

Ceftazidime-Avibactam Combination Therapy versus Monotherapy for the Treatment Carbapenem-Resistant Gram-Negative Bacterial Infections: A Retrospective Observational Study

Keyang Li^{1,*}, Debao Li^{2,*}, Hongliang Dong¹, Dongmei Ren², Dandan Gong¹, Shubo Wang¹, Yang Li¹, Yuanyuan Wu¹, Jikang Yang³, Wenjuan Yan⁴, Yi Li⁴

¹Department of Clinical Pharmacy, Jiaozuo People's Hospital, Jiaozuo, Henan, People's Republic of China; ²Department of Clinical Laboratory, Jiaozuo People's Hospital, Jiaozuo, Henan, People's Republic of China; ³Infectious Diseases Department, Jiaozuo People's Hospital, Jiaozuo, Henan, People's Republic of China; ⁴Department of Clinical Laboratory, Henan Provincial People's Hospital, Zhengzhou, Henan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenjuan Yan; Yi Li, Department of Clinical Laboratory, Henan Provincial People's Hospital, Weiwu Road 7#, Jinshui District, Zhengzhou, Henan, 450003, People's Republic of China, Tel +86 15225061830; +86 15939039006, Email yanwenjuan2008@126.com; liyilabmed@henu.edu.cn

Purpose: Since the introduction of ceftazidime-avibactam (CZA) in the Chinese market, accumulating clinical evidence has substantiated its efficacy in the treatment of infections caused by carbapenem-resistant gram-negative bacteria (CR-GNB). Nevertheless, an ongoing debate persists concerning the choice between monotherapy and combination therapy when devising clinical anti-infection protocols.

Patients and Methods: This retrospective, single-center observational study enrolled patients with CR-GNB infections who received CZA treatment between December 2019 and August 2023. The primary outcome assessed was 30-day mortality, and the secondary outcome measured was 14-day bacterial clearance. A multivariate Cox regression model was used to identify variables that were independently associated with 30-day mortality rate.

Results: Eighty-three patients were enrolled in the study; of which, 45 received CZA monotherapy, whereas 38 received combination therapy. The overall 30-day mortality rate was 31.3%, and no significant difference was observed in the 30-day mortality rates between the CZA combination therapy and monotherapy groups (31.6% vs 31.1%, $p=0.963$). After adjustment by propensity score matching, the 30-day mortality rate was not significantly different between the two groups (28.6% vs 31.4%, $p=0.794$). Multivariate COX analysis revealed that age and SOFA score were independent predictors of 30-day mortality.

Conclusion: Combination therapy with CZA and other antimicrobials was not found to have an advantage over monotherapy in reducing the 30-day mortality rate.

Keywords: ceftazidime-avibactam, carbapenem-resistant gram-negative bacteria, combination therapy *K. pneumoniae* carbapenemase

Introduction

Multidrug-resistant gram-negative bacterial infections have persistently been among the most urgent challenges in the field of infectious diseases.¹ Owing to limited antibiotic options and high mortality rates, infections caused by multidrug- and extensively drug-resistant gram-negative bacteria have become a major challenge for global health organizations.^{2,3} For decades, carbapenems have been the preferred choice for treating infections caused by these pathogens.⁴⁻⁷ However, the emergence and spread of carbapenemases threatens their efficacy as the last line of defense against multidrug-resistant bacteria.^{8,9} For domestic use, the most prevalent carbapenemases are *Klebsiella pneumoniae* carbapenemases (KPC),¹⁰ which belong to the Ambler class A enzymes and can hydrolyze all available traditional β -lactam antibiotics.

Ceftazidime-avibactam (CZA) is a novel combination of the cephalosporin antibiotic ceftazidime and non- β -lactam β -lactamase inhibitor avibactam. CZA exhibits broad activity against Ambler class A, C, and certain class D enzymes.¹¹ It has been approved for treating complicated urinary tract and complicated intra-abdominal infections, including hospital-acquired and ventilator-associated pneumonia, as well as for gram-negative bacterial infections in adult patients with limited treatment options.^{12,13}

Although there have been published reports of the clinical use of CZA in practical settings.^{14–19} The Infectious Diseases Society of America (IDSA) expert consensus released in 2023 recommends monotherapy for treating gram-negative bacteria that do not produce metalloenzymes,²⁰ controversy exists regarding whether CZA should be used as a monotherapy or in combination with other antimicrobial agents in patients with carbapenem-resistant gram-negative bacterial (CR-GNB) infections in China.²¹ Therefore, we conducted a single-center retrospective analysis to investigate whether CZA combination therapy is more effective than CZA monotherapy for patients with CR-GNB and to evaluate the risk factors associated with mortality outcomes.

