

Ceftazidime/Avibactam versus Polymyxin B in the Challenge of Carbapenem-Resistant *Pseudomonas aeruginosa* Infection

Juan Chen*, Qiqiang Liang*, Xinyi Chen, Jing Wu, Yanchao Wu, Gaoqin Teng , Man Huang 

Department of General Intensive Care Unit, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Man Huang, Department of General Intensive Care Unit, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China, Tel/Fax +86 571 89713427, Email huangman@zju.edu.cn

Purpose: Ceftazidime/avibactam (CAZ/AVI) monotherapy and polymyxin B-based combination therapy are currently two treatment options for patients with carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) infection; however, few studies have contrasted the relative efficacy of the two antibiotic regimens. The purpose of this study was to compare the effectiveness of CAZ/AVI and polymyxin B against CRPA infection and analyze the independent predictors of 30-day mortality or survival.

Patients and Methods: This single-center retrospective observational study included patients with CRPA infection treated with CAZ/AVI or polymyxin B between January 2018 and December 2020. The primary outcomes were the 14-day and 30-day mortality. The secondary outcomes were in-hospital mortality and bacterial clearance. Baseline characteristics and outcomes were compared between the two groups, and COX regression analysis was used to identify predictors of 30-day mortality.

Results: A total of 136 patients with CRPA infection were enrolled, including 51 patients in the CAZ/AVI group and 85 patients in the polymyxin B group. The 14-day mortality (5.9% vs 27.1%, $p=0.002$), 30-day mortality (13.7% vs 47.1%, $p<0.001$) and in-hospital mortality (29.4% vs 60.0%, $p=0.001$) in the CAZ/AVI group were significantly lower than the polymyxin B group. The bacterial clearance rate (45.1% vs 12.9%, $p<0.001$) in the CAZ/AVI group were higher than in the polymyxin B group. After adjustment by propensity score matching, the CAZ/AVI group still had lower 30-day mortality (14.3% vs 42.9%, $p=0.018$) and higher bacterial clearance rate (42.9% vs 14.3%, $p=0.018$) than the polymyxin B group. The multivariate COX analysis showed that the age was identified as independent predictor of 30-day mortality while CAZ/AVI therapy and central venous catheterization emerged as independent predictors of 30-day survival.

Conclusion: CAZ/AVI therapy was superior to polymyxin B therapy for patients with CRPA infection, and provided significant survival benefits, but further larger studies were needed to substantiate our findings.

Keywords: carbapenem-resistant *Pseudomonas aeruginosa*, ceftazidime/avibactam, polymyxin B, effectiveness, mortality

Introduction

In recent years, the rapid spread of carbapenem-resistant gram-negative bacteria (CRGNB) resistance has become a major public health concern worldwide due to the limitation of effective therapeutic options.¹ Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), as a member of CRGNB, is listed by the World Health Organization as a “priority pathogen” requiring urgent antibacterial drug research and development.² An epidemiological report on ICU-acquired healthcare associated infections (HAI) from the European Centre for Disease Prevention and Control (ECDC) stated that *Pseudomonas aeruginosa* was the most common cause of ICU-acquired pneumonia and one of the most prevalent microorganisms detected in ICU-acquired urinary tract infections and bloodstream infections.³ However, with the widespread and unreasonable use of carbapenem antibiotics, the resistance of *Pseudomonas aeruginosa* to these antibiotics has an upward tendency, and the total mortality rate of *Pseudomonas aeruginosa* infection is also at a high

level.^{4,5} Currently, the treatment options for CRPA infection are limited, usually based on polymyxin (including colistin or polymyxin B), aminoglycosides, carbapenems or combination therapy, as well as novel antibiotic therapies including ceftazidime/avibactam (CAZ/AVI).⁶ However, polymyxin B and aminoglycoside drugs have been associated with nephrotoxic side effects,⁷ with increasing number of reports of *Pseudomonas aeruginosa* resistance to these antibiotics worldwide.⁸ Accordingly, it is imperative to find effective treatment approaches against CRPA infection. In this respect, novel antibacterial drugs are constantly being developed against these resistant bacteria.

Ceftazidime-Avibactam is a new β -lactam/ β -lactamase inhibitor.⁹ In the European Union, ceftazidime-avibactam has been approved for the treatment of adults with complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired pneumonia, and other infections caused by Gram-negative organisms in patients with limited treatment options.¹⁰ A recent study in China showed that CAZ/AVI had strong antibacterial activity against Enterobacteriaceae and *Pseudomonas aeruginosa* isolates collected from 30 medical centers of China Antimicrobial Surveillance Network (CHINET) in 2017.¹¹ Likewise, studies in the United States and European countries had pointed out that, CAZ/AVI was effective against carbapenem-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in vitro, suggesting that CAZ/AVI might be an alternative treatment option for CRPA.^{12,13} At present, some published studies have illustrated the clinical therapeutic effects of CAZ/AVI on several different pathogens of CRGNB.^{14–16} Meanwhile, several studies have also displayed the benefits of CAZ/AVI in the treatment of CRGNB, with the reduced mortality to a certain extent compared with the control group.^{17–20}

Current treatment regimens against CRPA infection included CAZ/AVI monotherapy and polymyxin-based combination treatment. Nonetheless, there were limited data on the comparison of CAZ/AVI and polymyxin in the treatment of patients with CRPA infection. For this purpose, this study was designed to compare the effectiveness of CAZ/AVI versus polymyxin B in patients with CRPA infection and to analyze the independent predictors associated with mortality and survival.

