Ceftazidime-avibactam Versus Tigecycline for the Treatment of Carbapenem-resistant *Klebsiella Pneumoniae*-induced Pneumonia in Critically Ill Patients

Ying Shi

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Jing Hu

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Peiben Liu

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Tingting Wang

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Han Wang

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Yun Liu

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Quan Cao

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Xiangrong Zuo (✉ zuoxiangrong@njmu.edu.cn)

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Research

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Abstract

Background: To assess the safety patterns and outcomes of ceftazidime-avibactam (CAZ-AVI) versus tigecycline (TGC) for the treatment of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) pneumonia defined as either hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).

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

Results: A total of 105 cases were included in the study; 62 patients (59%) received TGC, and 43 patients (41%) received CAZ-AVI. Clinical cure rates and microbiological cure success of CAZ-AVI were superior to TGC [51.2% versus 29.0% ($P=0.022$) and 74.4% versus 33.9% ($P<0.001$), respectively]. There were no significant differences between the two groups with regard to 28-day survival rates (66.1% versus 69.8%, $P=0.695$). In analyses of conventional multivariate logistic regression and propensity score (PS) analysis, patients in the CAZ-AVI group were more likely to have achieved clinical cure and microbiological success compared with patients in the TGC group. However, the difference between the two groups with regard to 28-day survival rates were not significant. In terms of safety evaluation, generally, the CAZ-AVI group had a lower incidence of adverse reactions when compared with the TGC group.

Conclusions: CAZ-AVI may be a suitable alternative to TGC 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 > 35,000 deaths according to 2019 Antibiotic Resistance Threats Report (1, 2). Amongst the different strains of CREs, carbapenem-resistant *Klebsiella* (*K.*) *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). In intensive care units (ICUs), CRKP can result in serious hospital-acquired infections, the prevalence of which is high (27%), amongst which, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common (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 recommends that polymyxin B and colistin should be avoided for the treatment of CRE infections due to 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 (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 HAP or VAP patients 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 patients treated with either CAZ-AVI or TGC.

Patients And Methods

Patients and clinical data

The present 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. *All patients who were diagnosed with CRKP VAP/HAP and treated with TGC or CAZ-AVI between July 2019 and September 2020 were recruited.*

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 (21). All the isolates in the present study were defined as being CRKP when there was resistant to carbapenems, and susceptible to CAZ-AVI and TGC. Patients whose duration of treatment with CAZ-AVI or TGC was < 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 [for example mechanical ventilation, continuous renal replacement therapy (CRRT)], and laboratory findings. The additional antibacterial drugs were not effective against the *K. pneumonia* that grew in the respiratory secretions. VAP/HAP episodes that were either isolated or in conjunction with mixed microorganisms and multi-site 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 systems or E-test (Antobio, China) according to the Clinical and Laboratory Standards Institute (CLSI) methodology(22). Carbapenem resistance was defined as a 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 cat. no. 25922; ATCC) 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.

TGC-based and CAZ-AVI-based therapy excluded TGC and CAZ-AVI combination regime. In our centre, generally, TGC was administered intravenously with a 200 mg loading dosage, followed by a twice-daily maintenance dosage. 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. Patients with CRRT received a standard dosing for the adequacy of treatment. The dosage of CAZ-AVI was adjusted according to creatinine clearance (CLcr).

Outcome measurements

Clinical success was defined as the normalization of non-microbiological indicators (such as radiological examinations and laboratory tests) or 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 symptoms and signs disappeared, such that cultivable material was not available, the bacteriological results were presumed to be clear. The statistical clearance and hypothetical clearance of bacterial clearance were combined to calculate the clearance rate. 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. PS was estimated using multivariate logistic regression analysis of several covariates⁽²⁵⁾. The primary PS method was PS regression adjustment. The PS was an additional covariate in the binary logistic regression model. In the other methods of PS analysis, PS matching was performed, with a variable ratio of 1:2 based on a matching caliper of 0.2 on the PS scale. The balance of covariates between the two groups was evaluated by the standardized differences (< 0.20 : good balance for a particular covariate). Finally, inverse probability of treatment weighting (IPTW) was used to adjust for confounding variables. A weighting logistic regression model was built using the stabilized IPTW weight, which was calculated by 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(26, 27).