Materials and Methods

Study Design and Population

This was a single-center, retrospective, and observational study conducted at the People's Hospital of Jiaozuo City, an 1800-bed tertiary care hospital in Jiaozuo, Henan, China, from December 1, 2019, to August 31, 2023. The included patients met the following criteria: 1) age ≥ 18 years at admission and 2) received CZA for > 72 h. The following patients were excluded from the analysis: (1) who received previous CZA treatment before the current study began, (2) who received empirical treatment with CZA, and (3) who had missing follow-up data. This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Jiaozuo People's Hospital. The Ethics Committee waived the need for informed consent from patients because of the retrospective and anonymous nature of the study.

Data Collection and Definitions

For eligible patients, the baseline data comprised the following variables: demographic data; underlying diseases, including Charlson comorbidity index;²² clinical characteristics, including type of infection (according to CDC criteria),²³ sepsis,²⁴ and severity of illness at infection onset (SOFA,²⁵ APACHE II);²⁶ renal replacement therapy; source control; and the standard dose of 2.5 g CZA, administered intravenously every 8 h, with dose adjustments based on the recommended renal function in the product's instructions. Each dose was administered for 2 h. The CZA treatment regimen, classified as a combination therapy, included at least one other antimicrobial agent administered for ≥ 72 h. The primary outcome was all-cause mortality within 30 days of treatment onset. The secondary outcome was the bacterial clearance within 14 days. Bacterial clearance was defined as the absence of target bacteria in subsequent cultures. All data were extracted from the electronic medical record information system. All data were anonymized.

Microbiological Methods

All pathogen isolations and antimicrobial susceptibility tests (excluding CZA) were conducted using a Vitek 2 Compact System (bioMérieux, Inc.). The susceptibility to CZA was determined using the disk diffusion (Kirby–Bauer) method. A diameter of inhibition zone ≥ 21 mm indicated susceptibility, whereas that ≤ 20 mm indicated resistance. The interpretation of all antibiotic susceptibility test results was based on the evaluation standards and breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) in 2019.²⁷ For Enterobacterales, confirmatory MIC testing is indicated for isolates with zones of 20–22 mm to avoid reporting false-susceptible or false-resistant results. The MIC of CZA was determined using concentration gradient agar diffusion drug susceptibility strips (Etest, bioMérieux, France). Quality control strains ATCC 25922, ATCC 27853, ATCC BAA-1705, and ATCC BAA-2146 were purchased from the National Culture Collection Center, Rapid Detection of Carbapenemase Genotype. A colloidal gold enzyme immuno-chromatography (NG-Test CARBA 5) kit was purchased from Shanghai FosunPharma Co., Ltd.

Statistical Analysis

Statistical analyses were performed using the R software package (<http://www.R-project.org>, The R Foundation) and Empower-Stats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, MA, USA). Continuous variables were described using the median and interquartile range (IQR). Student's *t*- or Mann–Whitney *U*-test was used to compare normally and non-normally distributed continuous variables. The chi-squared or Fisher's exact test was used to compare categorical variables. Univariate logistic regression analysis was employed to evaluate the association between exposure variables, after which significant variables ($p < 0.05$) were entered into the multivariate regression model to identify independent risk factors for mortality. Propensity score matching was performed to control for confounding variables, and the propensity score was estimated using a logistic regression model. In this study, a one-to-one nearest neighbor matching algorithm was adopted with a caliper width of 0.05. Variables adjusted for propensity score matching included age, APACHE II score, SOFA score, sepsis, pulmonary infection, and ICU stay before initiating CZA. A two-sided *P* value of < 0.05 was considered statistically significant.

Results

Characteristics of Baseline and Microbiology

During the study, 121 patients prescribed CZA were assessed, and 83 patients were ultimately included in the analysis. The remaining 38 cases were excluded from the analysis due to the following reasons: CZA treatment duration ≤ 72 h ($n=24$), negative culture results ($n=10$), age < 18 years ($n=2$), and loss to follow-up ($n=2$), as depicted in Figure 1.