Materials and Methods

Patient and Study Setting

This was a single-center, retrospective and observational study conducted in the general intensive care unit (40 beds) of the Second Affiliated Hospital of Zhejiang University School of Medicine, a 3500-bed tertiary care teaching hospital in Hangzhou, Zhejiang in China, from January 2018 to December 2020. Patients with CRPA infection were included, and all received CAZ/AVI monotherapy or polymyxin B-based combination therapy. The usage of CAZ/AVI or polymyxin B was followed by the guideline recommendations during the period. The inclusion criteria consisted of (i) patients older than 16 years old, (ii) patients with monomicrobial CRPA infection diagnosed by clinicians, (iii) patients who received treatment with CAZ/AVI or polymyxin B. Exclusion criteria were as follows: patients with a duration of treatment of less than 72 hours; extremely severe burn; repeated study drug exposed. The primary outcomes were the 14-day and 30-day mortality rates. The secondary outcomes were in-hospital mortality and bacterial clearance. This study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University. The ethics committee waived the need for informed consent from patients due to the retrospective and anonymous characters of the study. In this study, a large amount of data was automatically collected and generated through the database to control selection bias and information bias related to the study.

Data Collection

Patients' information was obtained from the electronic medical records. The baseline data consisted of: demographic characteristics, underlying diseases and comorbidities, the use of corticosteroid and immunosuppressants, invasive procedures (including endotracheal intubation, tracheotomy, mechanical ventilation, central venous catheterization, continuous renal replacement therapy (CRRT), pulse indicator continuous cardiac output (PICCO), and extracorporeal membrane oxygenation (ECMO)) and recent surgical history. The Charlson comorbidity index (CCI) and age-adjusted Charlson comorbidity index (aCCI) were scored at admission according to the criteria, in order to quantify the comorbidity condition of patients.²¹ Other data were infection and treatment-related variables, including septic shock,

the site of infection, time duration from the onset of infection to initiation of treatment, and duration of treatment. In addition, outcome variables included therapeutic outcomes (14-day, 30-day, and in-hospital mortality), length of ICU and total hospital stay, and bacterial clearance.

Definitions

Septic shock was defined in accordance with Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).²² The definition of pulmonary infection was based on the Infectious Diseases Society of America (IDSA) standard of American.²³ Bloodstream infection was defined as the presence of at least one positive blood culture of the target pathogen accompanied by signs and symptoms of infection. The diagnosis of pulmonary infection and bloodstream infection was based on the guidelines by the (IDSA).²³ Intra-abdominal infection diagnosed on the basis of the guidelines by the SIS (Surgical Infection Society) and IDSA,²⁴ was defined as the spread of infection to the peritoneal cavity and was associated with abscess formation and the occurrence of peritonitis. Other sites of infections diagnosed according to the guidelines,^{23,25–28} included urinary tract infections, intracranial infections, intestinal infections, wound infections, and mediastinal infections. Bacterial clearance was confirmed when two negative cultures were obtained after treatment, and there was no recurrence within a week.

Microbiology

In this study, microorganisms were identified using the VITEK system (bioMérieux, Marcy l'Etoile, France), and susceptibility testing was performed and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The isolates from patients with CRPA infections was tested for susceptibility to some β -lactams, aminoglycosides and quinolones antibiotics. Carbapenem resistance was defined as: the resistance to ertapenem (the minimum inhibitory concentration (MIC) > 2 mg/mL), and the resistance to imipenem or meropenem (the MIC > 4 mg/mL) according to the CLSI guidelines.²⁹

Statistical Analysis

Categorical variables were expressed as absolute numbers and relative frequencies, and compared using the Chi-square test or Fisher's exact test. Continuous variables were expressed as the mean \pm variance and compared using the Student's *t*-test when they followed a normal distribution. Otherwise, continuous variables if not normally distributed were expressed as the median and interquartile range (IQR), and the Mann–Whitney *U*-test was used to compare groups. The COX proportional hazard model was used to estimate the crude and adjusted hazard ratios associated with mortality. After univariate analysis, significant variables ($p < 0.05$) were entered into the multivariate regression model for analysis to identify independent risk factors for mortality. Propensity score matching method was performed to control for confounding variables in our study with propensity score estimated using logistic regression model. In this study, a one-to-one nearest neighbor matching algorithm was adopted with a caliper width of 0.02. Variables adjusted for propensity score matching in the study included: age, chronic pulmonary disease, organ transplantation, immunosuppressants, corticosteroid use, surgical history, blood-stream infections, and septic shock. The Kaplan-Meier method was used for survival analysis. All statistical analyses were performed in IBM SPSS Statistics v.25.0, and *P* values < 0.05 were statistically significant.

Results

Characteristics of Baseline and Microbiology

During the study period, 136 patients with CRPA infection were eligible and enrolled in the study (Figure 1). Among them, 51 patients were treated with ceftazidime/avibactam monotherapy while 85 patients received the therapy of polymyxin B mostly combined with other antibiotics (carbapenems and amikacin etc.). Table 1 provides a comparison of the characteristics of patients receiving the treatment of CAZ/AVI or polymyxin B due to CRPA infection. In our study cohort, the overall median age was 61.5 (IQR, 51.25–70), with no significant difference between the two groups. The overall median CCI and aCCI scores were 3 (IQR, 2–4) and 4 (IQR, 3–6), respectively. The scores of the two groups were similar at baseline. However, the proportion of chronic pulmonary diseases comorbidity in the CAZ/AVI group was

