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A Tentative Clinical Study: Colistin Combined with Ceftazidime/Avibactam in the Treatment of Carbapenem-Resistant Gram-Negative Bacilli Infection

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Purpose: The emergence of carbapenem-resistant Gram-negative bacteria (CR-GNB) has led to a critical challenge in antimicrobial therapy. This study aimed to assess the efficacy of colistin (COL) combined with ceftazidime/avibactam (CAZ/AVI) in the treatment of CR-GNB infections.

Patients and Methods: A retrospective, single-center observational study was conducted on patients diagnosed with CR-GNB infections who were treated with COL combined with CAZ/AVI (C/C), COL combined with Tigecycline (C/T), and COL combined with meropenem (C/M). The primary outcome measure was the rate of microbiological clearance within seven days, while secondary outcomes included changes in inflammatory markers, severe illness-related scores, length of stay, and survival rates.

Results: Among the 95 patients analyzed, the C/C treatment regimen resulted in a higher rate of microbiological clearance (64.7%) compared to C/T (24.1%) and C/M (25.0%) (*P*=0.002 and *P*=0.001). In the subgroup analysis for treating infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP), the 7-day microbial clearance rates in the C/C, C/T, and C/M groups were 57.9%, 25.0%, and 29.4%, respectively (P = 0.122). Inflammatory markers, including white blood cell count, c-reactive protein, and procalcitonin, showed improvements in three groups. The decrease of some indicators was statistically significant. However, no significant differences in mortality rates were observed across the treatment groups. Furthermore, the survival curve analysis indicates that the survival time of the C/M treatment regimen is significantly longer than that of the C/C treatment regimen.

Conclusion: The C/C treatment regimen appears to be more effective in achieving microbiological clearance and improving inflammatory parameters in patients with CR-GNB infections. While the impact on survival rates and survival duration requires further investigation, the C/C regimen warrants consideration as a potent therapeutic option for CR-GNB infections.

Keywords: carbapenem-resistant Gram-negative bacteria, colistin, ceftazidime/avibactam, tigecycline, meropenem

Introduction

Infections caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) have become a major global public health challenge.[1] According to the 2017 World Health Organization global report, CR-GNB was listed as a priority pathogen in the highest priority category.[2] Classified by bacterial species, CR-GNB mainly includes carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB).[3] Among them, CRPA and CRAB are the most common, followed by members of the *Enterobacteriaceae* family, including carbapenem-resistant *Klebsiella pneumoniae* (CRKP)[4] and other carbapenem-

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resistant *Enterobacteriaceae*.[5] Based on existing literature reports, CR-GNB spreads widely across the globe, and the prevalence varies in different regions. The Centers for Disease Control and Prevention reported that in 2019, there were approximately 13,100 CRE infections in the United States, resulting in 1,100 deaths.[6] Data from European Antimicrobial Resistance Surveillance Network showed that in 2023, the estimated overall incidence of CRKP and CRPA bloodstream infection in the European Union is 3.97 and 2.01 per 100,000 population.[7] Antimicrobial resistance surveillance in China in 2023 showed that the resistance rates of *Acinetobacter baumannii* to imipenem (IPM) and meropenem (MEM) were 73.4% and 73.7%, respectively.[8] Relevant studies in other regions have reported that the carbapenem resistance rates of *Klebsiella pneumoniae* (KP), *Pseudomonas aeruginosa* (PA), and *Acinetobacter baumannii* (AB) have exceeded 50%, and the resistance rate of *Acinetobacter baumannii* has even reached as high as 90%.[9,10]

Colistin (COL), tigecycline (TIG), ceftazidime/avibactam (CAZ/AVI), MEM, and other drugs are commonly used in the treatment of multidrug-resistant bacteria. COL exerts its antibacterial effect by disrupting the lipopolysaccharide structure within the outer membrane of gram-negative bacteria, while TIG works by inhibiting bacterial protein synthesis, thereby achieving bactericidal and bacteriostatic effects.[11,12] Their therapeutic efficacy has been recognized and widely applied by clinicians. CAZ/AVI is a novel antibiotic that was approved and launched in the United States in 2015. It is a relatively new combination of a third-generation cephalosporin and a novel β-lactamase inhibitor.[13] AVI can reversibly bind to β-lactamases (eg *OXA-48*), effectively inactivating β-lactamases and preventing the hydrolysis of β-lactam compounds. In addition, AVI can also inhibit extended-spectrum β-lactamases (ESBLs) and class C cephalosporinases, providing a potential therapeutic option for infections caused by multidrug-resistant Gram-negative pathogens.[14] MEM belongs to the carbapenem class of antibiotics and does not have an advantage in treating CR-GNB infection. However, according to relevant studies, increasing the concentration of MEM and shortening the medication interval have shown satisfactory effects in the treatment of CR-GNB infections.[15]

