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Original Article

Efficacy and safety of ceftazidime-avibactam in carbapenem-resistant gram-negative bacilli sepsis according to infection site

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Abstract: Objective: To evaluate the clinical efficacy, microbiologic clearance, and safety of ceftazidime-avibactam (CAZ-AVI) in treating sepsis caused by carbapenem-resistant Gram-negative bacilli (CRO), with a focus on subgroup analyses by infection site. Methods: This retrospective cohort study included 156 patients with CRO sepsis treated between January 2020 and January 2026. Patients were divided into an observation group (CAZ-AVI, n=74) and a control group (conventional antimicrobials, n=82). Clinical outcomes, microbiological clearance rates, 28-day mortality, and adverse events were compared. Multivariate logistic regression was performed to identify factors associated with microbial clearance and 28-day mortality. Results: The clinical effective rate was significantly higher in the observation group (74.32% vs. 48.78%, P=0.001), as was the microbiological clearance rate (74.32% vs. 51.22%, P=0.003). ICU and total hospital stays were significantly shorter in the observation group (both P < 0.01). Subgroup analyses showed favorable outcomes for both pulmonary and urinary tract infections, with the urinary tract subgroup achieving 84.62% clinical efficacy. The intra-abdominal infection subgroup was not included in subgroup analysis due to an extremely small sample size. CAZ-AVI treatment was independently associated with microbial clearance (OR=3.74, 95% CI: 1.69-8.27, P=0.001). No significant difference in adverse events was observed between groups. Conclusion: CAZ-AVI demonstrated superior clinical efficacy and microbiological clearance compared to conventional antimicrobials in treating CRO sepsis, particularly in urinary tract infections, with favorable safety profiles. These findings support CAZ-AVI as a preferred therapeutic option and highlight the importance of infection site-guided antimicrobial strategies.

Keywords: Ceftazidime-avibactam, carbapenem-resistant gram-negative bacilli, sepsis, efficacy

Introduction

Carbapenem-resistant organisms (CRO) infections have become a serious challenge in the field of global public health [1, 2]. With the widespread use of carbapenem antibiotics, the detection rate of resistant strains such as carbapenem-resistant *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) has been rising year on year; sepsis caused by these bacteria is one of the leading causes of death among critically ill patients [3]. According to statistics, the mortality rate of sepsis caused by CRO infection is as high as 40%-60%, significantly higher than that of infections caused by sensitive bacterial strains [4, 5]. Although traditional therapeutic agents such as polymyxin and tigecycline exhibit some antibacterial activity against CRO, they are limited by a high incidence of adverse reactions and poor tissue penetration, resulting in unsatisfactory clinical efficacy [6, 7]. Therefore, exploring safer and more effective treatment options for combating CRO infections holds significant clinical importance for improving the prognosis of patients with sepsis.

Ceftazidime-Avibactam (CAZ-AVI) is a novel combination preparation of a β-lactam antibiotic and a β-lactamase inhibitor that has been launched in recent years [8]. By broadly inhibiting Class A, Class C and certain Class D β-lacta-

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mases with avibatan, CAZ-AVI effectively restores and enhances the antibacterial activity of ceftazidime against carbapenemase-producing CRO strains [9, 10]. Current evidence-based medical data indicate that CAZ-AVI demonstrates good efficacy and safety in the treatment of complicated intra-abdominal infections, complicated urinary tract infections, and hospital-acquired pneumonia, and is associated with a lower risk of nephrotoxicity compared to traditional drugs such as polymyxin [11, 12]. However, as a systemic inflammatory response syndrome, sepsis involves infections across multiple anatomical regions, including the lungs, urinary tract and abdominal cavity [13]; infections in different sites exhibit significant differences in terms of pathogen distribution, local drug concentrations, the host immune response, and the need for concomitant surgical intervention [14]. At present, there is a lack of systematic clinical data regarding differences in the efficacy of CAZ-AVI for treating sepsis caused by CRO infections at different sites, as well as the characteristics of microbiological outcomes.

Against this background, this study adopted a retrospective design and enrolled 156 patients with CRO-associated sepsis, to compare the clinical efficacy, microbial eradication rates and safety of CAZ-AVI to conventional antimicrobial regimens, with a focus on subgroup analyses based on different sites of infection. The aim is to clarify the therapeutic characteristics and potential influencing factors of CAZ-AVI in the treatment of CRO sepsis, thereby providing evidence-based support for the development of individualized antimicrobial strategies tailored to the site of infection.

