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ORIGINAL RESEARCH

Ceftazidime–Avibactam-Based Versus Tigecycline-Based Regimen for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae*-Induced Pneumonia in Critically Ill Patients

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ABSTRACT

Introduction: The aim of the present study was to assess the safety profile and outcomes of a ceftazidime–avibactam (CAZ-AVI)-based regimen and compare them with those of a tigecycline (TGC)-based regimen in intensive care unit (ICU) for the treatment of carbapenem-resistant *Klebsiella pneumoniae* (CRKP), which is classified into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

Methods: Clinical and microbiological cure rates, 28-day survival rates, and safety evaluation findings were compared between patients treated with CAZ-AVI-based regimen and those treated with TGC-based regimen in this retrospective study. Conventional multivariate logistic regression analysis and regression adjustment analysis with propensity score (PS) were performed to control for confounding variables.

Results: A total of 105 cases of critically ill ICU patients with CRKP-induced HAP or VAP were included in the present study from July 2019 to September 2020; 62 patients (59%) received TGC-based regimen and 43 patients (41%) received CAZ-AVI-based regimen. The most common concomitant agent in the CAZ-AVI group and TGC group was carbapenem (44.2% versus 62.9%, $P = 0.058$), while only a small proportion of the study population received CAZ-AVI and TGC monotherapy (20.9% versus 6.5%, $P = 0.027$). The clinical and microbiological cure rates of the CAZ-AVI group were superior to those of the TGC group [51.2% versus 29.0% ($P = 0.022$) and 74.4% versus 33.9% ($P < 0.001$), respectively]. No significant differences in the 28-day survival rates were identified between the two groups (69.8% versus 66.1%, $P = 0.695$). Conventional multivariate logistic regression and PS analyses showed that patients who had used CAZ-AVI were more likely to have achieved a clinical cure [4.767 (95%CI 1.694-13.414), P=0.003;3.405 (95%CI 1.304-8.889), P=0.012] and microbiological success [6.664 (95%CI 2.626-16.915), P<0.001;7.778 (95%CI 2.717-22.265), P<0.001] than patients who used TGC. However, the difference in the 28-day survival rates between the two groups was not significant. According to the safety evaluation findings, the CAZ-AVI

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group exhibited a generally lower incidence of adverse reactions compared with that in the TGC group.
Conclusions: CAZ-AVI may be a suitable alternative for TGC in the treatment of critically ill patients with CRKP-induced HAP or VAP. These observations require further confirmation in larger randomized prospective clinical trials.

Keywords: Carbapenem-resistant *Klebsiella pneumoniae*; Tigecycline; Ceftazidime–avibactam; Clinical outcomes; Safety evaluation; Hospital-acquired pneumonia; Ventilator-associated pneumonia

Key Summary Points

Why carry out this study?

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most urgent threat among carbapenem-resistant Enterobacteriaceae (CREs), with a rapidly increasing prevalence, and high morbidity and mortality rates.

There is still considerable uncertainty regarding the optimal clinical treatment when comparing the outcomes of CRKP-infected patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

What was learned from the study?

Clinical cure rates and microbiological cure success of ceftazidime–avibactam were superior to tigecycline, although in the 28-day survival rates there were no significant differences between the two groups.

Our retrospective study revealed that ceftazidime–avibactam may be a suitable alternative to tigecycline for the treatment of HAP or VAP caused by CRKP in critically ill patients.

INTRODUCTION

Carbapenem-resistant Enterobacteriaceae (CREs) have been categorized as an urgent threat, which results in around 2.8 million antibiotic-resistant infections, with more than 35,000 deaths according to the 2019 Antibiotic Resistance Threats Report [1, 2]. Amongst the different strains of CREs, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most common pathogenic bacteria, with a rapidly increasing prevalence, and high morbidity and mortality rates [3, 4]. Consistently, data obtained from the China Antimicrobial Resistance Surveillance System Report and China Antimicrobial Surveillance Network showed that the detection rate of carbapenem resistance in *K. pneumoniae* strains has increased steadily in recent years, with around a 1.2–18.9% increase in the different provinces of China, peaking at 20.3% in 2020 [5, 6]. CRKP can result in serious hospital-acquired infections, the prevalence of which is high (27%); amongst these, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common in intensive care unit (ICU) [3, 7]. Moreover, infections with CRKP, particularly in HAP/VAP, are associated with higher mortality rates and hospitalization costs [8].