Results

Patients

According to 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; 9 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 baseline clinical characteristics of the patients are as follows (Table 1): There were no significant differences with regard to age, comorbidities, severity of illness scores, CRRT, VAP and concurrent multisite infections between the two groups. There were statistical differences in sex, and monotherapy between the two groups, CAZ-AVI group included more male patients and monotherapy treatment options.

Evaluation of clinical outcomes

The data of the two groups were processed using a multivariate regression model and PS analyses, so as to further analyse 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 significant differences between the two groups with regard to the 28-day survival (66.1% vs. 69.8%, $P = 0.695$).

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 success. 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 the primary PS method; CAZ-AVI use 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 two groups with regard to 28-day survival rates.

As shown in Table 4, a total of 75 patients (30 in the CAZ-AVI group and 45 in TGC group) were included in the 1:2 variable ratio PS matched cohort. In the matched analytic sample, the differences between the two groups were attenuated (absolute standardized difference < 0.20). Clinical cure rates were 53.3% (16/30) in the CAZ-AVI group and 22.2% (10/45) in the TGC group. The rate of microbiological success was 73.3% (22/30) in the CAZ-AVI group and 28.9% (13/45) in the TGC group. Patients of the CAZ-AVI group were more likely to have achieved a clinical cure and microbiological success than patients of the TGC group (OR, 4.000; 95% CI, 1.446–11.064 and OR, 7.310; 95% CI, 2.510–21.286, respectively). Similarly, there was no significant difference between the two groups with regard to the 28-day survival rates. In addition, IPTW yielded similar results (Table 3).

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 creatinine(Scr)]; coagulation function [activated partial thromboplastin time (APTT), fibrinogen(Fib)]; other adverse reactions (the most prominent adverse reaction observed in this study were diarrhoea). Differences in the TBil, Fib or APTT values before and after treatment in TGC group were all statistically significant ($P < 0.001$; Table 6). By contrast, there was no marked difference in these indices before and after treatment in the CAZ-AVI group. The index differences of the two groups before and after treatment (Δ) was used to reflect the differences of the two drugs treatment. As shown in Table 5, there were statistically significant differences in Δ TBil, Δ Fib and Δ APTT between the TGC and CAZ-AVI groups. The only prominent adverse reaction observed in the present study was diarrhoea. In the TGC group, 27.4% (17/62) of cases developed diarrhoea during the treatment period, whereas only 7.0% (3/43) of cases had diarrhoea in the CAZ-AVI group ($P = 0.009$).

Discussion

To the best of our knowledge, the present study is the first to compare the effectiveness of CAZ-AVI and TGC for the clinical treatment of critically ill patients with HAP/VAP due to CRKP infection. The primary finding from this retrospective cohort study was that CAZ-AVI use was an independent factor in the conventional multivariate analysis of clinical cure and microbiological success. The clinical cure rates and microbiological success in the CAZ-AVI group were significantly higher than those of the TGC group after PS analysis, but there was no statistical differences in 28-day survival rates in the critically ill patients two treatment regimens. Several previous reports of CRE infections treated with CAZ-AVI based combination regimes similarly reported favourable outcomes in these patients (15, 19, 28). Additionally, safety evaluation between TGC and CAZ-AVI showed that TGC regime was associated with a greater occurrence of adverse reactions, including liver injury, coagulation disorder and diarrhoea.

Of note, the increase in antimicrobial resistance has encouraged the identification of novel antibiotics, such as meropenem/vaborbactam and plazomicin, although high prices and non-attainable precluded assessment for novel Gram-negative antibiotics in clinical practice has hampered their applicability. TGC has not been approved for the treatment of HAP or VAP, due to its inferiority compared with the imipenem/cilastatin regimen in HAP patients, and the increased mortality rates in the group of patients with VAP treated with standard dose of TGC (50 mg every 12 h; loading dose 100 mg) (29). However, favourable responses with a high TGC dose (200 mg followed by 100 mg every 12 h) has been shown amongst patients with severe systemic infections, with difficult to treat MDR or XDR Gram-negative bacteria (16, 30). As for CRKP infections, the cure rates of high-dose TGC in other studies was 34.6% (31) and 80% (32) in mixed infections, and 47.8% in bloodstream infections (33), all of which are higher than the results of the present study (29%). This may be explained by the different sites of infection. Since there are no previous studies specifically addressing the role of CRE in HAP/VAP, like-for-like comparisons with previous studies cannot be made. HAP caused by CRE is associated with a significantly higher infection-related mortality rate compared with CRE infections at other sites (61.4% versus 34.6%) (34). Accordingly, microbiological eradication rates of high dose TGC for CRKP has been widely reported, and they range from 31.2%-66.7%(32, 35), which are higher than that observed in the present study.