Materials and methods

Study design and patient population

This retrospective study was conducted at the Department of Critical Care Medicine of Huishan Third People's Hospital of Wuxi City and the Department of Intensive Care Medicine of Wuxi People's Hospital Affiliated to Nanjing Medical University. The study protocol was approved by the ethical committee of Huishan Third People's Hospital of Wuxi City (approval number: 2026-LW-01). A total of 156 patients diagnosed with sepsis caused by CRO between January 2020 and January 2026 were enrolled. Patients were divided into two groups based on the antimicrobial regimen received: the observation group (n=74) comprised patients treated with CAZ-AVI, while the control group (n=82) consisted of patients treated with conventional antimicrobial agents (non-CAZ-AVI).

Inclusion and exclusion criteria

Patients were included if they met the following criteria: (1) diagnosis of sepsis according to the Sepsis-3.0 definition, defined as an increase in Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points attributable to infection [15]; (2) microbiologically confirmed infection with carbapenem-resistant Gram-negative bacilli, including carbapenem-resistant *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA); (3) age ≥ 18 years; and (4) availability of complete clinical data for key outcome measures. Exclusion criteria were: (1) history of hypersensitivity to ceftazidime, avibactam, or other β-lactam antibiotics; (2) pregnancy or lactation; (3) treatment duration < 72 hours or premature discontinuation of therapy for non-medical reasons; and (4) concomitant infection with non-CRO pathogens that could confound efficacy assessment.

Data collection

Clinical data were extracted from the electronic medical record systems of both hospitals by two independent researchers, with discrepancies resolved through consultation with a senior clinician. Collected data included: (1) Demographic characteristics (age, gender, body mass index [BMI]); (2) Underlying diseases (diabetes, chronic obstructive pulmonary disease [COPD], cardiovascular disease, chronic kidney disease, liver cirrhosis); (3) Illness severity indices (Acute Physiology and Chronic Health Evaluation II [APACHE II] score [16], Sequential Organ Failure Assessment [SOFA] score [17], Charlson Comorbidity Index [CCI]) [18]; (4) Baseline inflammatory markers (procalcitonin [PCT], C-reactive protein [CRP]); (5) Infection site and pathogen distribution (carbapenemase genotype detection results); (6) Antimicrobial treatment regimens (dosage, administration frequency, treatment duration); (7) 28-day survival status was retrospectively extracted from nursing records and electronic medical docu-

mentation. For patients discharged before day 28, telephone follow-up records and outpatient clinic notes were retrospectively reviewed from the electronic database to ascertain survival status, ensuring complete endpoint capture for all enrolled patients. Follow-up data also included length of intensive care unit (ICU) stay and total length of hospital stay; (8) Adverse events during treatment.

Definitions of outcome measures

Clinical efficacy was defined as follows: cure= complete resolution of infection-related symptoms and signs with normalization of inflammatory markers and negative microbiological culture; improvement= partial resolution of clinical symptoms and inflammatory markers without complete normalization; ineffective= no improvement or worsening of clinical symptoms and inflammatory markers; death/not cured= death from any cause or persistence of infection despite treatment. Clinical effective rate was calculated as the sum of cured and improved cases divided by the total number of patients in each group. Microbiological clearance was defined as the absence of the originally isolated pathogen on follow-up culture from the primary infection site, with clearance time recorded as the number of days from treatment initiation to the first negative culture. Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine ≥ 1.5 times baseline or a rise in creatinine ≥ 0.3 mg/dL within 48 hours [19]. Acute liver injury was defined as an elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent samples t-test. Continuous variables with non-normal distribution were expressed as median (interquartile range) [M (Q_1, Q_3)] and compared using a Mann-Whitney U test. Categorical variables were expressed as number (percentage) [n (%)] and compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Univariate analyses were performed to identify potential factors associated with microbial clearance and 28-day mortality. Variables with $P < 0.10$ by univariate analysis were entered into multivariate logistic regression models to identify independent predictors. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). Model goodness-of-fit was assessed using the Hosmer-Lemeshow test. Subgroup analyses were performed for pulmonary and urinary tract infections; the intra-abdominal infection subgroup was not analyzed owing to its limited sample size (n=7). All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Baseline characteristics of patients

A total of 156 patients with carbapenem-resistant Gram-negative bacilli sepsis were included in this study, comprising 74 patients in the observation group (CAZ-AVI) and 82 patients in the control group (non-CAZ-AVI). As shown in **Table 1**, there were no significant differences between the two groups in terms of demographic characteristics, underlying diseases, severity of illness, or infection site distribution. The mean age was 65.83 ± 13.01 years, and 59.62% of patients were male. The most common infection site was pulmonary infection (61.54%), followed by urinary tract infection (33.97%) and intra-abdominal infection (4.49%). The intra-abdominal infection subgroup comprised only 7 patients (4.49%) and was not included in subsequent subgroup analyses. Baseline APACHE II and SOFA scores were comparable between groups (both $P > 0.05$), as were inflammatory markers including PCT and CRP (both $P > 0.05$).