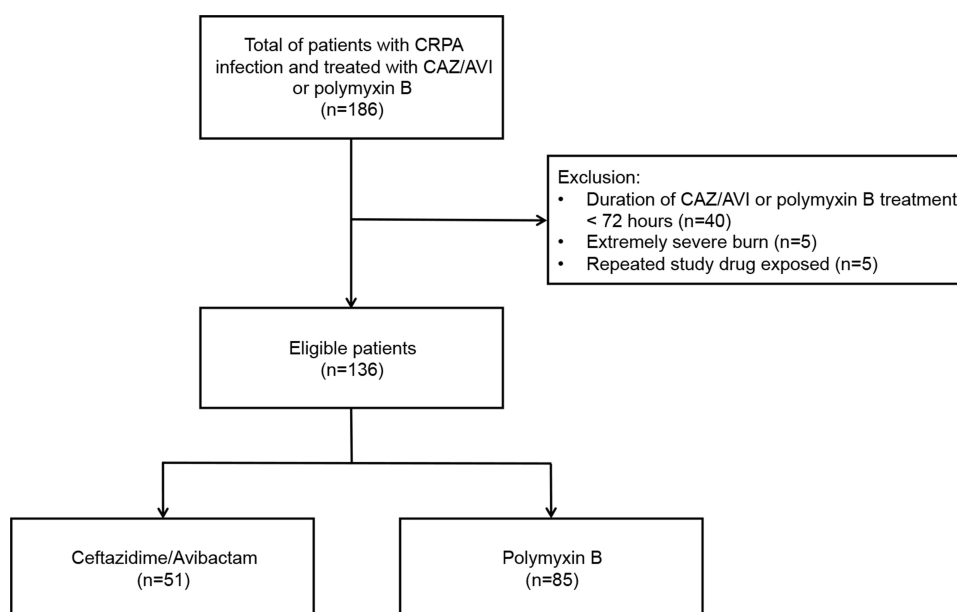


Figure 1 Study flow chart.

Abbreviations: CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CAZ/AVI, ceftazidime/avibactam.

significantly higher than in the polymyxin B group (49% vs 11.8%, $p<0.001$). In addition, the proportion of organ transplants in the CAZ/AVI group (41.2% vs 7.1%, $p<0.001$) was also apparently higher than that in the polymyxin B group, as were immunosuppressants (43.1% vs 11.8%, $p<0.001$) and corticosteroid (60.8% vs 31.8%, $p=0.001$) use. Overall, patients with a surgical history accounted for a relatively high proportion (74.3%), with significantly more patients in the CAZ/AVI group than in the polymyxin B group (88.2% vs 65.9%, $p=0.004$). Furthermore, there was no significant difference in the proportion of invasive operations between the two groups, including endotracheal intubation, tracheotomy, mechanical ventilation and central venous catheterization. Regarding the severity of disease, the incidence of septic shock (31.4% vs 48.2%, $p=0.054$) and CRRT (39.2% vs 54.1%, $p=0.092$) in the CAZ/AVI group was lower; however, there was no statistically significant difference.

In the overall study cohort, almost all patients had pulmonary infections (99.3%), while some had bloodstream infections (36%). Besides, about 21.3% of patients concurrently presented with other site infections, including skin and soft-tissue, urinary tract, intracranial infection etc. In the CAZ/AVI group, the proportion of pulmonary, bloodstream and other site infection was 100%, 23.5% and 25.5%, respectively. In the polymyxin B group, the ratio of pulmonary infection (98.8%) and other site infection (18.8%) was similar to the CAZ/AVI group; however, nearly half of the patients had bloodstream infections (43.5%), with a significantly higher incidence rate than in the CAZ/AVI group ($p=0.019$).

Treatment Characteristics

Treatment characteristics of patients in our study were outlined in Table 1 and details of the related antibiotics used in two groups were shown in Table S1. In addition, antimicrobial susceptibility of isolates from patients with CRPA infections in two groups was displayed in Table S2. As shown in Table 1, in the overall cohort, the median initiation time of CAZ/AVI or polymyxin B treatment was 6–7 days (IQR, 4–12.75 days), and the median duration of treatment was 9–10 days (IQR, 5–14 days); no statistical difference was found between the two groups. The median length of the overall ICU hospital stay was 28 days (IQR, 17–44.5 days), with a median length of 38 days (IQR, 25–74 days) and 23 days (IQR, 14–33 days) in the CAZ/AVI and polymyxin B groups, respectively. Obviously, the CAZ/AVI group had a longer ICU hospital stay than the polymyxin B group ($p<0.001$). Similarly, the total length of hospital stay was significantly longer in the CAZ/AVI group than in the polymyxin B group ($p<0.001$).

Table I Comparison of Clinical Characteristics Between CAZ/AVI and Polymyxin B in Patients with CRPA Infection