The patient characteristics following CZA treatment are compared in Table 1. There were 62 males (74.7%) and the mean \pm standard deviation age was 64.2 ± 15.1 years, with no significant difference between the two groups. Most patients presented with comorbidities at admission, with hypertension and cerebrovascular disease being the most common. The median Charlson comorbidity index scores for the monotherapy and combination therapy groups were 3 (1–4) and 3 (1–4), respectively, with no differences between the two groups. The APACHE II scores were 20 (16–23) and 18.5 (15.25–23) for the two groups, whereas the SOFA scores were 5 (4–6) and 4 (3–7.5), with no significant differences between the groups. The incidence of sepsis (44.4% vs 57.9%, $p=0.222$) was lower in the CZA monotherapy group; however, the difference was not statistically significant.

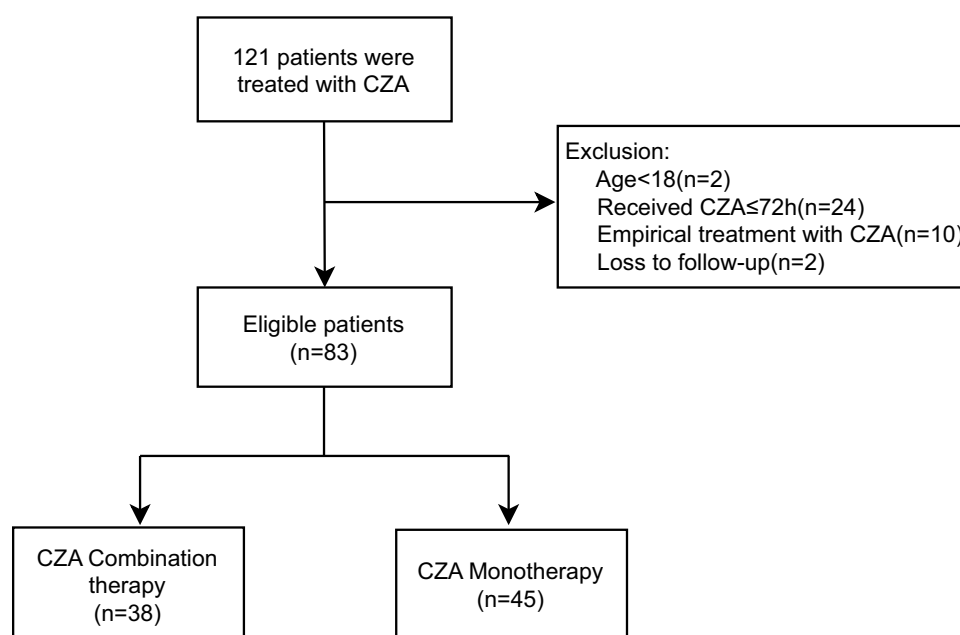


Figure 1 Study flow chart.

Abbreviation: CZA, ceftazidime/avibactam.