CAZ-AVI, a promising option for the treatment of carbapenem resistant Gram-Negative pathogens (excluding *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*), has been approved by the U.S. FDA and European Medicines Agency for the treatment of HAP/VAP for its attractive bactericidal broad-spectrum activity, linear pharmacokinetics with a high degree of lung penetration, and low risk of serious adverse events(36). Previous studies have shown the efficacy of CAZ-AVI in the treatment of infections due to CRE infection including CRKP (14, 20, 28, 37). Microbiological failure and crude mortality rates of pneumonia were 26.3% and 35.7% with adjusted analysis showing CAZ-AVI may be an important alternative for the treatment of KPC-Kp pneumonia (OR 6.73; 95% CI 1.39–34.94; $P = 0.02$) (38). Of importance, examination of the comparative effectiveness between polymyxin B and CAZ-AVI showed that all-cause 30-day hospital mortality and other clinical outcomes were improved in patients treated first with CAZ-AVI (14). Sousa A. et al showed that CAZ-AVI was a promising salvage therapy for the treatment of OXA-48-producing Enterobacteriaceae with a 14% mortality rate after 14 days and a 10% recurrence rate after 90 days, even in monotherapy(39). The clinical cure of CAZ-AVI in our study was 51.2% and microbiological cure success was 74.4%. Clinical cure at the test-of-cure visit was achieved by 68.8% of CAZ-AVI recipients in the clinically modified intent-to-treat population, and by 77.4% in the clinically evaluable population from data of phase III REPROVE trial(40). Recently, a study from Tsolaki et al showed that patients with CAZ-AVI had improved clinical cure rates (90.5%), microbiological eradication (94.3%) and 28-day survival rates (85.4%) than those with other available antibiotic

agents(41). It is hypothesized that these variations are primarily due to all the patients in the present study having HAP/VAP, higher Charlson's comorbidity scores, more complicated risk factors for multisite infections and a greater risk of mortality.

Inappropriate doses of antimicrobial agents may also lead to treatment failure or drug resistance of pathogens in critically ill patients who receive renal replacement therapy. No significant influence of CRRT on the pharmacokinetics of TGC has been found, considering their non-renal elimination(42). Shields et al showed that CRRT are risk factors for CAZ-AVI treatment failure amongst patients with CRE infections; whereas, adequate doses of CAZ-AVI when 46.5% patients received continuous venovenous hemodiafiltration guaranteed a 100% fT > 4MIC of CAZ as described in a previous case report(28, 43). However, pharmacokinetic and PK/PD studies are required for lung infections, as drug concentrations in the intracellular epithelial lining fluid were important for the treatment of "resistant" pathogens.

Understanding the specific types of carbapenemases produced by a CRE clinical isolate is very important for the choice of drug treatment. CRE includes heterogeneous pathogens with multiple potential resistance mechanisms, which are roughly divided into pathogens that produce carbapenemases and those that do not. Avibactam is similar in activity against SHV-4 as clavulanic acid and anti-CTX-M-15 with clavulanic acid and tazobactam, but more potent against KPC-2 producing carbapenemases and Class C β -lactamase (44–46). If a metallo- β -lactamase [such as the New Delhi metallo- β -lactamase 1 (NDM), Verona integrin-encoded] is identified, antibiotic options would be preferred to CAZ-AVI plus aztreonam for good clinical treatment (47, 48). The most notable difference between CAZ-AVI and TGC was that the activity of TGC against CRE is independent of the presence or type of carbapenemases. Currently 97.4% of clinically isolated CRE strains in China primarily produce bla_{KPC-2} (51.6%) and bla_{NDM} (35.7%) and bla_{OXA-48-like} carbapenemases (7.3%), whereas minor strains carry bla_{IMP} and several carbapenemases. Overall, 64.4% of *K. pneumoniae* were bla_{KPC-2} producers and 21.1% were NDM producers (including 9.0% bla_{NDM-1} producers, 12.0% bla_{NDM-5} producers and 0.1% bla_{NDM-3} producers), with few differences between various epidemiological studies (5, 49). Therefore, from the point of the mechanism of resistance, CAZ-AVI had a 20% higher failure rate in the treatment of CRE infection than TGC, but the present study still showed favourable clinical cure (OR, 3.405; 95% CI, 1.304 to 8.889) and microbiological cure success (OR, 7.778; 95% CI, 2.717 to 22.265) with fewer adverse reaction.