Pathogen distribution and antimicrobial susceptibility

Table 2 presents the pathogen distribution and antimicrobial susceptibility profiles. The most prevalent pathogen was CRKP (43.59%), followed by CRAB (33.33%) and CRPA (23.08%). No significant differences were observed in pathogen distribution between the two groups (all $P > 0.05$). Among carbapenemase genotypes, KPC was the most common (58.43%), followed by NDM (31.46%) and OXA-48 (10.11%). Antimicrobial susceptibility testing revealed that ceftazidime-avibactam demonstrated high susceptibility rates (98.72%), with all isolates in the observation group being susceptible to the study drug.

Table 1. Baseline characteristics of patients

Characteristic	Total (n=156)	Control group (n=82)	Observation group (n=74)	Statistic	*P*
Demographic characteristics					
Age (years, $\bar{x} \pm s$)	65.83 ± 13.01	65.18 ± 12.78	66.54 ± 13.32	t=-0.65	0.517
Male [n (%)]	93 (59.62)	45 (54.88)	48 (64.86)	χ^2=1.61	0.204
BMI (kg/m^2, $\bar{x} \pm s$)	23.83 ± 3.87	23.83 ± 3.59	23.84 ± 4.19	t=-0.01	0.995
Underlying diseases [n (%)]					
Diabetes	56 (35.90)	29 (35.37)	27 (36.49)	χ^2=0.02	0.884
COPD	57 (36.54)	31 (37.80)	26 (35.14)	χ^2=0.12	0.730
Cardiovascular disease	85 (54.49)	48 (58.54)	37 (50.00)	χ^2=1.14	0.285
Chronic kidney disease	32 (20.51)	19 (23.17)	13 (17.57)	χ^2=0.75	0.387
Liver cirrhosis	7 (4.49)	2 (2.44)	5 (6.76)	χ^2=0.83	0.361
Severity of the illness					
APACHE II ($\bar{x} \pm s$)	22.08 ± 6.78	22.79 ± 7.00	21.30 ± 6.48	t=1.38	0.170
SOFA ($\bar{x} \pm s$)	9.39 ± 3.59	9.46 ± 3.78	9.31 ± 3.40	t=0.26	0.792
CCI ($\bar{x} \pm s$)	5.13 ± 2.18	5.06 ± 2.28	5.22 ± 2.08	t=-0.44	0.659
PCT [ng/mL, M (Q_1, Q_3)]	7.02 (4.87, 13.91)	6.92 (4.72, 14.80)	7.38 (5.34, 11.61)	Z=-0.21	0.833
CRP [mg/L, M (Q_1, Q_3)]	121.90 (86.10, 157.75)	115.00 (79.52, 150.33)	132.10 (91.08, 160.30)	Z=-1.78	0.075
Infection site [n (%)]					
Pulmonary	96 (61.54)	51 (62.20)	45 (60.81)		
Urinary tract	53 (33.97)	27 (32.93)	26 (35.14)	-	0.961
Intra-abdominal	7 (4.49)	4 (4.88)	3 (4.05)		

Note: CCI, Charlson Comorbidity Index; PCT, procalcitonin; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

Primary clinical outcomes

The primary clinical outcomes are summarized in **Table 3**. The clinical effective rate was significantly higher in the observation group compared to the control group (74.32% vs. 48.78%, χ^2=10.66, P=0.001). Although the 28-day mortality rate was lower in the observation group (5.41% vs. 13.41%), this difference did not reach statistical significance (P=0.090). Microbiological clearance rate was significantly higher in the observation group (74.32% vs. 51.22%, χ^2=8.83, P=0.003), and the median clearance time was shorter (10.00 days vs. 13.00 days, Z=-3.55, P < 0.001). Additionally, both ICU LOS (12.00 days vs. 16.00 days, Z=-4.28, P < 0.001) and total LOS (20.00 days vs. 25.00 days, Z=-3.10, P=0.002) were significantly reduced in the observation group.