Table 1 Baseline Clinical Characteristics of Patients Treated with CZA

Variables	Total (n=83)	Monotherapy (n=45)	Combination (n=38)	P-value
Age, years	64.2±15.1	65.2±13.1	63.1±17.3	0.541
Sex(male)	62 (74.7)	36 (80.0)	26 (68.4)	0.227
BMI	24.65 ±4.75	24.55±5.39	24.76±4.01	0.854
Comorbidities				
COPD	7 (8.4)	5 (11.1)	2 (5.3)	0.445
Cardiovascular disease	60 (72.3)	36 (80.0)	24 (63.2)	0.088
Cerebrovascular disease	47 (56.6)	27 (60.0)	20 (52.6)	0.500
COVID-19	2 (2.4)	0 (0)	2 (5.3)	0.207
Cancer	6 (7.2)	3 (6.7)	3 (7.9)	1.000
Chronic kidney disease	10 (12.1)	4 (8.9)	6 (15.8)	0.336
Diabetes	24 (28.9)	13 (28.9)	11 (28.9)	0.995
Heart failure	16 (19.3)	9 (20.0)	7 (18.4)	0.856
CCI	3 (1–4)	3 (1–4)	3 (1–4)	0.706
APACHE II score	19 (15.5–23)	20 (16–23)	18.5 (15.25–23)	0.587
SOFA score	5 (3–6.5)	5 (4–6)	4 (3–7.5)	0.892
Sepsis	42 (50.6)	20 (44.4)	22 (57.9)	0.222
Vasoactive drugs	11 (13.3)	6 (13.3)	5 (13.2)	0.981
ICU stay positive	49 (59.0)	26 (57.8)	23 (60.5)	0.800
Healthcare interventions				
Surgery	39 (47.0)	21 (46.7)	18 (47.4)	0.949
CRRT	13 (15.7)	6 (13.3)	7 (18.4)	0.525
Mechanical ventilation	67 (80.7)	36 (80.0)	31 (81.6)	0.856
Infection variables				
Bloodstream infection	20 (24.1)	11 (24.5)	9 (23.7)	0.936
Pulmonary infection	54 (65.1)	29 (64.4)	25 (65.8)	0.898
Urinary tract	4 (4.8)	2 (4.4)	2 (5.3)	1.000
Intra-abdominal	4 (4.8)	1 (2.2)	3 (7.9)	0.328
Others	2 (2.4)	2 (4.4)	0 (0)	0.498
ICU stay before starting CZA	5 (0–8)	5 (0–9)	4 (0–6.75)	0.563
Duration of therapy	7 (6–10)	7 (5–9)	8.5 (6–11.75)	0.080
Time to CZA onset	2 (2–4)	3 (2–4)	2 (2–3)	0.176
Polymicrobial infections	18 (21.7)	10 (22.2)	8 (21.1)	0.898
Bacterial eradication (14 days)	34 (41.0)	18 (40.0)	16 (42.1)	0.846
30-day mortality	26 (31.3)	14 (31.1)	12 (31.6)	0.963

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

Abbreviations: BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; APACHE, Apache Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; CRRT, Continuous renal replacement treatment.

In the overall study cohort, there were 54 cases of pulmonary infection (65.1%) and 20 cases of bloodstream infections (24.1%). Other infections included urinary tract, abdominal cavity, and catheter-related infections. The distribution of each type of infection was similar between the CZA combination and monotherapy groups.

The infecting microorganisms included *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*, none of which produce metallo-beta-lactamases. These cells were sensitive to CZA. A total of six cases of infection involving multiple gram-negative bacteria were observed, among which five were simultaneously infected with *K. pneumoniae* and *P. aeruginosa* and one was simultaneously infected with *K. pneumoniae* and *E. coli*. Additionally, there were 77 cases of infection involving a single gram-negative bacterium, with 75 cases infected with *K. pneumoniae*, 1 infected with *P. aeruginosa*, and 1 infected with *E. coli* (Table S1).

Treatment Regimens and Outcomes

In this cohort of 83 patients, 45 received CZA monotherapy and 38 received combination therapy. The median duration of CZA therapy was 7 days (6–10). The duration of treatment in the combination therapy group was 8.5 days (6–11.75), whereas that in the monotherapy group was 7 days (5–9). The duration of combination therapy was slightly longer than that of monotherapy; however, the difference was not statistically significant.

Regarding the primary outcome, there was no significant difference in the 30-day mortality rates between the CZA combination therapy and monotherapy groups (31.6% vs 31.1%, $p=0.963$). In addition, after adjusting for some variables using the propensity score matching between the two groups, we compared the outcome variables of the monotherapy group with those of the combination therapy group (Table 2) and found that the 30-day mortality rate of CZA treatment was not significantly different (31.4% vs 28.6%, $p=0.794$), and there was no statistical difference in the 14-day bacterial clearance rate (42.9% vs 42.9%, $p=1.00$).

Table 2 Baseline Clinical Characteristics of Patients Treated with CZA After Adjustment