Characteristics	Total (n=136)	CAZ/AVI (n=51)	Polymyxin B (n=85)	P value
Demographic variables				
Male sex	100 (73.5)	37 (72.5)	63 (74.1)	0.841
Age (years)	61.5 (51.25–70)	65 (58–70)	58 (48–69)	0.052
BMI	23.55±4.47	23.28±5.07	23.71±4.10	0.588
CCI	3 (2–4)	3 (2–4)	3 (2–4)	0.248
aCCI	4 (3–6)	5 (3–6)	4 (3–6)	0.493
APACHE II score	16 (12–22)	15 (12–19)	18 (12–22)	0.175
SOFA score	6 (4–8)	5 (4–7)	7 (4–8)	0.054
Comorbidities				
Cardiovascular disease	46 (33.8)	17 (33.3)	29 (34.1)	0.925
Chronic pulmonary disease	35 (25.7)	25 (49.0)	10 (11.8)	<0.001
Chronic kidney disease	7 (5.1)	3 (5.9)	4 (4.7)	1
Chronic liver disease	9 (6.6)	3 (5.9)	6 (7.1)	1
Cerebrovascular disease	39 (28.7)	10 (19.6)	29 (34.1)	0.070
Gastrointestinal diseases	15 (11.0)	7 (13.7)	8 (9.4)	0.437
Hypertension	57 (41.9)	20 (39.2)	37 (43.5)	0.622
Diabetes mellitus	32 (23.5)	13 (25.5)	19 (22.4)	0.676
Solid tumor	16 (11.8)	5 (9.8)	11 (12.9)	0.582
Hematologic malignancy	2 (1.5)	1 (2.0)	1 (1.2)	1
Organ transplant	27 (19.9)	21 (41.2)	6 (7.1)	<0.001
Chemotherapy	2 (1.5)	1 (2.0)	1 (1.2)	1
Immunosuppressants use	32 (23.5)	22 (43.1)	10 (11.8)	<0.001
Corticosteroid use	58 (42.6)	31 (60.8)	27 (31.8)	0.001
Surgical history	101 (74.3)	45 (88.2)	56 (65.9)	0.004
Invasive procedures				
Endotracheal intubation	122 (89.7)	43 (84.3)	79 (92.9)	0.109
Tracheotomy	81 (59.6)	30 (58.8)	51 (60.0)	0.892
Mechanical ventilation	136 (100)	51 (100)	85 (100)	1
Central venous catheter	118 (86.8)	48 (94.1)	70 (82.4)	0.050
CRRT	66 (48.5)	20 (39.2)	46 (54.1)	0.092
Septic shock	57 (41.9)	16 (31.4)	41 (48.2)	0.054
Infection variables				
Pulmonary infection	135 (99.3)	51 (100)	84 (98.8)	1
Bloodstream infection	49 (36.0)	12 (23.5)	37 (43.5)	0.019
Intra-abdominal infection	4 (2.9)	0 (0)	4 (4.7)	0.294
Other infection sites	29 (21.3)	13 (25.5)	16 (18.8)	0.358
Treatment variables				
Duration of therapy	9 (5–14)	10 (6–17)	9 (5–12)	0.108
Time to initiation of treatment	6.5 (4–12.75)	6 (4–15)	7 (3.5–10.5)	0.580
Outcomes				
The length of ICU (days)	28 (17–44.5)	38 (25–74)	23 (14–33)	<0.001
The length of hospitals (days)	34 (22.67–61)	48 (33–83)	29 (19–43)	<0.001
14-day mortality	26 (19.1)	3 (5.9)	23 (27.1)	0.002
30-day mortality	47 (34.6)	7 (13.7)	40 (47.1)	<0.001
In-hospital mortality	66 (48.5)	15 (29.4)	51 (60.0)	0.001
Bacterial eradication	34 (25.0)	23 (45.1)	11 (12.9)	<0.001

Notes: Data are expressed as number (%) or mean± SD or median (IQR).

Abbreviations: CAZ/AVI, Ceftazidime/avibactam; BMI, Body mass index; CCI, Charlson comorbidity index; aCCI, age-adjusted Charlson comorbidity index; CRRT, Continuous renal replacement therapy; ICU, Intensive care unit; IQR, Interquartile range.

Outcomes

Regarding primary outcomes (Table 1), the 14-day mortality rate (5.9 vs 27.1%, $p=0.002$) and the 30-day mortality rate (13.7% vs 47.1%, $p<0.001$) in the CAZ/AVI group were significantly lower than in the polymyxin B group. Meanwhile, the difference in in-hospital mortality between the two groups was also significant (29.4% vs 60.0%, $p=0.001$). Furthermore, a higher frequency of bacterial eradication was observed with the use of CAZ/AVI compared with polymyxin B (45.1% vs 12.9%, $p<0.001$). In addition, after adjusting some variables using the propensity matching scoring method to control the consistency of baseline levels between the two groups, we compared the outcome variables of the CAZ/AVI group with polymyxin B group (Table 2), and found that the 30-day mortality rate of CAZ/AVI treatment was still significantly lower than that of the polymyxin B group (14.3% vs 42.9%, $p=0.018$), but there was no statistical difference in 14-day mortality rate (7.1% vs 25%, $p=0.146$) and in-hospital mortality (35.7% vs 53.6%, $p=0.179$). Besides, the bacterial clearance rate in the CAZ/AVI group was higher than in the polymyxin B group (42.9% vs 14.3%, $p=0.018$); however, the CAZ/AVI group had longer ICU hospital stay ($p=0.021$) and total hospital stay ($p=0.008$) compared with the polymyxin B group.

Independent Predictors of Mortality

Characteristics of the survivor and non-survivor sub-groups at 30 days were described in Table 3. Significant differences in CCI ($p=0.015$), aCCI ($p=0.045$), chronic pulmonary disease ($p=0.003$), organ transplant ($p=0.016$), surgical history ($p=0.004$), tracheotomy ($p=0.010$), CRRT treatment ($p<0.001$), septic shock ($p<0.001$) were observed. Table 4 showed the univariate and multivariate analysis of factors related to 30-day mortality. During the multivariate COX regression analysis (Table 4), CRRT and septic shock were independent predictors of 30-day mortality while CAZ/AVI therapy, surgical history and the duration of therapy were independent predictors of 30-day survival. After adjustment by propensity score matching, the adjusted multivariate COX analysis showed (Table 5) that the age was identified as independent predictor of 30-day mortality while CAZ/AVI therapy and central venous catheterization emerged as independent predictors of 30-day survival. The Kaplan-Meier curves of patients who received CAZ/AVI or polymyxin B for the treatment of CRPA infection were depicted in Figure 2 ($p<0.001$). The survival curve analysis visually showed that the risk of mortality in CAZ/AVI treatment for patients with CRPA infection was reduced.