Carbapenem resistance through the acquisition of resistance genes encoding metallo-β-lactamases, non-metallo-carbapenemases, and a mutation in the expression of the outer membrane protein and exoprotein may underlie the limited efficacy of the antibiotics used [often polymyxins, tigecycline (TGC), or aminoglycosides] [9]. Polymyxins have suboptimal pharmacokinetic/pharmacodynamics properties, non-satisfactory therapeutic effects, toxicity, and an increasing trend of resistant bacteria [10, 11]. The Infectious Diseases Society of America (IDSA) recommends that polymyxin B and colistin should be avoided for the treatment of CRE infections because of a rapid increase in colistin resistance, with increased mortality rates and excess nephrotoxicity [12–15]. TGC shows high cure rates, and may thus be the preferred antibiotic for the treatment of infections caused by CRE [16]. Avibactam, a novel

synthetic non-β-lactam (diazabicyclooctane), enhances the antibacterial activity of ceftazidime against Enterobacteriaceae and some Gram-negative nonfermentative bacilli by inhibiting carbapenemases without affecting the activity of ceftazidime against ceftazidime-susceptible organisms or most anaerobic Gram-negative rods [17, 18]. Although certain studies have demonstrated the effectiveness and safety of ceftazidime–avibactam (CAZ-AVI), and shown that it is superior to colistin for the treatment of CRE in vivo [14, 15], there is still considerable uncertainty regarding the optimal clinical treatment when comparing the outcomes of CRKP-infected patients with HAP or VAP treated with CAZ-AVI to those treated with TGC [19, 20]. The aim of the present study was to assess the safety patterns and outcomes of CRKP defined as either HAP or VAP in critically ill ICU patients treated with either CAZ-AVI or TGC.

METHODS

Patients and Clinical Data

Our study was a retrospective study approved by the Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University, a tertiary care teaching hospital, and the need for patient consent was waived (Approval No. 2021-SR-228). All complete data were afterwards retrospectively extracted from electrical medical records and this study did not directly interfere with the enrolled patients; in addition, the data were de-identified and anonymously analyzed. Our study was performed in accordance with the Helsinki Declaration. All patients who were diagnosed with CRKP VAP/HAP and treated with TGC or CAZ-AVI between July 2019 and September 2020 in ICUs were recruited.

Patients with HAP or VAP were included. The definition of HAP and VAP is described in the American Thoracic Society (ATS)/IDSA 2016 guideline [21]. HAP is defined as a pneumonia not presented at the time of hospital admission and occurring 48 h or more after admission, while VAP is defined as a pneumonia occurring 48 h or more after endotracheal intubation. The inclusion criteria were patients over the age of 18 years old who had a quantitative culture result from bronchial alveolar lavage fluid (BALF) or endotracheal aspirates (ETAs) with growth higher than the defined thresholds (1×10^5 CFU/ml for ETAs; 1×10^4 CFU/ml for BALF), which was proven to be HAP or VAP. All the isolates in the present study were defined as being CRKP and all the strains were susceptible to CAZ-AVI and TGC. Combination treatment had no significant difference in the selection of concomitant agents which were not effective against the *K. pneumoniae* in vitro. Patients whose duration of treatment with CAZ-AVI or TGC was less than 72 h were excluded from this study protocol. The data obtained included age, sex, comorbidities, the Charlson's weighted index of comorbidity score at admission, Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores at onset of infection, combination antibiotic treatments, concurrent multisite infections, treatment and procedures [e.g., mechanical ventilation, continuous renal replacement therapy (CRRT)], and laboratory findings. VAP/HAP episodes that were either isolated or in conjunction with mixed microorganisms and multisite infection were included in the present study.