Clinical outcomes in pulmonary infection subgroup

Of the 96 patients with pulmonary infection (51 in the control group, 45 in the observation group), the clinical effective rate was significantly higher in the observation group (68.89% vs. 45.10%, χ^2=5.50, P=0.019), while the overall clinical efficacy distribution showed no statistical difference (P=0.072) (**Table 4**). The 28-day mortality rate was 6.67% in the observation group and 11.76% in the control group, with no significant intergroup difference (χ^2= 0.25, P=0.614). The observation group had a significantly higher microbial clearance rate (68.89% vs. 49.02%, χ^2=3.88, P=0.049) and shorter clearing time [11.00 (7.00, 13.00) d vs. 13.00 (10.00, 16.00) d, Z=-2.42, P=0.016]. ICU LOS (Z=-3.00, P=0.003) and total LOS (Z=-2.23, P=0.026) were also significantly shorter in the observation group.

Clinical outcomes in urinary tract infection subgroup

Among the 53 patients with urinary tract infection (27 in control group, 26 in observation group), the observation group had a significantly higher clinical effective rate (84.62% vs. 51.85%, χ^2=6.53, *P*=0.011), whereas the overall clinical efficacy distribution had no statistical difference (*P*=0.092) (**Table 5**). The 28-day mortality rate was lower in the observation group (3.85% vs. 14.81%) with no significant intergroup difference (χ^2=0.80, *P*=0.370). Microbial clearance rate was significantly higher

Table 2. Pathogen distribution and antimicrobial susceptibility

Variable	Total (n=156)	Control group (n=82)	Observation group (n=74)	Statistic	*P*
Pathogen distribution, n (%)					
CRKP	68 (43.59)	37 (45.12)	31 (41.89)	χ^2=0.17	0.685
CRAB	52 (33.33)	26 (31.71)	26 (35.14)	χ^2=0.21	0.650
CRPA	36 (23.08)	19 (23.17)	17 (22.97)	χ^2=0.00	0.976
Carbapenemase genotype, n (%)					
KPC	52 (58.43)	28 (58.33)	24 (58.54)	χ^2=0.05	0.821
NDM	28 (31.46)	18 (37.50)	10 (24.39)	χ^2=1.88	0.170
OXA-48	9 (10.11)	2 (4.17)	7 (17.07)	-	0.086
Antimicrobial susceptibility, n (%)					
Polymyxin B	152 (97.44)	80 (97.56)	72 (97.30)	χ^2=0.00	1.000
Tigecycline	131 (83.97)	71 (86.59)	60 (81.08)	χ^2=0.88	0.349
Ceftazidime-avibactam	154 (98.72)	80 (97.56)	74 (100.00)	-	0.498

Note: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase. Carbapenemase genotyping was performed in only 89 patients.

Table 3. Comparison of primary clinical outcomes

Outcome	Total (n=156)	Control group (n=82)	Observation group (n=74)	Statistic	*P*
Clinical efficacy [n (%)]				χ^2=12.13	0.007
Cure	47 (30.13)	17 (20.73)	30 (40.54)		
Improvement	48 (30.77)	23 (28.05)	25 (33.78)		
Ineffective	46 (29.49)	31 (37.80)	15 (20.27)		
Death/Not cured	15 (9.62)	11 (13.41)	4 (5.41)		
Clinical effective rate [n (%)]	95 (60.90)	40 (48.78)	55 (74.32)	χ^2=10.66	0.001
28-day mortality rate [n (%)]	15 (9.62)	11 (13.41)	4 (5.41)	χ^2=2.87	0.090
Microbiological indicators					
Clearance rate [n (%)]	97 (62.18)	42 (51.22)	55 (74.32)	χ^2=8.83	0.003
Clearing time [d, M (Q_1, Q_3)]	11.00 (7.00, 13.00)	13.00 (9.00, 15.75)	10.00 (6.50, 12.00)	Z=-3.55	< 0.001
Length of hospital stay [d, M (Q_1, Q_3)]					
ICU LOS	14.00 (10.00, 18.00)	16.00 (12.00, 20.00)	12.00 (8.00, 15.00)	Z=-4.28	< 0.001
Total LOS	23.00 (19.00, 30.00)	25.00 (21.00, 31.00)	20.00 (17.00, 26.00)	Z=-3.10	0.002

Note: Clinical effective rate = (Cure + Improvement)/total × 100%. ICU, intensive care unit; LOS, length of stay.