Variables	Total (n=70)	Monotherapy (n=35)	Combination (n=35)	P-value
Age, years	63.8±15.4	65.4±13.9	62.3±16.7	0.409
Sex(male)	54 (77.1)	29 (82.9)	25 (71.4)	0.255
BMI	24.89±4.96	24.93±5.81	24.86±4.10	0.957
Comorbidities				
COPD	7 (10.0)	5 (14.3)	2 (5.7)	0.428
Cardiovascular disease	50 (71.4)	27 (77.1)	23 (65.7)	0.290
Cerebrovascular disease	40 (57.1)	21 (60.0)	19 (54.3)	0.629
COVID-19	2 (2.9)	0 (0)	2 (5.7)	0.493
Cancer	5 (7.1)	2 (5.7)	3 (8.6)	1.000
Chronic kidney disease	8 (11.4)	2 (5.7)	6 (17.1)	0.259
Diabetes	21 (30.0)	11 (31.4)	10 (28.6)	0.794
Heart failure	13 (18.6)	8 (22.9)	5 (14.3)	0.356
CCI	3 (1–4)	3 (1–4)	3 (1–4)	0.778
APACHE II score	19.5 (16–23)	21 (17–23)	18 (14.5–22.5)	0.313
SOFA score	5 (3–6.75)	5 (3–6)	4 (2.5–8)	0.860
Sepsis	36 (51.4)	17 (48.6)	19 (54.3)	0.632
Vasoactive drugs	9 (12.9)	5 (14.3)	4 (11.4)	1.000
ICU stay positive	42 (60.0)	22 (62.9)	20 (57.1)	0.626
Healthcare interventions				
Surgery	33 (47.1)	16 (45.7)	17 (48.6)	0.811
CRRT	8 (11.4)	1 (2.9)	7 (20.0)	0.055
Mechanical ventilation	58 (82.9)	30 (85.7)	28 (80.0)	0.526
Infection variables				
Bloodstream infection	17 (24.3)	8 (22.9)	9 (25.7)	0.780
Pulmonary infection	44 (62.9)	22 (62.9)	22 (62.9)	1.000
Urinary tract	4 (5.7)	2 (5.7)	2 (5.7)	1.000
Intra-abdominal	4 (5.7)	1 (2.9)	3 (8.6)	0.614
Others	1 (2.9)	2 (5.7)	0 (0)	0.493
ICU stay before starting CZA	5 (0–8)	5 (0–8.5)	4 (0–7.5)	0.731
Duration of therapy	7 (6–10)	7 (5–8)	9 (6–12)	0.063
Time to CZA onset	2 (2–4)	3 (2–4)	2 (2–3)	0.248
Polymicrobial infections	16 (22.9)	9 (25.7)	7 (20.0)	0.569
Bacterial eradication (14 days)	30 (42.9)	15 (42.9)	15 (42.9)	1.000
30-day mortality	21 (30.0)	11 (31.4)	10 (28.6)	0.794

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

Abbreviations: BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; APACHE, Apache Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; CRRT, Continuous renal replacement treatment.

Independent Predictors of Mortality

In the univariate analysis (Table 3), the following variables demonstrated significant associations with the 30-day mortality rate: the APACHE II score ($p<0.0001$), age ($p=0.007$), sepsis ($p<0.001$), pulmonary infection ($p=0.005$), ICU stay before initiating CZA ($p=0.024$), duration of therapy ($p=0.030$), SOFA score ($p<0.0001$), CCI ($p=0.007$), vasoactive drug use ($p<0.001$), ICU stay positive ($p=0.002$), surgery history ($p=0.048$). In the multivariate COX regression analysis (Table 3), the SOFA score was identified as an independent predictor of 30-day mortality. The duration of therapy was an independent predictor of 30-day survival. After adjusting for propensity score matching, adjusted multivariate COX analysis showed that age and SOFA score were independent predictors of 30-day mortality (Table 4).

Discussion

Since its introduction into the Chinese market in 2019, CZA has been widely used for the clinical treatment of infections caused by CR-GNB. However, traditional viewpoints have led to the belief that combination therapy with two or more antibiotics is superior to monotherapy for the treatment of CR-GNB infections.^{28–30} Consequently, the formulation of CZA-based treatment regimens is controversial in clinical practice. Therefore, this study aimed to compare the efficacy of CZA combination therapy with that of CZA monotherapy in patients with CR-GNB infections.

Table 3 Univariate and Multivariate COX Regression Analysis Associated with 30-Day Mortality

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
APACHE II score	1.19 (1.10, 1.28)	<0.0001		
Age	1.06 (1.03, 1.10)	0.007		
Sepsis	16.02 (3.78, 67.93)	<0.001		
Pulmonary infection	7.86 (1.86, 33.31)	0.005		
ICU stay before starting CZA	1.07 (1.01, 1.14)	0.002		
Duration of therapy (1-day increments)	0.86 (0.74, 0.99)	0.030	0.87 (0.75, 1.00)	0.049
SOFA score	1.26 (1.15, 1.37)	<0.0001	1.27 (1.06, 1.52)	0.009
CCI (1-point increments)	1.28 (1.07, 1.54)	0.007		
Vasoactive drugs	4.51 (1.95, 10.44)	<0.001		
ICU stay positive	6.45 (1.93, 21.50)	0.002		
Surgery	0.43 (0.19, 0.99)	0.048		

Abbreviations: APACHE, Apache Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; CCI, Charlson comorbidity index; HR, Hazard ratio; CI, confidence interval.