Discussion

This was a single-center retrospective observational cohort study of critically ill patients with CRPA infection treated with CAZ/AVI or polymyxin B. Importantly, we found that CAZ/AVI therapy provided a significant survival benefit compared to polymyxin B therapy in patients with CRPA infection; patients treated with CAZ/AVI had lower 14-day, 30-day and in-hospital mortality than those treated with polymyxin B. After adjusting for confounders, the 30-day mortality in the CAZ/AVI group was still significantly lower than that in the polymyxin B group. In terms of bacterial clearance, the clearance rate of the CAZ/AVI group was obviously higher than polymyxin B group, even after the adjustment of PSM. Besides, the adjusted multivariate COX analysis showed that the age was identified as independent predictor of 30-day mortality while CAZ/AVI therapy and central venous catheterization were independent predictors of 30-day survival.

Based on the above analysis results, CAZ/AVI was demonstrated to effectively treat patients with CRPA infection in this cohort. In terms of outcome variables, this study showed the clinical efficacy of CAZ/AVI in the treatment of CRPA infection, characterized by a lower in-hospital mortality rate (29.4%), and a lower mortality rate at 14 and 30 days (5.9%, 13.7%, respectively) and a higher bacterial clearance rate (45.1%). A retrospective study designed to evaluate and describe the characteristics and outcomes of 8 patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* infections treated with CAZ/AVI showed that the 30-day mortality rate was 12.5%, which was consistent with our findings.¹⁶ Another multi-center retrospective study was conducted in 6 medical centers in the United States from 2015 to 2019, enrolling a total of 203 subjects with carbapenem-resistant Enterobacteriaceae ($n=117$) and *Pseudomonas aeruginosa* ($n=63$) isolated from culture specimens. The 30-day mortality rate after CAZ/AVI treatment was 17.2%, which was also in line with our findings.¹⁹ These studies shown that CAZ/AVI had apparent clinical effects on patients with CRPA infection, and the potential reason might be that CAZ/AVI had

Table 2 Comparison of Clinical Characteristics Between CAZ/AVI and Polymyxin B in Patients with CRPA Infection After Adjustment

Characteristics	Total (n=56)	CAZ/AVI (n=28)	Polymyxin B (n=28)	P value
Demographic variables				
Male sex	42 (75.0)	20 (71.4)	22 (78.6)	0.537
Age (years)	62.5 (48.25–70.75)	62.5 (58–70)	62.5 (47.25–71)	0.780
BMI	23.24±4.02	23.84±4.77	22.63±3.07	0.264
CCI	3 (2–4)	3 (2–3)	3 (1.25–5)	0.363
aCCI	4.70±2.51	4.57±2.22	4.82±2.80	0.713
APACHE II score	16 (12.25–20)	15.5 (14–24.25)	16 (10.5–19.5)	0.485
SOFA score	6 (4–8)	6 (4–8)	6 (4–8)	0.954
Comorbidities				
Cardiovascular disease	17 (30.4)	9 (32.1)	8 (28.6)	0.771
Chronic pulmonary disease	11 (19.6)	6 (21.4)	5 (17.9)	0.737
Chronic kidney disease	5 (8.9)	3 (10.7)	2 (7.1)	1
Chronic liver disease	5 (8.9)	1 (3.6)	4 (14.3)	0.349
Cerebrovascular disease	16 (28.6)	8 (28.6)	8 (28.6)	1
Gastrointestinal diseases	5 (8.9)	2 (7.1)	3 (10.7)	1
Hypertension	23 (41.1)	11 (39.3)	12 (42.9)	0.786
Diabetes mellitus	11 (19.6)	7 (25.0)	4 (14.3)	0.313
Solid tumor	8 (14.3)	3 (10.7)	5 (17.9)	0.703
Hematologic malignancy	1 (1.8)	1 (3.6)	0 (0.0)	1
Organ transplant	10 (17.9)	5 (17.9)	5 (17.9)	1
Chemotherapy	1 (1.8)	1 (3.6)	0 (0.0)	1
Immunosuppressants use	11 (19.6)	6 (21.4)	5 (17.9)	0.737
Corticosteroid use	27 (48.2)	14 (50.0)	13 (46.4)	0.789
Surgical history	46 (82.1)	22 (78.6)	24 (85.7)	0.485
Invasive procedures				
Endotracheal intubation	50 (89.3)	23 (82.1)	27 (96.4)	0.195
Tracheotomy	37 (66.1)	19 (67.9)	18 (64.3)	0.778
Mechanical ventilation	56 (100)	28 (100)	28 (100)	1
Central venous catheter	50 (89.3)	26 (92.9)	24 (85.7)	0.666
CRRT	27 (48.2)	12 (42.9)	15 (53.6)	0.422
Septic shock	25 (44.6)	13 (46.4)	12 (42.9)	0.788
Infection variables				
Pulmonary infection	55 (98.2)	28 (100)	27 (96.4)	1
Bloodstream infection	18 (32.1)	10 (35.7)	8 (28.6)	0.567
Intra-abdominal infection	2 (3.6)	0 (0)	2 (7.1)	0.471
Other infection sites	15 (26.8)	9 (32.1)	6 (21.4)	0.365
Treatment variables				
Duration of therapy	9 (5.25–14.75)	10 (6–16.75)	8.5 (5–11)	0.109
Time to initiation of treatment	7 (4–14.5)	10.5 (4–18)	6 (4–10.5)	0.366
Outcomes				
The length of ICU (days)	28 (17–43.75)	32.5 (19.52–72)	24.5 (14–32.5)	0.021
The length of hospitals (days)	33.5 (24.3–60.5)	46 (27.5–78.5)	29.5 (19–43.25)	0.008
14-d mortality	9 (16.1)	2 (7.1)	7 (25.0)	0.146
30-d mortality	16 (28.6)	4 (14.3)	12 (42.9)	0.018
In-hospital mortality	25 (44.6)	10 (35.7)	15 (53.6)	0.179
Bacterial eradication	16 (28.6)	12 (42.9)	4 (14.3)	0.018

Notes: Data are expressed as number (%) or mean± SD or median (IQR).