In the present study, there were notable differences in the rates of adverse events observed between CAZ-AVI and the TGC group. Although high-dose TGC has better efficacy and tolerability (30), nausea and vomiting were common adverse events. The primary concern associated with a high dose of TGC remains the reported safety problems. More recently, severe coagulopathy with hypofibrinogenemia associated with the use of high-dose TGC has gained increasing attention (50, 51). In addition, TGC-induced liver toxicity has been reported previously (35, 52); however, the relationship remains unclear. In the present study, the effects of pre-treatment TBil levels were adjusted for, and it was found that TGC induced an increase in TBil. Another prominent adverse reaction observed in this study was that 27.4% patients treated with a high-dose of TGC suffered diarrhoea, similar to the rate (34.3%) of the study by Chen et al. (35). In contrast, there were no differences with regard to kidney, liver and coagulation indices and diarrhoea before and after CAZ-AVI treatment, thus confirming the safety profile of CAZ-AVI observed in previous studies(19, 20, 38).

The present study is limited by its retrospective, small clinical sample size and single-centre observational design, which could not exclude indication biases. Additionally, definitive identification of carbapenemases in clinical isolates were not routinely achieved by PCR and the combined medication regime did not monitor the *in vitro* synergistic sensitivity. Penetration into the bronchial ELF by CAZ-AVI and TGC in intrapulmonary pharmacokinetic and pharmacodynamics study shows that the ratios of lung ELF and serum AUC or concentration were 0.3 and 0.76 in healthy adults respectively (53, 54). Thirdly, in our study, the CAV-AVI and TGC regimen were combinations of antibiotics, whether such combinations cover the wide range of bacteria involved in polymicrobial infections were underestimated. Finally, outside of randomized trials, all conclusions regarding the efficacy of CAZ-AVI versus TGC should be validated in sole site infections and in multiple centres.

In conclusion, the present study first revealed the clinical value of CAZ-AVI for the treatment of HAP/VAP caused by CRKP. The data showed the superiority of CAZ-AVI over TGC 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. Further larger randomized clinical trials are required to confirm or exclude these observations.

Abbreviations

ICU: Intensive care unit; CRKP: Carbapenem-resistant *Klebsiella pneumoniae*; HAP: Hospital-acquired pneumonia; VAP: Ventilator-associated pneumonia; CRE: Carbapenem-resistant Enterobacteriaceae; CAZ-AVI: Ceftazidime-avibactam; TGC: Tigecycline;

Declarations

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Authors' contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. ZXR conceptualized and designed the study and designed the data collection. SY and HJ was a major contributor in writing the manuscript. LPB and WTT interpreted and collected data. WH performed statistical analysis. LY and CQ coordinated and supervised data collection and carried out antibiotic appropriateness assessments. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Informed consent was obtained from patients’ parents.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1.