However, in recent years, with the extensive use of antibiotics and the spread of drug resistance, the emergence of bacterial resistance to COL, TIG, and CAZ/AVI in the treatment of CR-GNB infections has been observed. A 2022 systematic review and meta-analysis of the global prevalence of colistin resistance in KP bloodstream infections showed that antibiotic resistance rates of KP isolates from bloodstream infections in the seven included countries ranged from 0.8% to 19.2%.[16] Antimicrobial resistance surveillance in China in 2023 showed that the TIG resistance rates in KP and Acinetobacter isolates were 2.5% and 1.7%, respectively. And the CAZ/AVI resistance rates in KP and PA were 5.9% and 7.5%, respectively.[8] The combination of antibiotics is only considered when the effect of single-drug treatment is poor or there is a combined infection with multiple bacteria. Amat T et al and Park SY et al, respectively, explored the effects of COL combined with TIG (C/T) and COL combined with MEM (C/M) in the treatment of CRAB.[17,18] Overall, the mortality rate of combined therapy is lower than that of COL monotherapy. It can be seen from the literature we published last year that COL combined with CAZ/AVI (C/C) is valuable in the treatment of CR-GNB infections, and the overall inflammatory indicators significantly decreased after combined treatment.[19] However, this study lacks a control group study of commonly used antibiotic combinations in the clinic. Therefore, based on this study, we added two control group of C/T and C/M to further discuss the efficacy of COL-based antibiotic combination therapy.

Materials and Methods

Study Design and Population

This is a single-center, retrospective study conducted in the Intensive Care Unit (ICU) of Zhejiang Provincial People's Hospital, a tertiary teaching hospital with 3,000 beds in Hangzhou, Zhejiang Province, China, from January 2019 to January 2024. The use of CAZ/AVI, COL, TIG, MEM during this period followed the guideline recommendations or medicine instruction.[20,21] The pharmaceutical companies, dosage, and administration methods of the combination drugs are as follows: CAZ/AVI (ACS Dobfar S.p.A, Italy, 2.5g q8h, intravenous titration), COL (Shanghai Sangya Pharmaceutical Co., Ltd., China, 750,000 IU q12h, intravenous titration), TIG (Wyeth Lederle S.r.l., Italy, 100mg q12h, intravenous infusion), and MEM (Shenzhen Haibin Pharmaceutical Co., Ltd., Chian, 1g q8h, intravenous infusion). The drug dose and administration interval can be adjusted according to the severity of the disease or organ function. The inclusion criteria include (1) patients older than 18 years, (2) patients with CR-GNB isolated from sputum, blood, or urine bacterial cultures, and (3) patients who received C/C, C/T or C/M treatment and whose total treatment duration exceeded 48 hours. Exclusion criteria was the addition of other antibiotics to the gram-negative bacteria during treatment. The primary outcome is the 7-day microbiological clearance rate, and the secondary outcomes are changes in inflammatory indicators, critical illness-related score changes, 14- and 28-day mortality rates, total hospital length of stay, and ICU length of stay. This study was conducted in accordance with the Helsinki Declaration and was approved by the Research Ethics Committee of Zhejiang Provincial People's Hospital (ethics approval number: QT2024269, Date of approval: 3/12/2024). For this retrospective analysis, individual consent was waived, and the data involving patients were fully confidential.

Data Collection

Patient information was obtained from electronic medical records. Baseline data included: demographic characteristics, underlying diseases, inflammatory indicators (white blood cell [WBC] count, c-reactive protein [CRP] and procalcitonin [PCT]), ventilation modes, Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores, infection sites and types, treatment complications, use of sedative drugs, use of vasoactive drugs, use of antibiotics against gram-positive bacteria and antifungal drugs, whether continuous renal replacement therapy (CRRT) was performed, the duration of combination therapy, and changes in inflammatory indicators during treatment. In addition, outcome indicators included treatment outcomes (7-day microbial clearance rate, 14-day and 28-day mortality rates, changes in inflammatory indicators and severe illness-related scores), and the lengths of stay in the ICU and in the hospital overall. Safety evaluation mainly referred to nephrotoxicity, and also included antibiotic-associated diarrhea, neurotoxicity, etc.