Abbreviations: CAZ/AVI, Ceftazidime/avibactam; BMI, Body mass index; CCI, Charlson comorbidity index; aCCI, age-adjusted Charlson comorbidity index; CRRT, Continuous renal replacement therapy; ICU, Intensive care unit; IQR, Interquartile range.

Table 3 Comparison of Clinical Characteristics Between 30-Day Survivors and Non-Survivors with CRPA Infection

Characteristics	Total (n=136)	Survivors (n=89)	Non-Survivors (n=47)	P value
Demographic variables				
Male sex	100 (73.5)	67 (75.3)	33 (70.2)	0.524
Age (years)	61.5 (51.25–70)	62 (50.5–70.0)	61 (53–71)	0.980
BMI	23.55±4.47	23.76±4.67	23.15±4.10	0.446
CCI	3 (2–4)	3 (1–4)	3 (3–4)	0.015
aCCI	4 (3–6)	4 (3–6)	5 (4–6)	0.045
APACHE II score	16 (12–22)	16 (12–20)	17 (12–23)	0.277
SOFA score	6 (4–8)	6 (4–8)	7 (4–9)	0.338
Comorbidities				
Cardiovascular disease	46 (33.8)	33 (37.1)	13 (27.7)	0.270
Chronic pulmonary disease	35 (25.7)	30 (33.7)	5 (10.6)	0.003
Chronic kidney disease	7 (5.1)	5 (5.6)	2 (4.3)	1
Chronic liver disease	9 (6.6)	7 (7.9)	2 (4.3)	0.658
Cerebrovascular disease	39 (28.7)	23 (25.8)	16 (34.0)	0.315
Gastrointestinal diseases	15 (11.0)	10 (11.2)	5 (10.6)	0.916
Hypertension	57 (41.9)	38 (42.7)	19 (40.4)	0.799
Diabetes mellitus	32 (23.5)	19 (21.3)	13 (27.7)	0.409
Solid tumor	16 (11.8)	9 (10.1)	7 (14.9)	0.411
Hematologic malignancy	2 (1.5)	1 (1.1)	1 (2.1)	1
Organ transplant	27 (19.9)	23 (25.8)	4 (8.5)	0.016
Chemotherapy	2 (1.5)	1 (1.1)	1 (2.1)	1
Immunosuppressants use	32 (23.5)	23 (25.8)	9 (19.1)	0.381
Corticosteroid use	58 (42.6)	37 (41.6)	21 (44.7)	0.727
Surgical history	101 (74.3)	73 (82.0)	28 (59.6)	0.004
Invasive procedures				
Endotracheal intubation	122 (89.7)	78 (87.6)	44 (93.6)	0.427
Tracheotomy	81 (59.6)	60 (67.4)	21 (44.7)	0.010
Mechanical ventilation	136 (100)	89 (100)	47 (100)	1
Central venous catheter	118 (86.8)	77 (86.5)	41 (87.2)	0.907
CRRT	66 (48.5)	30 (33.7)	36 (76.6)	<0.001
Septic shock	57 (41.9)	25 (28.1)	32 (68.1)	<0.001
Infection variables				
Pulmonary infection	135 (99.3)	88 (98.9)	47 (100.0)	1
Bloodstream infection	49 (36.0)	28 (31.5)	21 (44.7)	0.127
Intra-abdominal infection	4 (2.9)	2 (2.2)	2 (4.3)	0.900
Other infection sites	29 (21.3)	24 (27.0)	5 (10.6)	0.027
Treatment variables				
Duration of therapy	9 (5–14)	11 (7–17)	6 (4–9)	<0.001
Time to initiation of treatment	6.5 (4–12.75)	6 (4–15)	7 (3–10)	0.348
CAZ/AVI use	51 (37.5%)	44 (49.4)	7 (14.9)	<0.001
Polymyxin B use	85 (62.5%)	45 (50.6)	40 (85.1)	<0.001
Outcomes				
The length of ICU (days)	28 (17–44.5)	34.09 (24.5–58)	18 (13–25)	<0.001
The length of hospital (days)	34 (22.67–61)	46 (30–78.5)	21 (15–33)	<0.001
Bacterial eradication	34 (25.0)	34 (38.2)	0 (0)	<0.001

Notes: Data are expressed as number (%) or mean±SD or median (IQR).

Abbreviations: BMI, Body mass index; CCI, Charlson comorbidity index; aCCI, age-adjusted Charlson comorbidity index; CRRT, Continuous renal replacement therapy; ICU, Intensive care unit; IQR, Interquartile range.

a good activity against CRPA. A CHINET report in 2017 showed that 86.5% of CRPA isolates were susceptible to CAZ/AVI in vitro.¹¹ Meanwhile, another study by Alatoom et al demonstrated the sensitivity of 29 strains (94%) of *Pseudomonas aeruginosa* to CAZ/AVI (MIC₅₀ 1.5µg/mL).³⁰ In contrast, a study collecting Gram-negative clinical isolates from 45 medical centers across China in the CHINET Program in 2018, mentioned that the resistance rate of PA

Table 4 Univariate and Multivariate COX Regression Analysis Associated with 30-Day Mortality