Microbiology and Antibiotic Regimens

Antibiotic susceptibility testing was performed using a VITEK-2 (BioMérieux, Marcy-l'Étoile, France) automatized system or *E*-test (Antobio, China) according to the Clinical and Laboratory Standards Institute (CLSI) methodology [22]. Carbapenem resistance was defined as the MIC of imipenem or meropenem of at least 4 mg/l [23]. CRKP was resistant to most classes of antibiotics, except for TGC, polymyxins, and CAZ-AVI. *Escherichia coli* ATCC 25922TM served as a laboratory quality control strain of MIC measurements. CRE colonization on respiratory tracts was identified by the patient's chest radiograph and laboratory examinations.

Treatment with TGC and any other antibiotics, excluding CAZ-AVI, was classified as TGC-

based therapy. Treatment with CAZ-AVI and any other antibiotics, except for TGC, was considered as CAZ-AVI-based therapy. In our center, TGC was administered intravenously with a 200 mg loading dosage, followed by a twice-daily maintenance dosage. For patients with normal liver functions, the maintenance dosage was 100 mg twice daily. The dosage of TGC was adjusted for alterations in liver function using the pharmaceutical direction. CAZ-AVI (2 g CAZ and 500 mg AVI) was given by 2 h intravenous infusions every 8 h. The dosage of CAZ-AVI was adjusted according to creatinine clearance (CLcr). Patients with CRRT received a standard dosing for the adequacy of treatment.

Outcome Measurements

Clinical success was defined as the normalization of non-microbiological indicators (such as radiological examinations and laboratory tests) and resolution in clinical symptoms (such as respiratory secretions volume and signs of fever) [19]. Microbiological cure success was defined as culture-confirmed eradication of the pathogen; no pathogen growth in the final cultured specimen during the entirety of the hospital stay. Progressive or persistent symptoms and signs of infection, emergence of new episodes following active therapy, and addition of other antibacterial treatments for the disease were considered clinically ineffective [24]. If the patient's clinical response was success, such that cultivable material was not available, the bacteriological results were presumed to be hypothetical clearance. The microbiological cure success and hypothetical clearance of bacterial clearance were combined to calculate the bacterial clearance rate [25]. Bacteriological failure was defined by persistence of *K. pneumonia* isolates (1×10^5 CFU/ml for ETAs; 1×10^4 CFU/ml for BALF) on the follow-up cultures of the respiratory specimen.

Statistical Analysis

Continuous variables were compared using a Student's *t* test, Mann–Whitney *U* test or a Wilcoxon's rank sum test. Categorical variables were compared using a χ^2 test or a Fisher's exact test. A binary logistic regression was used to identify factors associated with clinical cure, microbiological success, and 28-day survival rates.

Meaningful variables based on clinical judgment, and other variables with $P < 0.10$ in the univariate analyses, were included in the multivariate analysis. To prevent multicollinearity, certain factors were excluded from the multivariate analysis. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and model calibration was assessed using a Hosmer–Lemeshow test. In addition, propensity score (PS) analysis was performed to control for confounding variables, referring specifically to combined treatment and all other existent confounding factors that underlie their value in observational analysis. PS was estimated using multivariate logistic regression analysis of several covariates [26]. The PS method was PS regression adjustment. This method takes PS as an additional covariate in the binary logistic regression model. Association between CAZ-AVI use (TGC group as the reference group) and the primary outcome was estimated by a multivariable logistic regression model with the use of PS. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the relative risk of clinical outcomes. All tests of significance reported were two-tailed, and a $P < 0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS version 22.0 (IBM, Corp), with a R2.15.X-psmatching 3.04 plug-in [Empower (R); empowerstats.com, X&Y solutions, Boston, Massachusetts, USA) and R [27, 28].