(84.62% vs. 51.85%, χ^2=6.53, *P*=0.011) and clearing time significantly shorter [9.00 (5.00, 11.00) d vs. 12.50 (7.25, 14.75) d, *Z*=-2.03, *P*=0.042] in the observation group. Furthermore, the observation group had significantly shorter ICU LOS (*Z*=-2.62, *P*=0.009) and total LOS (*Z*=-2.44, *P*=0.015) compared to the control group.

Clinical outcomes by pathogen type

Table 6 presents the comparison of clinical effective rates by pathogen type. Among patients with CRKP infection, the observation group had a significantly higher clinical effective rate than the control group (80.65% vs. 51.35%, χ^2=6.34, P=0.012). Similarly, for CRAB infection, the observation group demonstrated a significantly higher clinical effective rate compared to the control group (76.92% vs. 50.00%, χ^2=4.06, P=0.044). For CRPA infection, although the observation group showed a numerically higher clinical effective rate (58.82% vs. 42.11%), the difference was not significant (P=0.505).

Safety analysis

The incidence of adverse events is summarized in **Table 7**. The overall adverse event rate was

Table 4. Comparison of outcomes in the pulmonary infection subgroup

Outcome	Total (n=96)	Control group (n=51)	Observation group (n=45)	Statistic	*P*
Clinical efficacy [n (%)]				-	0.072
Cure	31 (32.29)	11 (21.57)	20 (44.44)		
Improvement	23 (23.96)	12 (23.53)	11 (24.44)		
Ineffective	33 (34.38)	22 (43.14)	11 (24.44)		
Death/Not cured	9 (9.38)	6 (11.76)	3 (6.67)		
Clinical effective rate [n (%)]	54 (56.25)	23 (45.10)	31 (68.89)	χ^2=5.50	0.019
28-day mortality rate [n (%)]	9 (9.38)	6 (11.76)	3 (6.67)	χ^2=0.25	0.614
Microbiological indicators					
Clearance rate [n (%)]	56 (58.33)	25 (49.02)	31 (68.89)	χ^2=3.88	0.049
Clearing time [d, M (Q_1, Q_3)]	11.00 (8.75, 13.25)	13.00 (10.00, 16.00)	11.00 (7.00, 13.00)	Z=-2.42	0.016
Length of hospital stay [d, M (Q_1, Q_3)]					
ICU LOS	14.50 (10.00, 19.00)	16.00 (11.50, 20.50)	12.00 (9.00, 16.00)	Z=-3.00	0.003
Total LOS	23.00 (19.00, 28.25)	24.00 (21.00, 28.00)	20.00 (17.00, 29.00)	Z=-2.23	0.026

Note: Clinical effective rate = (Cure + Improvement)/total × 100%. ICU, intensive care unit; LOS, length of stay.

Table 5. Comparison of outcomes in the urinary tract infection subgroup

Outcome	Total (n=53)	Control group (n=27)	Observation group (n=26)	Statistic	*P*
Clinical efficacy [n (%)]				-	0.092
Cure	14 (26.42)	5 (18.52)	9 (34.62)		
Improvement	22 (41.51)	9 (33.33)	13 (50.00)		
Ineffective	12 (22.64)	9 (33.33)	3 (11.54)		
Death/Not cured	5 (9.43)	4 (14.81)	1 (3.85)		
Clinical effective rate [n (%)]	36 (67.92)	14 (51.85)	22 (84.62)	χ^2=6.53	0.011
28-day mortality rate [n (%)]	5 (9.43)	4 (14.81)	1 (3.85)	χ^2=0.80	0.370
Microbiological indicators					
Clearance rate [n (%)]	36 (67.92)	14 (51.85)	22 (84.62)	χ^2=6.53	0.011
Clearing time [d, M (Q_1, Q_3)]	9.00 (6.75, 12.25)	12.50 (7.25, 14.75)	9.00 (5.00, 11.00)	Z=-2.03	0.042
Length of hospital stay [d, M (Q_1, Q_3)]					
ICU LOS	13.00 (10.00, 16.00)	15.00 (12.50, 19.00)	11.50 (8.00, 14.00)	Z=-2.62	0.009
Total LOS	23.00 (17.00, 30.00)	28.00 (20.00, 34.50)	21.00 (15.50, 24.75)	Z=-2.44	0.015

Note: Clinical effective rate = (Cure + Improvement)/total × 100%. ICU, intensive care unit; LOS, length of stay.

lower in the observation group compared to the control group (18.92% vs. 28.05%), but this difference did not reach statistical significance (χ^2=1.79, P=0.181). The most common adverse events were acute kidney injury (8.11% in observation group vs. 17.07% in control group), thrombocytopenia (9.46% vs. 14.63%), and acute liver injury (5.41% vs. 10.98%). No severe adverse events or treatment-related deaths were reported in either group.