Variables	Univariate Analysis		Multivariate Analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
CCI (1-point increments)	0.040	1.179 (1.008–1.379)		
Chronic pulmonary disease	0.012	0.302 (0.120–0.765)		
Organ transplant	0.035	0.332 (0.119–0.926)		
Surgical history	0.002	0.389 (0.217–0.698)	0.026	0.506 (0.277–0.923)
Tracheotomy	0.004	0.425 (0.239–0.757)		
CRRT	<0.001	4.461 (2.266–8.786)	0.003	3.159 (1.479–6.745)
Septic shock	<0.001	3.739 (2.020–6.919)	0.030	2.133 (1.078–4.222)
Other infection sites	0.028	0.353 (0.140–0.894)		
Duration of therapy (1-day increments)	<0.001	0.847 (0.785–0.913)	<0.001	0.853 (0.794–0.917)
CAZ/AVI use	<0.001	0.235 (0.105–0.525)	0.028	0.394 (0.172–0.902)

Abbreviations: HR, Hazard ratios; CI, Confidence interval; CCI, Charlson comorbidity index; CRRT, Continuous renal replacement therapy; CAZ/AVI, Ceftazidime/avibactam.

Table 5 Univariate and Multivariate COX Regression Analysis Associated with 30-Day Mortality After Adjustment

	Univariate Analysis		Multivariate Analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age (1-year increments)	0.033	1.047 (1.004–1.093)	0.022	1.050 (1.007–1.094)
Central venous catheter	0.021	0.262 (0.084–0.816)	0.027	0.268 (0.084–0.859)
Duration of therapy (1-day increments)	0.027	0.871 (0.771–0.984)		
CAZ/AVI use	0.031	0.287 (0.092–0.890)	0.016	0.244 (0.078–0.765)

Abbreviations: HR, Hazard ratios; CI, Confidence interval; CAZ/AVI, Ceftazidime/avibactam.

(657 isolates) to polymyxin B was 3.8%, and that of CRPA (171 isolates) to polymyxin B was 5.3% in vitro.³¹ The CHINET surveillance (<http://www.chinets.com>) also revealed that, from 2019 to 2021, the resistance rates to polymyxin B were 0.8%, 0.7% and 1.3% respectively while the resistance rates to colistin were 1.1%, 2.0% and 1.6% respectively. Another retrospective study collecting 71880 PA isolates in Zhejiang Province during 2015–2017, showed that PA isolates were highly sensitive to polymyxin B and colistin (98.50% and 99.07% respectively) in our region.³² The above data indicated that the factor of polymyxin B resistance was less likely to disturb the outcome. Accordingly, CAZ/AVI therapy showed good antibacterial effects in vitro and in vivo, providing a more effective treatment option for patients with CRPA infection.

In this study, it was observed that compared with the polymyxin B group, patients treated with CAZ/AVI for CRPA infection had longer ICU hospital stays and overall hospital stays, which might be due to the fact that the incidence of bloodstream infection and the mortality of 14-day and 30-day in the polymyxin B group were apparently higher than those in the CAZ/AVI group, leading to differences in survival time between the two groups, thus resulting in significant differences in length of hospital stay. In addition, compared with the polymyxin B group, there was a higher proportion of immunocompromised patients (transplantation, malignancy, immunosuppressant and corticosteroids use, etc) in the CAZ/AVI group. In view of the delayed course of immunosuppressive patients, it might be one of the reasons. Therefore, it was shown that patients with CRPA infection treated with CAZ/AVI had a longer hospital stay.

In this study, the characteristics of the survivors and non-survivors at 30 days were compared to find potential independent predictors. Multivariate COX analysis showed that the age was identified as independent predictor of 30-day mortality while CAZ/AVI therapy and central venous catheterization emerged as independent predictors of 30-day survival. A multicenter retrospective study by Tumbarello et al was conducted in adult patients infected with KPC-

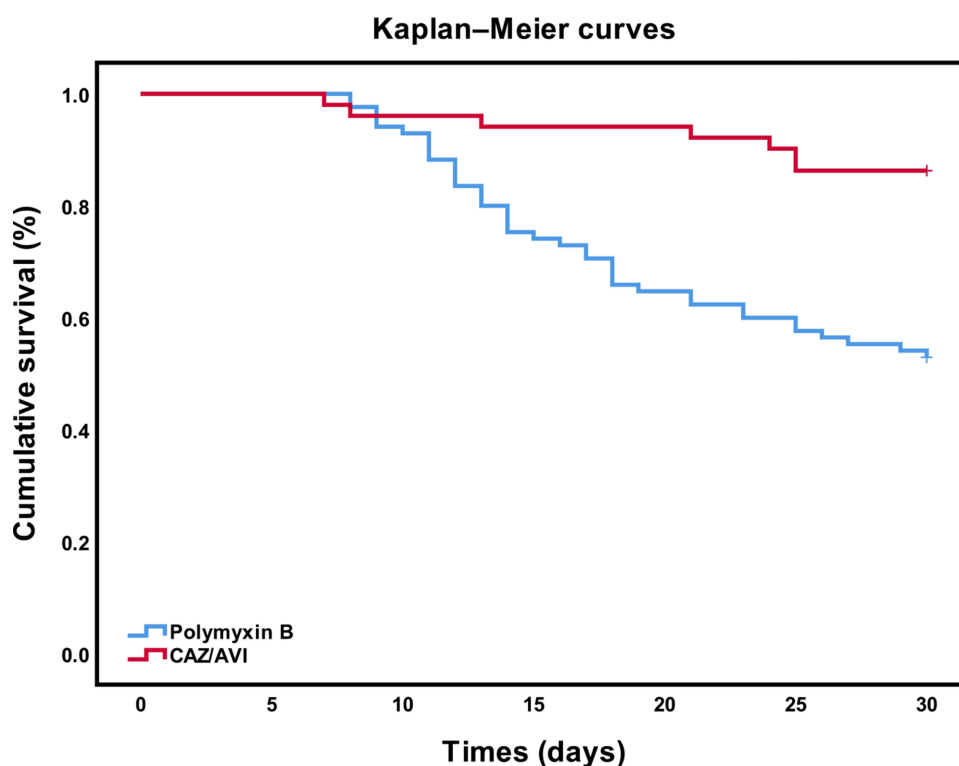


Figure 2 Kaplan–Meier curves of patients with CRPA infection treated with CAZ/AVI or polymyxin B.