RESULTS

Patients

In accordance with the inclusion criteria, a total of 114 patients in the ICU were diagnosed with HAP or VAP caused by CRKP, and were treated with CAZ-AVI-based therapy or TGC-based therapy; nine cases were excluded from the

study, as they received a combination of CAZ-AVI and TGC therapy. Finally, 105 cases were included in the final analyses; 62 patients (59%) received TGC-based therapy and 43 patients (41%) received CAZ-AVI-based therapy. The most common concomitant agent used was carbapenem (44.2% in the CAZ-AVI group versus 62.9% in the TGC group, $P = 0.058$), while CAZ-AVI and TGC monotherapy were applied in a small proportion of the study population (20.9% versus 6.5%, $P = 0.027$). Concomitant agents included aztreonam, fosfomycin, amikacin, and polymyxin B, among which no statistically significant difference was found between CAZ-AVI-based and TGC-based therapy.

The baseline clinical characteristics of the patients are presented in Table 1. A small percentage of the patients presented with different locations of the infection, 39.5% in the CAZ-AVI group versus 27.5% in the TGC group. Further, a comparison of APACHE II scores for CAZ-AVI-based therapy versus TGC-based therapy found that APACHE II scores at onset of infection did not differ (CAZ-AVI-based, APACHE II score = 12; TGC-based, APACHE II score = 13; $P = 0.794$). Similarly, no difference was found for SOFA score in the CAZ-AVI and TGC groups. There were no significant differences with regard to age, comorbidities, CRRT, VAP, and concurrent multisite infections between the two groups. There were statistical differences in sex between the two groups; the CAZ-AVI group included more male patients.

Evaluation of Clinical Outcomes

The data of the two groups were processed using a multivariate regression model and PS analyses, so as to further analyze whether there were differences in terms of clinical efficacy, microbiological clearance, and 28-day survival.

Table 1 shows the clinical outcomes of the study patients. The clinical cure rate was 51.2% (22/43) in the CAZ-AVI group and 29.0% (18/62) in the TGC group ($P = 0.022$). The rate of microbiological cure success was 74.4% (32/43) in the CAZ-AVI group and 33.9% (21/62) in the TGC group ($P < 0.001$). There were no

Table 1 Baseline clinical characteristics and clinical outcomes of the study patients

Variable	CAZ-AVI group ($n = 43$)	TGC group ($n = 62$)	*P* value
Male sex	38 (88.4%)	44 (71.0%)	0.034[a]
VAP	33 (76.7%)	42 (67.7%)	0.136[a]
Age (year)	59.2 ± 19.4	64.1 ± 17.0	0.175[b]
Comorbidity			
Cancer	7 (16.3%)	8 (12.9%)	0.627[a]
Heart disease	27 (62.8%)	36 (58.1%)	0.627[a]
Chronic pulmonary disease	1 (2.3%)	7 (11.3%)	0.137[c]
Diabetes	13 (30.2%)	14 (22.6%)	0.378[a]
Chronic liver disease	2 (4.7%)	4 (6.5%)	1.000[c]
Chronic kidney disease	5 (11.6%)	9 (14.5%)	0.669[a]
Charlson's score	2 (0–4)	2 (0–4)	0.926[d]
Renal replacement therapy	20 (46.5%)	20 (32.3%)	0.139[a]
Mechanical ventilation	37 (86.0%)	59 (95.2%)	0.155[c]
Sepsis	6 (14.0%)	6 (9.7%)	0.544[c]
SOFA score at onset of infection	7 (3–10)	6 (4–8)	0.175[d]
APACHE II score at onset of infection	12 (10–16)	13 (9–16.75)	0.794[d]
Time from the onset of infection until the start of CAZ-AVI or TGC, days	4 (1–8)	2 (1–5.5)	0.122[d]
Concurrent multisite infection			