Baseline clinical characteristics and clinical outcomes of the study patients.^a

Variable	CAZ-AVI group (n=43)	TGC group (n=62)	P Value
Male sex	38(88.4%)	44(71.0%)	0.034 ^b
VAP	33(76.7%)	42(67.7%)	0.136 ^b
Age (yr)	59.2±19.4	64.1±17.0	0.175 ^c
Comorbidity			
Cancer	7(16.3%)	8(12.9%)	0.627 ^b
Heart disease	27(62.8%)	36(58.1%)	0.627 ^b
Chronic pulmonary disease	1(2.3%)	7(11.3%)	0.137 ^d
Diabetes	13(30.2%)	14(22.6%)	0.378 ^b
Chronic liver disease	2(4.7%)	4(6.5%)	1.000 ^d
Chronic kidney disease	5(11.6%)	9(14.5%)	0.669 ^b
Charlson's score	2(0-4)	2(0-4)	0.926 ^e
Renal replacement therapy	20(46.5%)	20(32.3%)	0.139 ^b
Mechanical ventilation	37(86.0%)	59(95.2%)	0.155 ^d
SOFA score at onset of infection	7(3-10)	6(4-8)	0.175 ^e
APACHE II score at onset of infection	12(10-16)	13(9-16.75)	0.794 ^e
Time from the onset of infection until the start of CAZ-AVI or TGC, days	4(1-8)	2(1-5.5)	0.122 ^e
Concurrent multisite infection			
Concurrent CR-KP bacteremia	6(14.0%)	6(9.7%)	0.544 ^d
Concurrent urinary infection	9(20.9%)	9(14.5%)	0.391 ^b
Concurrent soft tissue infection	4(9.3%)	3(4.8%)	0.441 ^d
Concurrent intra-abdominal infection	4(9.3%)	5(8.1%)	1.000 ^d
Combination antibiotic treatment			
Carbapenems	19(44.2%)	39(62.9%)	0.058 ^b
Amikacin	9(20.9%)	5(8.1%)	0.057 ^b
Aztreonam	2(4.7%)	1(1.6%)	0.566 ^d
Fosfomycin	3(7.0%)	3(4.8%)	0.687 ^d
Colistin	6(14.0%)	7(11.3%)	0.684 ^b
Monotherapy	9(20.9%)	4(6.5%)	0.027 ^b
Clinical outcomes			
Clinical cure	22(51.2%)	18(29.0%)	0.022 ^b
Microbiological success	32(74.4%)	21(33.9%)	<0.001 ^b
28-day survival	30(69.8%)	41(66.1%)	0.695 ^b
a: Data are presented as the median (interquartile range) , mean ± SD or number (percentage) of patients.			
b: Determined with χ^2 test.			
c: Determined with Student t-test			
d: Determined with Fisher's exact test.			

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 has been excluded for the multivariate analysis to prevent multicollinearity).				
b: Discrimination (AUC = 0.809) and calibration (Hosmer and Lemeshow χ^2 =13.519; P = 0.095).				
c: Discrimination (AUC = 0.743) and calibration (Hosmer and Lemeshow χ^2 =14.239; P = 0.076).				
d: Discrimination (AUC = 0.727) and calibration (Hosmer and Lemeshow χ^2 =8.439; P = 0.392).				

Table 3.

Associations between CAZ-AVI Use and the Clinical Outcomes in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses.

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
Propensity-Score Analyses						
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
PS matching^c	4.000(1.446-11.064)	0.008	7.310(2.510-21.286)	<0.001	1.231(0.451-3.361)	0.685
IPTW^d	2.881 (1.266-6.557)	0.012	6.098 (2.574-14.445)	<0.001	1.182(0.512-2.729)	0.678
a: Shown is the odds ratio/P-value from the multivariate analysis model with those covariates (including age, VAP, renal replacement therapy, SOFA score before medication and oral temperature before medication). The analysis included all 104 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.						
c: Shown is the odds ratio/P-value from a multivariable analysis model in the PS matched cohort. The analysis included 75 patients (30 who received CAZ-AVI and 45 received TGC).						
d: Shown is the odds ratio/P-value from a weighting logistic regression model with the stabilized inverse-probability-weighting weight. The analysis included all the patients.						

Table 4.

Main baseline clinical characteristics and clinical outcomes of two groups after Propensity-Score Matching^a