Identification of Micro-Organisms and Drug Susceptibility Test

Select a chocolate agar plate, inoculate the suspicious (or infected) part of the sample, label the plate, and place the IPM and MEM susceptibility disks on either side of the midline. The cells were then incubated in an incubator for 18 to 24 hours and the results were interpreted. According to the size of inhibition rings in IPM and MEM, the growing colonies less than 18mm from the disc were judged as suspected CR-GNB strains. The selected strains were cultured for 18–24 hours and then identified and tested for drug sensitivity. The type of bacteria was identified by VITEK 2-COMPACT automatic microbial analyzer and the minimum inhibitory concentration (MIC) of bacteria was determined by manual drug sensitivity test. The MICs of antibiotics against bacterial isolates were determined using the broth microdilution method, following the guidelines of the Clinical and Laboratory Standards Institute.[22]

Definition

Carbapenem resistance is defined as an IPM or MEM MIC of ≥4 mg/L. The definition of pulmonary infection is based on the American criteria of the Infectious Diseases Society of America.[23] Bloodstream infection is defined as a positive blood culture for at least one target pathogen, accompanied by signs and symptoms of infection. Urinary tract infection is defined as a positive urine culture for at least one target pathogen, with a colony count greater than 5×10^3 CFU/mL, and accompanied by urinary tract irritation symptoms. If the urine routine test indicates a urinary tract infection and the colony count is $\leq 5\times10^3$ CFU/mL, and the culture colonies are single, the name of the first colony is recorded. If the same bacteria are cultured again on the second test, it will also be treated as a positive result. The enrollment time is defined as 24 hours prior to combination drug use. The length of stay in the ICU is defined as the time from the enrollment time to discharge or death. All-cause mortality within 14 and 28 days is calculated from the enrollment time. 7-day microbial clearance rate is defined as the absence of the initially isolated pathogen in the microbial culture on the 7th day.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics v.25.0 (IBM Corp., Armonk, NY, USA). All data were expressed as mean ± standard deviation or median (interquartile range) based on normality tests. Unpaired *t*-tests, ANOVA, Mann–Whitney *U*-tests, or Fisher's exact tests were used as appropriate when performing univariate analysis. Indicators with $P<0.1$ in the univariate indicators that may affect 28-day all-cause mortality were included in the multivariate analysis. Graph plotting was performed using GraphPad Prism v.8.03 (GraphPad Software, Inc., La Jolla, CA, USA) and R Software v.4.3.1. Statistical significance was defined as a two-tailed P-value of<0.05.

Results

Clinical and Microbiological Characteristics

After excluding 47 patients, a total of 95 patients were included in this study (Figure 1). A total of 34, 29, and 32 patients received C/C, C/T, and C/M, respectively. No significant differences were observed in terms of gender, body mass index (BMI), smoking, and drinking habits among the treatment groups. It is worth noting that the average age of patients in the C/T group was significantly lower than that in the C/C group (*P*=0.015). In addition, there were differences in CRP among the three groups (*P*=0.034), while no significant differences were found in APACHE II score, SOFA score, WBC, PCT, ventilation mode, and drug use.

There were multiple infection sites in 95 patients with infection. The main infection site was respiratory tract infection (89 cases, 93.7%), bloodstream infection (10 cases), and urinary tract infection (4 cases). The main pathogenic bacteria were CRKP and CRAB, with 48 cases each, and 18 cases of CRPA. Among the 13 patients infected with CRAB in the C/C group, 12 patients were co-infected with CRKP and 1 patient was co-infected with CRPA. Similarly, 2 of the 4 CRPA infected patients in the C/T group were co-infected with CRKP and CRAB, respectively. Furthermore, with the progression of the disease, 55 patients developed sepsis, 45 patients developed septic shock (*P*=0.002), 62 patients had severe pneumonia, 43 patients had respiratory failure, and 36 patients had renal insufficiency. Table 1 describes the statistical data of the 95 patients.