Table 1 continued

Variable	CAZ-AVI group (n = 43)	TGC group (n = 62)	P value
Concurrent urinary infection	9 (20.9%)	9 (14.5%)	0.391[a]
Concurrent soft tissue infection	4 (9.3%)	3 (4.8%)	0.441[c]
Concurrent intra-abdominal infection	4 (9.3%)	5 (8.1%)	1.000[c]
Combination antibiotic treatment			
Carbapenems	19 (44.2%)	39 (62.9%)	0.058[a]
Amikacin	9 (20.9%)	5 (8.1%)	0.057[a]
Aztreonam	2 (4.7%)	1 (1.6%)	0.566[c]
Fosfomycin	3 (7.0%)	3 (4.8%)	0.687[c]
Polymyxin B	6 (14.0%)	7 (11.3%)	0.684[a]
Monotherapy	9 (20.9%)	4 (6.5%)	0.027[a]
Clinical outcomes			
Clinical cure	22 (51.2%)	18 (29.0%)	0.022[a]
Microbiological success	32 (74.4%)	21 (33.9%)	< 0.001[a]
28-day survival	30 (69.8%)	41 (66.1%)	0.695[a]

Data are presented as the median (interquartile range), mean ± SD or number (percentage) of patients

[a] Determined with χ^2 test

[b] Determined with Student t test

[c] Determined with Fisher's exact test

[d] Determined with Mann–Whitney U test

significant differences between the two groups with regard to the 28-day survival (69.8% versus 66.1%, P = 0.695).

As shown in Table 2, a multivariate analysis model indicated that CAZ-AVI use, age, and the SOFA score at onset of infection were independently associated with clinical cure rates. In the multivariate analysis model of microbiological cure success, CAZ-AVI use was an independent factor in the analysis model. SOFA score at onset of infection was a significant prognostic factor for the 28-day survival rate. Conversely, CAZ-AVI use was not significantly associated with a decreased 28-day survival rate. PS was derived from the multivariate logistic regression analyses of the covariates (sex, age, comorbidities, Charlson's score, VAP, CRRT, SOFA score at onset of infection, APACHE II score at onset of infection, and monotherapy). PS regression adjustment was used as PS method; CAZ-AVI usage and PS (derived from the aforementioned covariates) were included in the binary logistic regression model in order to calculate the OR of clinical cure. The ORs (95% CI) for use of CAZ-AVI according to the PS regression adjustment model are shown in Table 3. Patients who had used CAZ-AVI were more likely to have achieved a clinical cure (OR 3.405; 95% CI 1.304–8.889) and microbiological success (OR 7.778; 95% CI 2.717–22.265) than patients who used TGC. However, there was no statistical significance between the two groups with regard to 28-day survival rates.

Safety Evaluation

The safety of CAZ-AVI or TGC in this study was evaluated from four aspects: liver function [alanine transaminase (ALT), total bilirubin (TBil)]; renal function [serum creatine (Scr)]; coagulation function [activated partial thromboplastin time (APTT), fibrinogen (Fib)]; other adverse reactions (the most prominent adverse reaction observed in this study was diarrhea). Differences in the TBil, Fib, or APTT values before and after treatment in the TGC group were all statistically significant ($P < 0.001$; Table 4). The only prominent adverse reaction observed in the present study was diarrhea. In the TGC group, 27.4% (17/62) of cases developed diarrhea during the treatment period, whereas only 7.0% (3/43) of cases had diarrhea in the CAZ-AVI group (P = 0.009).

Table 2 Univariate and multivariate analyses of factors for clinical cure, microbiological success, and 28-day survival