Factors associated with microbial clearance

Multivariate logistic regression analysis was performed to identify factors independently associated with microbial clearance (**Table 8**). After adjusting for potential confounders, treatment with CAZ-AVI was identified as an independent predictor of microbial clearance (OR=3.74, 95% CI: 1.69-8.27, P=0.001). Higher APACHE II score was significantly associated with reduced likelihood of microbial clearance (OR=0.90, 95% CI: 0.84-0.96, P < 0.001). Both higher PCT level (OR=0.94, 95% CI: 0.90-0.98, P=0.004) and higher CRP level (OR=0.99, 95% CI: 0.98-0.99, P=0.004) were also independently associated with reduced microbial clearance. The Hosmer-Lemeshow test indicated good model fit (χ^2=4.76, P=0.783).

Factors associated with 28-day mortality

Multivariate logistic regression analysis was conducted to identify factors independently

Table 6. Comparison of outcomes by pathogen type

Pathogen	Group	n	Clinical effective rate [n (%)]	Statistic	P
CRKP	Observation	31	25 (80.65)	χ^2=6.34	0.012
	Control	37	19 (51.35)		
CRAB	Observation	26	20 (76.92)	χ^2=4.06	0.044
	Control	26	13 (50.00)		
CRPA	Observation	17	10 (58.82)	χ^2=1.00	0.317
	Control	19	8 (42.11)		

Note: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*. OR and 95% CI for the CRPA subgroup were calculated by Pearson's chi-square test with risk assessment: OR=1.96, 95% CI=0.52-7.41.

Table 7. Comparison of adverse events between groups

Adverse events [n (%)]	Observation group (n=74)	Control group (n=82)	Statistic	P
Total adverse events	14 (18.92)	23 (28.05)	χ^2=1.79	0.181
Acute kidney injury	6 (8.11)	14 (17.07)		
Acute liver injury	4 (5.41)	9 (10.98)		
Leukopenia	5 (6.76)	8 (9.76)		
Thrombocytopenia	7 (9.46)	12 (14.63)		
Skin allergy	3 (4.05)	5 (6.10)		
Neurological adverse events	1 (1.35)	2 (2.44)		

Note: Total adverse events indicate patients experiencing at least one adverse event.

Table 8. Multivariate logistic regression analysis of factors associated with microbial clearance

Variables	β	S.E	Wald χ^2	OR	95% CI	*P*
Treatment groups (CAZ-AVI vs. control)	1.32	0.41	10.56	3.74	1.69-8.27	0.001
APACHE II	-0.11	0.03	11.06	0.90	0.84-0.96	< 0.001
PCT (ng/mL)	-0.07	0.02	8.09	0.94	0.90-0.98	0.004
CRP (mg/L)	-0.01	0.00	8.20	0.99	0.98-0.99	0.004

Note: OR, odds ratio; CI, confidence interval. Model goodness-of-fit: Hosmer-Lemeshow χ^2=4.76, P=0.783.

Table 9. Multivariate logistic regression analysis of factors associated with 28-day mortality

Variables	β	S.E	Wald χ^2	OR	95% CI	*P*
APACHE II	0.13	0.06	4.57	1.14	1.01-1.28	0.033
SOFA	0.29	0.10	9.08	1.34	1.11-1.62	0.003
AKI (Yes vs. No)	1.63	0.72	5.15	5.08	1.25-20.66	0.023

Note: OR, odds ratio; CI, confidence interval; AKI, acute kidney injury. Model goodness-of-fit: Hosmer-Lemeshow χ^2=7.81, P=0.453.

associated with 28-day mortality (**Table 9**). Higher APACHE II score was significantly associated with increased mortality risk (OR=1.14, 95% CI: 1.01-1.28, P=0.033). Higher SOFA score was also independently associated with increased mortality risk (OR=1.34, 95% CI: 1.11-1.62, P=0.003). Additionally, the presence of acute kidney injury was identified as a strong independent risk factor for 28-day mortality (OR=5.08, 95% CI: 1.25-20.66, P=0.023). The Hosmer-Lemeshow test indicated acceptable model fit (χ^2=7.81, P=0.453). Notably, treatment group was not included in the final model due to limited number of mortality events and the absence of significant association in univariate analysis.