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

Exposure	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
APACHE II score	1.15 (1.06, 1.25)	0.001		
Age	1.05 (1.01, 1.09)	0.007	1.06 (1.00, 1.12)	0.035
Sepsis	11.72 (2.72, 50.40)	<0.001		
Pulmonary infection	14.62 (1.96, 109.03)	0.009		
ICU stay before starting CZA	1.08 (1.01, 1.15)	0.034		
Duration of therapy (1-day increments)	0.82 (0.69, 0.97)	0.021		
SOFA score	1.25 (1.14, 1.37)	<0.0001	1.34 (1.10, 1.64)	0.004

Abbreviations: APACHE, Apache Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; CCI, Charlson comorbidity index; HR, Hazard ratio; CI, confidence interval.

Our study found that CZA combination therapy is not superior to CZA monotherapy in reducing the 30-day mortality rate of patients. Considering the individual differences in illness severity between the CZA monotherapy and combination therapy groups, propensity score matching was conducted for indicators of illness severity and age. However, the results remain unchanged. This finding is consistent with those of previous studies. A meta-analysis of seven randomized controlled trials and six retrospective studies involving 503 patients found no difference in the mortality rates between patients receiving CZA monotherapy and those receiving combination therapy for CRE infections.³¹ In a recent large multicenter retrospective study involving 577 patients,¹⁴ the overall mortality rate did not decrease with combination therapy using active agents compared with monotherapy, even in severe cases associated with septic shock or a high mortality score. However, other studies reached conflicting conclusions. In a retrospective study by Zheng G et al,²¹ this study involving 62 critically ill patients, CZA combined with other in vitro non-susceptible antimicrobials, especially carbapenems, fosfomycin, and tigecycline, could significantly lower the mortality risk in critically ill patients with CRKP infection.

The mortality rate of patients with CR-GNB infections treated with CZA in this study cohort was 31.3%, which is similar to the previously reported results of CZA studies.³² Adjusted multivariate Cox regression survival analysis suggested that age and SOFA score were independent risk factors for 30-day mortality in patients with CR-GNB infections. This finding is consistent with those of previous studies.^{33,34} Some studies have shown that the duration of antimicrobial drug use may be a protective factor.³⁵ In our study, this may be due to the small sample size, but it also reflects the fact that clinical symptoms improve during treatment, allowing for the continued use of antimicrobial drugs until the infection is under control.

This study has several limitations. First, this was a single-center study, and the sample size was insufficient. It is worth mentioning that this study included the largest number of patients compared to previous studies from China. Moreover, this was a retrospective cohort study that may have been subject to incomplete data and inclusion bias. Well-designed prospective studies or randomized controlled trials with larger sample sizes should be conducted. Furthermore, all infected patients underwent CZA susceptibility testing, and the clinical application of antibiotics may have been delayed by explicit antimicrobial susceptibility testing. Nevertheless, this is the most common route of administration in clinical practice.

Conclusion

In conclusion, our study showed that combination therapy with CZA and other antimicrobials was not associated with a better clinical or microbiological response. Given the potential toxicity associated with certain multi-drug regimens and the adverse effects resulting from the unnecessary use of antibiotics, the efficacy of CZA as monotherapy should not be overlooked.

Abbreviations

CR-GNB, carbapenem-resistant gram-negative bacteria; CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CZA, ceftazidime–avibactam; APACHE, Apache Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; HAP, hospital-acquired pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Review Board of Jiaozuo People's Hospital (Number: 2023-007-K07).

Acknowledgments

We thank the hospital for its assistance with this study. We would like to thank Editage for English language editing.

Author Contributions

All the authors have read and approved the final version of the manuscript. All authors made a significant contribution to the work reported, whether that is in the study design, execution, acquisition of data, analysis, and interpretation, or in all

these areas; took part in drafting, revising, or critically reviewing the article; approved the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This work was supported by the Science and Technology Research Project of the Henan Province (LHGJ20230021). The funder had no role in the study design, data collection and interpretation, or decision to submit the work for publication.

Disclosure

The authors report no conflicts of interest related to this work.

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