Variable	Unadjusted OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Clinical cure[b]				
CAZ-AVI use	2.561 (1.138–5.764)	0.023	4.767 (1.694–13.414)	0.003
Age	0.966 (0.943–0.989)	0.004	0.966 (0.935–0.997)	0.034
VAP	0.412 (0.173–0.979)	0.045	0.560 (0.200–1.564)	0.268
Renal replacement therapy	0.318 (0.131–0.773)	0.011	0.351 (0.110–1.117)	0.076
SOFA score at onset of infection	0.801 (0.694–0.924)	0.002	0.802 (0.681–0.945)	0.008
Charlson's score	0.823 (0.687–0.985)	0.033	1.011 (0.791–1.293)	0.927
Mechanical ventilation	0.150 (0.029–0.762)	0.022		
APACHE II score at onset of infection	0.915 (0.852–0.984)	0.016		
Microbiological success[c]				
CAZ-AVI use	5.680 (2.395–13.471)	< 0.001	6.664 (2.626–16.915)	< 0.001
SOFA score at onset of infection	0.963 (0.879–1.055)	0.418	0.917 (0.824–1.020)	0.112
Age	0.986 (0.964–1.007)	0.193	0.992 (0.969–1.016)	0.508
28-day survival[d]				
CAZ-AVI use	1.182 (0.512–2.729)	0.695	1.284 (0.470–3.509)	0.626
Age	0.946 (0.917–0.975)	< 0.001	0.964 (0.926–1.003)	0.070
Heart disease	0.208 (0.077–0.565)	0.002	0.326 (0.092–1.157)	0.083
Chronic pulmonary disease	0.256 (0.057–1.142)	0.074	0.507 (0.089–2.896)	0.445
SOFA score at onset of infection	0.883 (0.797–0.979)	0.018	0.864 (0.765–0.975)	0.018
Charlson score	0.850 (0.722–1.002)	0.052	1.076 (0.867–1.335)	0.504
APACHE II score at onset of infection	0.887 (0.825–0.954)	0.001		

[a] CAZ-AVI use, some meaningful indicators by clinical judgment, and the other variables with $P < 0.10$ (in the univariate analysis) were included in the multivariate analysis (some factors have been excluded for the multivariate analysis to prevent multicollinearity)

[b] Discrimination (AUC = 0.809) and calibration (Hosmer–Lemeshow $\chi^2 = 13.519$; $P = 0.095$)

[c] Discrimination (AUC = 0.743) and calibration (Hosmer–Lemeshow $\chi^2 = 14.239$; $P = 0.076$)

[d] Discrimination (AUC = 0.727) and calibration (Hosmer–Lemeshow $\chi^2 = 8.439$; $P = 0.392$)

DISCUSSION

To the best of our knowledge, the present study was the first to compare the effectiveness of CAZ-AVI- and TGC-based therapy for the clinical treatment of critically ill patients with HAP or VAP caused by CRKP infection. The primary finding of this retrospective cohort study was that the use of CAZ-AVI was an independent factor in the conventional multivariate analysis of a clinical and microbiological cure. In the multivariate logistic regression analysis using PS, CAZ-AVI-based treatment was associated with a clinical and microbiological cure, with no statistical differences in the 28-day survival rates of critically ill patients observed between

Table 3 Associations between CAZ-AVI usage and the clinical outcomes in the crude analysis, multivariable analysis, and propensity score analysis

Analysis	Clinical cure		Microbiological success		28-day survival	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Crude analysis	2.561 (1.138–5.764)	0.023	5.680 (2.395–13.471)	< 0.001	1.182 (0.512–2.729)	0.695
Multivariable analysis[a]	4.767 (1.694–13.414)	0.003	6.664 (2.626–16.915)	< 0.001	1.284 (0.470–3.509)	0.626
PS regression adjustment[b]	3.405 (1.304–8.889)	0.012	7.778 (2.717–22.265)	< 0.001	1.102 (0.424–2.861)	0.842

[a] Shown is the odds ratio/*P* value from the multivariate analysis model. The analysis included all 105 patients

[b] Shown is the odds ratio/*P* value from a multivariable analysis model with additional adjustment for the PS. The analysis included all the patients

the two different regimen groups. In addition, according to the safety evaluation findings in the TGC and CAZ-AVI groups, the TGC regimen was found to be associated with a higher occurrence of adverse reactions, including liver injury, coagulation disorder, and diarrhea.