Types of Carbapenemases

Among the CR-GNB isolates, 51, 19, and 44 cases produced Ambler class A, B, and D carbapenemases, respectively. In CRKP infections, KPC enzymes, which belong to Ambler class A, were the predominant carbapenemase type, accounting for 89.6%, with a small number of Ambler class B enzymes also present. In CRAB infections, OXA-23, an Ambler class D enzyme, was the predominant carbapenemase type, accounting for 87.5%, with a small number of NDM and OXA-48 enzymes also detected. Additionally, in CRPA infections, the carbapenemase types were IMP and KPC enzymes, accounting for 55.6% and 44.4%, respectively (Table 2).

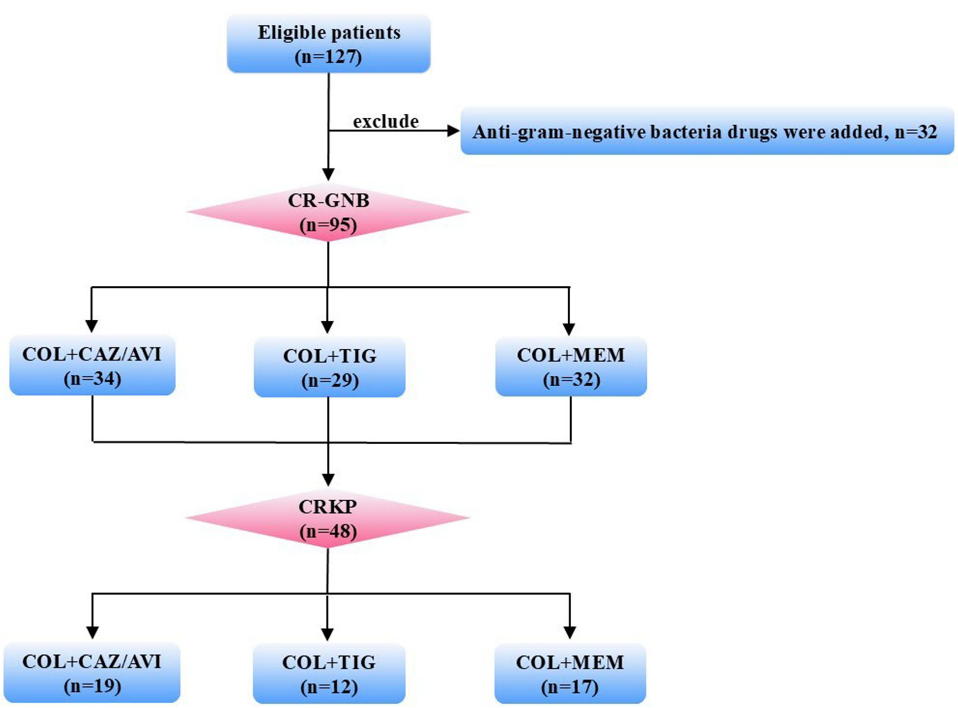

Figure 1 Flow chart.
Abbreviations: COL, colistin; CAZ/AVI, ceftazidime/avibactam; TIG, tigecycline; MEM, meropenem; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRKP, carbapenem-resistant *Klebsiella pneumoniae*.

