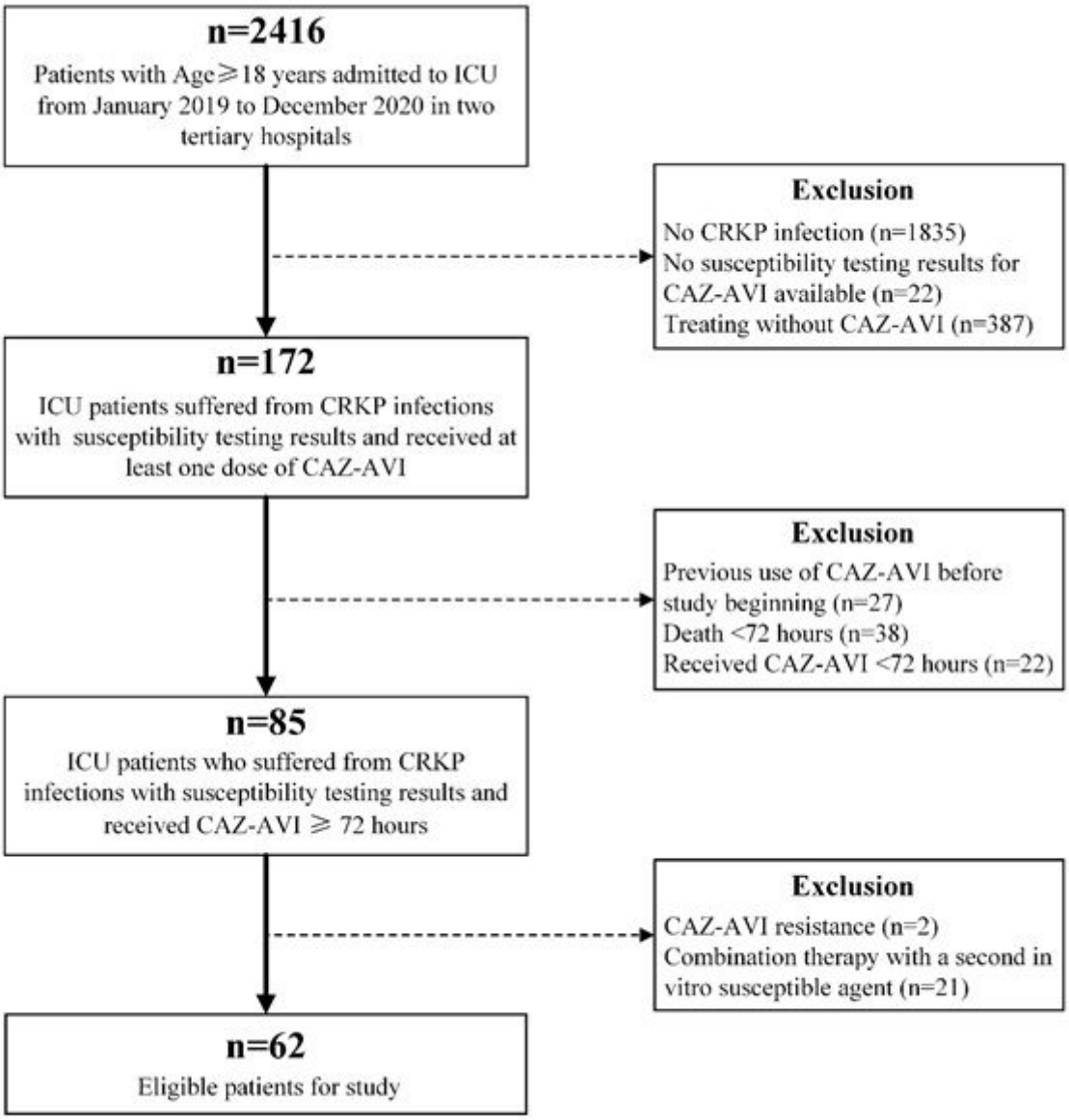

Figure 1

Study design.

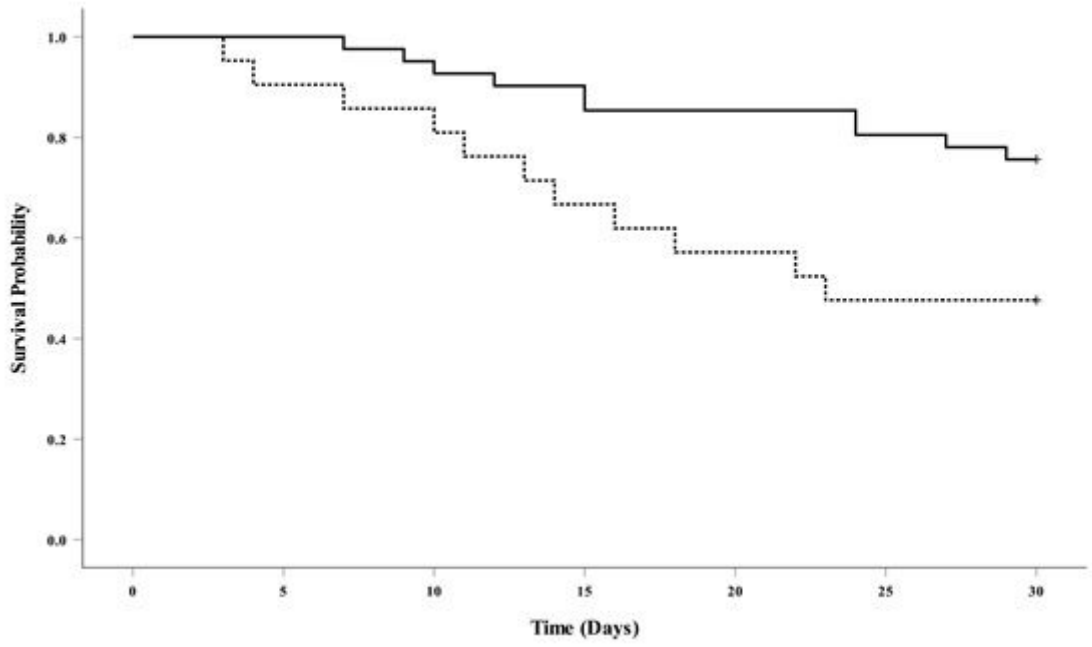

Figure 2

Survival curves of critically ill patients with CAZ-AVI combination therapy (CAZ-AVI and another in vitro non-susceptible antimicrobial) (solid line) and CAZ-AVI monotherapy (dashed line) for treating CRKP infection. The mortality rates were 9.3/1000 patient days in combination therapy group and 24.9/1000 patient days in monotherapy group, P=0.014.