Variable	CAZ-AVI group (n=30)	TGC group (n=45)	P Value	standardized mean difference after matching
Male sex	25(83.3%)	37(82.2%)	0.901 ^b	0.051
VAP	21(70.0%)	29(64.4%)	0.617 ^b	-0.039
Age (yr)	60.73±19.2	62.2±16.3	0.715 ^c	-0.121
Comorbidity				
Cancer	4(13.3%)	5(11.1%)	1.000 ^d	0.045
Heart disease	18(60%)	28(62.2%)	0.846 ^b	-0.068
Chronic pulmonary disease	1(3.3%)	3(6.7%)	0.646 ^d	-0.109
Diabetes	7(23.3%)	10(22.2 %)	0.910 ^b	0
Chronic liver disease	1(3.3%)	2(4.4%)	1.000 ^d	0
Chronic kidney disease	4(13.3%)	7(15.6%)	1.000 ^d	-0.051
Charlson score	2(0-4)	1(0-4)	0.847 ^e	-0.019
Renal replacement therapy	11(13.3%)	19(8.9%)	0.714 ^b	-0.033
Concurrent CR-KP bacteremia	4(13.3%)	4(8.9%)	0.706 ^d	0.095
SOFA score before medication	6(3-9.25)	6(4-8)	0.939 ^e	0.050
APACHE II score before medication	12.70±5.43	13.27±6.34	0.690 ^c	-0.086
Monotherapy	3(10.0%)	3(6.7%)	0.678 ^d	0
Clinical outcomes				
Clinical cure	16(53.3%)	10(22.2%)	0.006 ^b	
Microbiological success	22(73.3%)	13(28.9%)	<0.001 ^b	
28-day survival	21(70.0%)	29 (64.4%)	0.617 ^b	
<p>a: Data are presented as the median (interquartile range) , mean ± SD or number (percentage) of patients.</p> <p>b: Determined with χ^2 test.</p> <p>c: Determined with Student t-test</p> <p>d: Determined with Fisher's exact test.</p> <p>e: Determined with Mann-Whitney U test.</p>				

Table 5.

Comparison of laboratory indicators before and after treatment between the two groups.^a

Laboratory indicators		TGC group ^b	CAZ-AVI group ^b	Statistic(Z)	P value
Before treatment	ALT (U/L)	40.5(20.18, 82.85)	38.60(16.50, 80.10)	-0.296	0.767
	TBil (umol/L)	11.50(8.18, 28.41)	16.90(8.10-45.80)	-0.623	0.534
	Scr (umol/L)	74.10(38.25, 134.73)	120.4(45.70, 221.90)	-1.847	0.065
	Fib(g/L)	3.41(2.47, 4.33)	3.56 (2.49, 4.84)	-0.391	0.696
	APTT(s)	33.85(31.20, 41.68)	35.60(32.0-39.60)	-0.430	0.667
After treatment	ALT (U/L)	34.7(20.48, 59.25)	35.70(20.60, 76.60)	-0.642	0.521
	TBil (umol/L)	23.55(13.13, 44.70)	14.70(8.00, 55.81)	-1.007	0.314
	Scr (umol/L)	69.7(41.5, 107.68)	87.7(41.5, 170.40)	-1.290	0.197
	Fib(g/L)	1.84(1.51, 2.25)	3.47(3.04, 4.21)	-6.533	<0.001
	APTT(s)	43.20(34.48, 53.78)	36.20(29.60, 41.40)	-3.405	<0.001
Differences before and after treatment (Δ) ^c	Δ ALT (U/L)	-1.60(-34.15, 12.70)	0.20(-24.40, 18.00)	-0.502	0.616
	Δ TBil (umol/L)	8.00(-0.43, 16.39)	1.5(-3.60, 10.01)	-2.621	0.009
	Δ Scr (umol/L)	-1.85(-36.33, 12.53)	-2.19(-46.50, 12.30)	-0.091	0.927
	Δ Fib(g/L)	-1.35(-2.11, -0.60)	-0.14(-1.01, 1.00)	-4.350	<0.001
	Δ APTT(s)	8.95(1.73, 16.1)	0.60(-1.10, 5.10)	-3.744	<0.001
a: Statistical methods: Mann-Whitney U test.					
b: Data are presented as the median (interquartile range).					
c: Δ was defined as differences between the index before and after the use of TGC or CAZ-AVI.					

Table 6.

Comparison the changes of laboratory indicators in each group. ^a

Laboratory indicators		Before treatment ^b	After treatment ^b	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 (umol/L)	11.50(8.18, 28.41)	23.55(13.13, 44.70)	-4.486	<0.001
	Scr (umol/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 (umol/L)	16.90(8.10-45.80)	14.70(8.00, 55.81)	-0.411	0.681
	Scr (umol/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).					