Table 1 Characteristics of Patients Treated with Different Type of Antibiotics

Characteristic	C/C (n=34)	C/T (n=29)	C/M (n=32)	*P*-Value	**P*-Value	#*P*-Value
Demographic variables						
Male, n (%)	27 (79.4)	26 (89.7)	22 (68.8)	0.145		
Age (years)	72.03±12.81	62.00±18.81	69.13±16.91	0.049	0.015	
Body mass index (kg/m^2)	22.84±3.76	24.41±6.84	23.40±5.76	0.527		
Smoke, n (%)	7 (20.6)	7 (24.1)	6 (18.8)	0.904		
Drink, n (%)	4 (11.8)	6 (20.7)	3 (9.4)	0.456		
APACHE II score	22.21±6.71	21.17±8.04	22.38±7.23	0.788		
SOFA score	10.21±3.44	8.55±4.51	8.66±3.55	0.154		
WBC (×10^9/L)	9.88 (6.25–13.86)	12.17 (8.18–14.91)	11.54 (7.31–14.94)	0.520		
PCT (ng/mL)	2.89 (1.24–5.27)	0.93 (0.31–4.59)	1.19 (0.57–4.38)	0.126		
CRP (mg/L)	165.35 (83.08–206.00)	94.40 (75.20–135.15)	112.05 (53.08–171.38)	0.034	0.008	
Respiratory support way, n (%)						
Mechanical ventilation	30 (88.2)	26 (89.7)	25 (85.3)	0.380		
High-Flow oxygen therapy	4 (11.8)	2 (6.9)	7 (21.9)	0.254		
Others	0 (0.0)	1 (3.4)	0 (0.0)	0.305		
Underlying disease, n (%)						
Hypertension	18 (52.9)	16 (55.2)	20 (62.5)	0.706		
Diabetes	12 (35.3)	6 (20.7)	8 (25.0)	0.422		
Atrial fibrillation	1 (2.9)	0 (0.0)	2 (6.3)	0.642		
Clinical presentation, n (%)						
Sepsis	26 (76.5)	16 (55.2)	13 (40.6)	0.011		0.012
Septic shock	24 (70.6)	12 (41.4)	9 (28.1)	0.002		0.018
Comorbidities, n (%)						
Severe pneumonia	20 (58.8)	20 (69.0)	22 (68.8)	0.639		
Respiratory failure	13 (38.2)	15 (51.7)	15 (46.9)	0.421		
Renal insufficiency	13 (38.2)	12 (41.4)	11 (34.4)	0.835		
Use of sedatives, n (%)	23 (67.6)	19 (65.5)	24 (75.0)	0.724		
Use of a vasopressor, n (%)						
Norepinephrine	21 (61.8)	11 (37.9)	15 (46.9)	0.166		
Aramine	7 (20.6)	6 (20.7)	5 (15.6)	0.847		
Hypophysin	8 (23.5)	2 (6.9)	4 (12.5)	0.193		
Type of infection, n (%)						
Respiratory tract	30 (88.2)	27 (93.1)	32 (100.0)	0.134		
Bloodstream	7 (20.6)	2 (6.9)	1 (3.1)	0.068		
Urinary tract	2 (5.9)	0 (0.0)	2 (6.3)	0.544		
Pathogen, n (%)						
CRKP	19 (55.9)	12 (41.4)	17 (53.1)	0.521		
CRAB	13 (38.2)	21 (72.4)	14 (43.8)	0.018	0.011	0.038
CRPA	7 (20.6)	4 (13.8)	7 (21.9)	0.722		
Other antibiotics, n (%)						
Caspofungin	12 (35.3)	6 (20.7)	6 (18.8)	0.266		
Voriconazole	4 (11.8)	1 (3.4)	1 (3.1)	0.364		
Linezolid	4 (11.8)	1 (3.4)	6 (18.8)	0.186		
Vancomycin	1 (2.9)	1 (3.4)	4 (12.5)	0.314		
Teicoplanin	2 (5.9)	1 (3.4)	1 (3.1)	1.000		
Daptomycin	1 (2.9)	0 (0.0)	5 (15.6)	0.027		
Renal replacement therapy, n (%)	20 (58.8)	13 (44.8)	15 (46.9)	0.487		
Days of combination therapy (days)	8.26±4.33	8.07±4.18	10.16±5.41	0.153		

Notes: **P*-value represents the difference between C/C group and C/T group; #*P*-value represents the difference between C/T group and C/M group.
Abbreviations: C/C, colistin combined with ceftazidime/avibactam; C/T, colistin combined with tigecycline; C/M, colistin combined with meropenem; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; PCT, procalcitonin; CRP, c-reactive protein; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*.

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Table 2 Type of Carbapenemase Produced in CR-GNB Infected Patients

Type	CRKP (n=48)	CRAB (n=48)	CRPA (n=18)
Ambler class A, n (%)			
KPC	43 (89.6)		8 (44.4)
Ambler class B, n (%)			
IMP	3 (6.2)		10 (55.6)
NDM	2 (4.2)	4 (8.3)	
Ambler class D, n (%)			
OXA-48		2 (4.2)	
OXA-23		42 (87.5)	

Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*.

Clinical Effects of Different Antibiotics

In terms of outcome indicators, the C/C group treatment regimen shows excellent performance in the 7-day microbial clearance rate, reaching 64.7%, which is significantly better than that in the C/T and C/M groups. In addition, the C/C group also shows more significant improvements in the reduction of inflammatory indicators PCT and CRP and in the APACHE II score and SOFA score. No significant differences are observed in the 14-day and 28-day mortality rates, the total length of hospital stay, and the length of ICU stay. During the treatment process, 5 and 2 cases in C/C group had acute kidney injury (AKI) and diarrhea, respectively, while in C/T group, there were 3 and 8 cases, respectively. Moreover, compared with C/C group, the proportion of diarrhea in C/T group is significantly higher (P=0.035). In C/M group, 4 and 5 cases had AKI and diarrhea, respectively. Four patients in C/M group had neurological epilepsy symptoms, and 3 cases were observed in C/T group, while this symptom did not occur in C/C group (Table 3).