Discussion

This study conducted a retrospective cohort analysis of 156 patients with sepsis caused by CRO, systematically comparing the efficacy and safety of CAZ-AVI with conventional antimicrobial agents across different sites of infection. The results showed that the clinical response rate in the CAZ-AVI group was significantly higher than that of the control group, and the micro-

bial clearance rate was also significantly higher than that of the control group. Furthermore, both the LOS in the ICU and the total LOS were significantly reduced. Subgroup analysis further revealed that CAZ-AVI demonstrated significant advantages in both the pulmonary infection and urinary tract infection subgroups, with clinical efficacy and microbial clearance rates as high as 84.62% in the urinary tract infection subgroup. Multivariate analysis confirmed that CAZ-AVI treatment was an independent protective factor for microbial clearance, while elevated APACHE II scores, PCT and CRP levels were significantly associated with difficulty in achieving microbial clearance. In terms of safety, the overall incidence of adverse reactions in the CAZ-AVI group was lower than in the control group, although the difference was not statistically significant. The above results indicate that CAZ-AVI therapy for CRO sepsis demonstrates definite clinical efficacy and good safety, with particularly significant benefits observed in patients with urinary tract infections.

The therapeutic benefits of CAZ-AVI observed in this study are broadly consistent with the findings of previous studies. The retrospective analysis conducted by Xu et al. [20] showed that the overall clinical efficacy rate of CAZ-AVI in treating *Klebsiella pneumoniae* infections was 65.68%, which was similar to that of this study. The multicenter cohort study conducted by Almangour et al. [21] compared the efficacy of CAZ-AVI and colistin in treating infections caused by carbapenem-resistant *Enterobacteriaceae bacteria*. The results showed that the clinical cure rate in the CAZ-AVI group was significantly higher than that of the colistin group (71% vs. 50%), which was highly consistent with the therapeutic differences observed in this study's observation group and control group. The subgroup analysis of our study revealed that the clinical efficacy rate of CAZ-AVI in patients with urinary tract infections was 84.62%, significantly higher than 68.89% in the pneumonia subgroup. This difference can be reasonably explained from the perspective of pharmacokinetics [22]. Gul et al. [23] conducted pharmacokinetic studies on CAZ-AVI in normal lung tissue and pneumonia models, finding that the concentration of CAZ-AVI in the alveolar epithelial lining fluid was only 30% to 50% of the blood drug concentration. Meanwhile, Zazo et al. [24] confirmed through pharmacodynamic model simulation that the standard dose of CAZ-AVI could achieve a much higher drug exposure level in urine than in the blood. Therefore, patients with urinary tract infections benefit more significantly from the higher concentration of drugs excreted by the kidneys, resulting in better local drug exposure and more pronounced benefits in terms of pathogen clearance and clinical outcomes [25]. Furthermore, the microbial clearance rate in the observation group was 74.32%, which further confirmed the potent bactericidal activity of CAZ-AVI against the CRO strains.

Another important finding of this study was that CAZ-AVI treatment was significantly associated with the clearance of microorganisms, while an increase in APACHE II score, PCT, and CRP levels is independently associated with the difficulty in microbial clearance. Zhang et al.'s study [26] on the treatment of CRKP infections in critically ill patients with CAZ-AVI revealed that an APACHE II score of ≥ 20 was an independent risk factor for 28-day mortality, and was closely related to the failure of microbial clearance, which is consistent with the results of this study. Ahmed et al.'s [27] retrospective analysis of CAZ-AVI-resistant bacterial strains further revealed that the baseline severity of the disease was positively correlated with the failure rate of treatment. From the perspective of the mechanism, the APACHE II score reflects the degree of multi-organ dysfunction. Patients with high scores often have immune function suppression, insufficient tissue perfusion, and changes in drug distribution volume [28, 29]. These factors can all affect the antibacterial activity of CAZ-AVI and the efficiency of pathogen clearance. Lopez-Montesinos et al. [30] demonstrated through in vitro and in vivo experiments that subtherapeutic concentrations of CAZ-AVI in CRPA infection can induce the development of drug resistance. This explains why the microbial clearance rate is lower in patients with a high APACHE II score (possibly due to excessive renal function or increased distribution volume, resulting in insufficient drug exposure). Furthermore, PCT and CRP, as biomarkers of bacterial infection, show that their elevated levels directly reflect the infection load and the intensity of the inflammatory response [31]. Severe infections often involve the formation of biofilms and an increase in

bacterial persistence, which are resistance mechanisms that make it difficult to eliminate the pathogen. Wen et al. [32] employed metabolomics-proteomics integrated analysis to discover that CAZ-AVI-resistant CRKP can evade drug killing by regulating metabolic pathways and membrane protein expression. This provides a molecular-level explanation for the difficulty in clearing pathogens under a high inflammatory load.