Of note, the increase in antimicrobial resistance has prompted the research and development of novel antibiotics; however, the combination of their high cost and unattainability significantly hampers their applicability and assessment in clinical practice. The efficacy of TGC and CAZ-AVI, which are currently recommended drugs for CRE treatment, in the clinical treatment of critically ill patients with HAP or VAP caused by CRKP infection is also somewhat lacking. To date, favorable responses to high-dose TGC (200 mg followed by 100 mg every 12 h) have been observed in patients with severe systemic infections, such as infections with multidrug-resistant or extensively drug resistant Gram-negative bacteria [16, 29], which are difficult to treat. In previous studies, the clinical cure rate of high-dose TGC for CRKP infections was 34.6% [30] and 80% [31] in mixed infections, and 47.8% in bloodstream infections [32], all of which were higher than the rates in our study (29%). This may be explained by the fact that CRE-induced HAP is associated with a significantly higher infection-related mortality rate than that observed in CRE infections at other sites (61.4% versus 34.6%) [33]. Accordingly, microbiological eradication rates of high-dose TGC for CRKP have been widely reported at 31.2–66.7% [31, 34], which are higher than the rates observed in the present study.

CAZ-AVI, a promising option for the treatment of carbapenem-resistant Gram-negative bacteria, has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of HAP/VAP owing to its attractive bactericidal broad-spectrum activity, linear pharmacokinetics with a moderate degree of lung penetration, and low risk of serious adverse events [35]. Previous studies have shown the efficacy of CAZ-AVI in the treatment of CRE infection, including CRKP, with low mortality and recurrence rates even following monotherapy [14, 20, 36–40]. In agreement with other similar findings, the clinical cure rate of CAZ-AVI in the present study was 51.2% and the microbiological cure rate was 74.4%. However, a higher efficacy has also been reported; recently, a study by Tsolaki et al. [41] showed that critically ill, mechanically ventilated patients suffering from CRE infections who received CAZ-AVI exhibited improved clinical cure rates (80.5%), microbiological eradication (94.3%), and 28-day survival

Table 4 Comparison the changes of laboratory indicators in each group

Laboratory indicators		Before treatment[a]	After treatment[a]	Statistic (*Z*)	*P* value
TGC group	ALT (U/l)	40.5 (20.18, 82.85)	34.7 (20.48, 59.25)	− 1.052	0.293
	TBil (μmol/l)	11.50 (8.18, 28.41)	23.55 (13.13, 44.70)	− 4.486	< 0.001
	Scr (μmol/l)	74.10 (38.25, 134.73)	69.7 (41.5, 107.68)	− 1.031	0.303
	Fib (g/l)	3.41 (2.47, 4.33)	1.84 (1.51, 2.25)	− 6.18	< 0.001
	APTT (s)	33.85 (31.20, 41.68)	43.20 (34.48, 53.78)	− 5.028	< 0.001
CAZ-AVI group	ALT (U/l)	38.60 (16.50, 80.10)	35.70 (20.60, 76.60)	− 0.223	0.823
	TBil (μmol/l)	16.90 (8.10, 45.80)	14.70 (8.00, 55.81)	− 0.411	0.681
	Scr (μmol/l)	120.4 (45.70, 221.90)	87.7 (41.5, 170.40)	− 1.461	0.144
	Fib (g/l)	3.56 (2.49, 4.84)	3.47 (3.04, 4.21)	− 0.103	0.918
	APTT (s)	35.60 (32.0, 39.60)	36.20 (29.60, 41.40)	− 0.976	0.329

[a] Statistical methods: Wilcoxon rank sum test
[b] Data are presented as the median (interquartile range)

rates (85.4%) than those who received other available antibiotic agents. It was hypothesized that these variations were primarily because all patients in the present study had HAP or VAP, higher Charlson's comorbidity scores, more complicated risk factors for multisite infections, and a higher risk of mortality.