Clinical Effects of Different Antibiotics in the Treatment of CRKP Infection

After excluding patients with CRAB and CRPA infections, 19, 12, and 17 patients were included in the subgroup analysis, respectively, and the baseline data of each group were relatively stable (Table 4). The 7-day microbial clearance rate in the C/C group was 57.9%, which was still higher than that in C/T group (25.0%) and C/M group (29.4%), although the result was not

Table 3 Outcome Indicator for Patients Treated with Different Type of Antibiotics

Characteristic	C/C (n=34)	C/T (n=29)	C/M (n=32)	*P*-Value	**P*-Value	~*P*-Value
Primary outcome						
Microbial clearance within seven days, n (%)	22 (64.7)	7 (24.1)	8 (25.0)	0.001	0.002	0.001
Secondary outcomes						
Length of hospital stay (days)	34.5 (23.8–51.0)	32.0 (18.0–65.0)	35.0 (20.5–70.3)	0.939		
Length of ICU stay (days)	13.5 (7.0–24.0)	15.0 (7.5–29.5)	18.0 (10.0–33.5)	0.410		
14-day mortality, n (%)	8 (23.5)	7 (24.1)	9 (28.1)	0.914		
28-day mortality, n (%)	10 (29.4)	8 (27.6)	11 (34.4)	0.852		
APACHE II score day 7	21.08±5.81	18.92±7.94	19.65±6.68	0.651		
APACHE II score day 14	21.15±7.01	17.08±7.09	17.76±6.76	0.301		
SOFA score day 7	9.92±3.06	6.85±4.45	8.53±4.75	0.243		
SOFA score day 14	9.31±4.37	7.31±3.88	7.71±4.47	0.458		
Safety evaluation, n (%)						
AKI	5 (14.7)	3 (10.3)	4 (12.5)	0.928		
Epilepsy	0 (0.0)	3 (10.3)	4 (12.5)	0.090		
Diarrhea	2 (5.9)	8 (27.6)	5 (15.6)	0.061	0.035	

Notes: **P*-value represents the difference between C/C group and C/T group. ~*P*-value represents the difference between C/C group and C/M group.
Abbreviations: C/C, colistin combined with ceftazidime/avibactam; C/T, colistin combined with tigecycline; C/M, colistin combined with meropenem; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury.

Table 4 Characteristics of Patients Treated with Different Type of Antibiotics for *Klebsiella pneumoniae* Infection