Abbreviations: CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CAZ/AVI, ceftazidime/avibactam.

producing *K. pneumoniae* and treated with CAZ/AVI salvage treatment. The results of related multivariate analysis showed that septic shock, neutropenia, Charlson comorbidity index ≥ 3 and recent mechanical ventilation were independent predictors of 30-day mortality, while receiving CAZ/AVI treatment was the only independent predictor of survival.³³ The independent predictor of survival was consistent with our findings. In another retrospective study of patients with CRKP bacteremia who received CAZ/AVI for more than three days, the multivariate analysis also concluded that CAZ/AVI was an independent predictor of clinical success.¹⁷ Therefore, it could be inferred from the above findings that CAZ/AVI therapy was an effective, and alternative treatment for CRPA infection.

CAZ/AVI is a novel antimicrobial agent that can be used as a treatment option for severe infections caused by carbapenem-resistant gram-negative bacteria.³⁴ It was approved by the US Food and Drug Administration (FDA) in 2015 and was the first combination of β -lactams to cover extensively drug-resistant gram-negative pathogens including *Pseudomonas aeruginosa*.³⁵ Interestingly, data from real-world studies showed that CAZ/AVI therapy was superior to polymyxin-based treatment in the fight against CRE from the perspective of efficacy and safety.³⁶ However, currently available data on the outcomes of CRPA infection treated with CAZ/AVI is limited, as few clinical studies sought to observe and compare the efficacy of treatment between CAZ/AVI and polymyxin against CRPA infection. Notwithstanding that the effectiveness of CAZ/AVI therapy with polymyxin has been contrasted in several studies, the infectious pathogens were somewhat different. A study by van Duin et al provided evidence of the superiority of ceftazidime-avibactam over colistin in the initial treatment of infections caused by *K. pneumoniae* carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CRE), indicating that the use of CAZ/AVI was associated with improved clinical outcomes, especially decreasing of all-cause hospital mortality and improving benefit-risk outcomes,¹⁸ but the cohort population were patients with CRE (mainly CRKP) infection. In a study by Hakeam et al, patients with CRE infection experienced a lower 14-day mortality rate with CAZ/AVI than with colistin.³⁷ Another retrospective study was also conducted in patients with CRKP bacteremia, and it was observed that CAZ/AVI treatment had a higher clinical success rate and survival rate than other treatment regimens (including colistin treatment).¹⁷ To the best of our knowledge, this is the first real-world study designed to compare the clinical efficiency between CAZ/AVI and polymyxin B in

patients with CRPA infection. In summary, our study found that CAZ/AVI treatment was superior to polymyxin B therapy in patients with CRPA infection with lower 14-and 30-day mortality and in-hospital mortality and higher bacterial clearance rate compared with polymyxin B treatment, validating the survival benefits of CAZ/AVI therapy in patients with CRPA infection.

There were many limitations in this study. First of all, this study was a single-center study and the sample size obtained was insufficient. However, it should be borne in mind that our sample size was relatively small since CAV/AVI was marketed in China in 2019. Moreover, due to the observational nature of our study, the generalizability of our study results was limited. Furthermore, our study did not include relevant indicators of the study drug sensitivity test for infectious pathogens, and details were not available.

Conclusion

This single-center observational study provided valuable information on the efficacy of two important antimicrobial agents and risk factors of mortality in patients with CRPA infection. Herein, we provided evidence that CAZ/AVI therapy was superior to polymyxin B therapy for patients with CRPA infection in the real world, demonstrating significant survival benefits for CRPA-infected patients. However, larger study populations and well-designed randomized clinical trials are needed to corroborate our findings.

Abbreviations

CAZ/AVI, Ceftazidime/avibactam; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; PSM, Propensity score matching; CRGNB, Carbapenem-resistant gram-negative bacteria; HAI, Healthcare associated infections; ECDC, European Centers for Disease Control and Prevention; CHINET, China Antimicrobial Surveillance Network; CRRT, Continuous renal replacement therapy; PICCO, Pulse indicator continuous cardiac output; ECMO, Extracorporeal membrane oxygenation; CCI, Charlson comorbidity index; aCCI, age-adjusted Charlson comorbidity index; IDSA, Infectious Diseases Society of America; CLSI, Clinical and Laboratory Standards Institute; MIC, Minimum inhibitory concentration; IQR, Interquartile range; MDR, Multidrug-resistant; XDR, Extensively drug-resistant; SOT, solid organ transplantation; HSCT, Hematopoietic stem cell transplantation; CDI, Clostridium difficile infection; FDA, Food and Drug Administration; CRE, Carbapenem-resistant Enterobacteriaceae.

Data Sharing Statement

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

Ethics Approval

This study was approved by the Research Ethics Committee of Second Affiliated Hospital of Zhejiang University. In addition, for organ transplantation, all organs were donated voluntarily with written informed consent, and the organ donations and transplants were conducted in accordance with the Declaration of Istanbul.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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