Concomitant medications should also be discussed. In our research, the majority of patients received combination treatment (79.1% in CAZ-AVI-based versus 93.5% in TGC-based regimen; $P > 0.05$). In previous studies, rates of combination treatment were markedly different (27.7–65.8%), which was consistent with the present results [14, 39, 42]. Of note, the available studies appeared to recommend CAZ-AVI-based regimen or monotherapy as the first option for CRE infectious diseases. However, no recommendation on the optimum CZA-AVI combination scheme was formulated in the present study because of the limited number of participants. In a recent study, combination treatment significantly lowered the mortality risk in critically ill patients with CRKP infection [43]. Therefore, it was shown herein that the CAZ-AVI-based regimen was superior to the TGC-based regimen, but it could not be determined whether monotherapy or combination treatment was more effective because of the limited number of participants and observational design.

In the present study, there were notable differences in the rates of adverse events observed between the CAZ-AVI and TGC groups. Although high-dose TGC exhibited a better efficacy and tolerability, severe coagulopathy with hypofibrinogenemia has recently been reported to be associated with the use of high-dose TGC [44, 45]. In the present study, it was found that TGC induced an increase in the TBil levels compared with the pre-treatment levels, which was consistent with the results of previous studies [34, 46]. Another prominent adverse reaction observed in the present study was that 27.4% of patients treated with high-dose TGC suffered diarrhea, a rate similar to that (34.3%) reported by Chen and Shi [34]. By contrast, there were no differences in the kidney, liver, and coagulation indices, as well as diarrhea before and after CAZ-AVI treatment, thus confirming the previously reported safety profile of CAZ-AVI [19, 20, 39].

The present study was limited by its retrospective nature, small clinical sample size, and single-center observational design, which could not exclude indication biases. In addition, the definitive identification of carbapenemases in clinical isolates and synergistic sensitivity in vitro of concomitant medications was not routinely achieved. Moreover, we can only show that the CAZ-AVI-based regimen was superior to the TGC-based regimen, but we could not determine whether monotherapy or a combination regimen was more effective because of the limited number of participants and observational design. To the best of our knowledge, the intrapulmonary pharmacokinetic and pharmacodynamic parameters of the two drugs in critically ill patients have not been systematically compared, although ELF/free serum AUC (or concentration) ratios being 0.3 and 0.76 in healthy adults, respectively, have been reported [47, 48]. In addition, in the present study, the CAV-AVI- and TGC-based regimens were combination treatments; whether such combinations can be used for the treatment of a wide range of bacteria involved in polymicrobial infections remains unclear, to the best of our knowledge. Finally, outside of randomized trials, all conclusions regarding the efficacy of CAZ-AVI versus TGC should be validated in single-site infections and in multiple centers.

CONCLUSIONS

The present study first revealed the clinical value of CAZ-AVI for the treatment of HAP/VAP caused by CRKP in ICUs. The data showed the superiority of CAZ-AVI-based over TGC-based regimen with regard to clinical cure rates, microbiological cure success, and safety issues, although no statistical differences in the 28-day survival rate in the critically ill patients with clinically confirmed HAP/VAP were observed. Furthermore, the curative effectiveness of CAZ-AVI-based therapy versus monotherapy for the treatment of HAP/VAP caused by CRKP was unknown. However, CAZ-AVI may be a suitable alternative for TGC in the treatment of critically ill patients with CRKP-induced HAP or VAP. Further larger randomized clinical trials are required to confirm or exclude these observations.

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Author Contributions. We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. XZ conceptualized and designed the study, designed the data collection and reviewed the manuscript. YS and JH were major contributors in writing the manuscript. PL and TW interpreted and collected data. YS and HW performed statistical analysis. YL and QC coordinated and supervised data collection and carried out antibiotic appropriateness assessments. All authors have read and approved the final manuscript.

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Compliance with Ethics Guidelines. Our study was a retrospective study approved by the Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University, a tertiary care teaching hospital, and the need for patient consent was waived (Approval No. 2021-SR-228). All complete data were afterwards retrospectively extracted from electrical medical records and this study did not directly interfere with the enrolled patients; in addition, the data were de-identified and anonymously analyzed. Our study was performed in accordance with the Helsinki Declaration.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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