In terms of safety, this study observed that the overall incidence of adverse reactions in the CAZ-AVI group was lower than that of the control group, but this difference did not reach statistical significance. The study by Almangour et al. [21] also confirmed that the incidence of AKI in the CAZ-AVI group was significantly lower than that of the colistin group, which was consistent with the results of this study. The main renal toxicity mechanism of colistin lies in its accumulation in the epithelial cells of renal tubules and its induction of cell apoptosis [33]. While CAZ-AVI is mainly excreted through the renal prototype and has no obvious damaging effect on renal tubules. It is worth noting that in this study, the incidences of liver function impairment, hematologic adverse reactions, and neurological adverse reactions in both groups were relatively low, and no serious adverse events were reported. This further supports the good safety profile of CAZ-AVI in clinical applications. However, it is necessary to be vigilant that as the clinical application of CAZ-AVI increases, the emergence of drug-resistant strains has become an issue that cannot be ignored. Giufrè et al. [34] reported a new KPC-3 variant, KPC-216, which mediates the simultaneous resistance of *Klebsiella pneumoniae* to CAZ-AVI and cefodizime, suggesting that the drug resistance mechanism is showing a diversified evolution trend. Wang et al.'s systematic review [35] and meta-analysis further revealed the global prevalence trend of CAZ-AVI resistance in Gram-negative bacilli, emphasizing the urgency of drug resistance monitoring and rational drug use. Therefore, in clinical applications, the indications should be strictly controlled, and unnecessary use should be avoided to prevent the spread of drug resistance.

This study has several limitations that should be acknowledged. First, the retrospective design inherently introduces potential selection bias, as treatment allocation was based on clinicians' decisions rather than randomization. This non-randomized allocation may have led to selection bias, including a preference for using CAZ-AVI in patients with lower illness severity. Although our multivariate analysis adjusted for several measured confounders, we acknowledge the possibility of unmeasured confounding factors (e.g., subtle differences in disease severity that may have influenced clinicians' choice of CAZ-AVI) that could not be fully accounted for. Consequently, residual confounding cannot be completely excluded. Second, no *a priori* sample size calculation was performed prior to this retrospective study, which may limit the statistical power of subgroup analyses. Third, the assessment of clinical efficacy and adverse events was conducted by researchers who were not blinded to the treatment allocation, introducing the potential for detection bias and possibly leading to an overestimation of the treatment effect. Fourth, detailed data on total drug exposure, including the precise duration of CAZ-AVI therapy, dose adjustments based on renal function, and the specific rationale for or use of concomitant antibacterial agents, were not systematically recorded. This limits our ability to conduct a comprehensive "drug exposure-efficacy" analysis. Fifth, this was a single-center study, which may limit the generalizability of our findings to other populations or healthcare settings. Finally, the number of 28-day mortality events was relatively small (15 cases), which constrained the number of variables that could be included in the multivariate mortality model. Future large-scale, multicenter, prospective randomized controlled trials are warranted to validate our conclusions and to further explore the role of CAZ-AVI combination therapy, particularly against less susceptible strains such as CRAB and CRPA.

Conclusion

This retrospective study demonstrated that CAZ-AVI was superior to conventional antimicrobial regimens in treating sepsis caused by CRO, with significantly higher clinical efficacy and microbiological clearance rates, shorter hospital stays, and comparable safety profiles. The therapeutic advantage was particularly pronounced in patients with urinary tract infections, likely attributable to favorable pharmacokinetic characteristics. CAZ-AVI treatment independently predicted microbial clearance, while higher APACHE II scores, PCT, and CRP

levels were associated with reduced clearance. These findings support CAZ-AVI as a preferred therapeutic option for CRO sepsis, especially in urinary tract infections, and highlight the importance of individualized treatment strategies based on infection site and disease severity.

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Disclosure of conflict of interest

None.

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