Characteristic	C/C (n=19)	C/T (n=12)	C/M (n=17)	*P*-Value	**P*-Value
Demographic variables					
Male, n (%)	16 (84.2)	11 (91.7)	13 (76.5)	0.632	
Age (years)	72.75±9.18	66.00±13.26	71.44±15.16	0.794	
Body mass index (kg/m^2)	24.15±3.32	27.92±6.99	22.35±4.04	0.650	
Smoke, n (%)	7 (36.8)	2 (16.7)	4 (23.5)	0.503	
Drink, n (%)	4 (21.1)	1 (8.3)	2 (11.8)	0.670	
APACHE II score	24.38±6.12	18.20±7.73	20.56±6.27	0.848	
SOFA score	9.50±2.20	5.80±4.97	7.78±4.06	0.452	
WBC (×10^{9}/L)	9.88 (6.01–13.81)	11.01 (8.28–13.20)	12.82 (7.19–14.89)	0.766	
PCT (ng/mL)	3.20 (1.29–6.68)	3.44 (0.39–11.1)	1.18 (0.59–3.78)	0.399	
CRP (mg/L)	146.20 (82.10–190.50)	86.00 (62.95–135.05)	115.10 (76.40–188.95)	0.160	
Respiratory support way, n (%)					
Mechanical ventilation	16 (84.2)	11 (91.7)	12 (70.6)	0.412	
High-Flow oxygen therapy	3 (15.8)	0 (0.0)	5 (29.4)	0.101	
Others	0 (0.0)	1 (8.3)	0 (0.0)	0.250	
Underlying disease, n (%)					
Hypertension	11 (57.9)	8 (66.7)	14 (82.4)	0.279	
Diabetes	9 (47.4)	1 (8.3)	3 (17.6)	0.046	0.046
Atrial fibrillation	0 (0.0)	0 (0.0)	2 (11.8)	0.179	
Clinical presentation, n (%)					
Sepsis	16 (84.2)	7 (58.3)	5 (29.4)	0.004	
Septic shock	15 (78.9)	5 (41.7)	3 (17.6)	0.001	
Comorbidities, n (%)					
Severe pneumonia	11 (57.9)	8 (66.7)	12 (70.6)	0.745	
Respiratory failure	7 (36.8)	7 (58.3)	8 (47.1)	0.504	
Renal insufficiency	5 (26.3)	4 (33.3)	8 (47.1)	0.445	
Use of sedatives, n (%)	13 (68.4)	9 (75.0)	12 (70.6)	1.000	
Use of a vasopressor, n (%)					
Norepinephrine	12 (63.2)	4 (33.3)	6 (35.3)	0.164	
Aramine	6 (31.6)	2 (16.7)	2 (11.8)	0.363	
Hypophysin	4 (21.1)	0 (0.0)	2 (11.8)	0.213	
Type of infection, n (%)					
Respiratory tract	17 (89.5))	10 (83.3)	17 (100.0)	0.134	
Bloodstream	6 (31.6)	2 (16.7)	1 (5.9)	0.182	
Urinary tract	1 (5.3)	0 (0.0)	2 (11.8)	0.608	
Other antibiotics, n (%)					
Caspofungin	9 (47.4)	0 (0.0)	3 (17.6)	0.007	
Voriconazole	2 (10.5)	0 (0.0)	1 (5.9)	0.776	
Linezolid	3 (15.8)	0 (0.0)	1 (5.9)	0.432	
Vancomycin	1 (5.3)	0 (0.0)	1 (5.9)	1.000	
Teicoplanin	1 (5.3)	0 (0.0)	0 (0.0)	1.000	
Daptomycin	1 (5.3)	0 (0.0)	2 (11.8)	0.608	
Renal replacement therapy, n (%)	12 (63.2)	6 (50.0)	7 (41.2)	0.445	
Days of combination therapy (days)	8.74±4.15	7.75±4.63	9.65±5.10	0.555	

Notes: **P*-value represents the difference between C/C group and C/T group.
Abbreviations: C/C, colistin combined with ceftazidime/avibactam; C/T, colistin combined with tigecycline; C/M, colistin combined with meropenem; APACHE, Acute Physiology and Chronic Health Evaluation, SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; PCT, procalcitonin; CRP, c-reactive protein.

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statistically significant. Similarly, the 7-day and 14-day severe illness-related scores in C/C group were higher than those in C/T group and C/M group. However, in terms of mortality, the 14-day (15.8%) and 28-day (21.1%) mortality rates in C/C group were lower than those in C/T group (33.3% and 33.3%) and C/M group (29.4% and 35.3%). The overall trends of inflammatory indicators (WBC, CRP, PCT) and severe illness-related scores showed a decreasing pattern. Before the combination therapy, the median CRP in C/T group and C/M group were 86.00 (62.95–135.05) and 115.10 (76.40–188.95) mg/mL, respectively. After 14 days of combination therapy, CRP in both groups showed a significant decrease (P=0.037 and P=0.016). In the C/C group, after 7 days of combined treatment (P = 0.055) and 14 days of combined treatment, CRP also showed a downward trend. The 14-day PCT decrease in C/M group also had a statistical difference (P=0.016) (Figure 2). However, there was no statistical significance for the outcome indicators (Table 5).

Clinical Effects Between Survivors and Non-Survivors

According to the 28-day mortality situation, patients were divided into the survival group and the non-survival group, with 66 patients in the survival group. In the baseline data, through univariate analysis, it was found that the death group had more severe conditions. There were significant differences in APACHE II score (P=0.001), SOFA score (P=0.006), inflammatory indicators (PCT, CRP), and the number of septic patients (P=0.024). Moreover, in the non-survival group, 20 (69.0%) patients required CRRT due to AKI, which was significantly higher than that in the survival group (P=0.025). In terms of clinical efficacy, the 7-day microbial clearance rate, total length of hospital stay, and length of ICU stay were significantly higher in the survival group, while the 7-day APACHE II and SOFA scores were significantly lower in the survival group (Table 6). Based on the univariate analysis study, the characteristic factors with $P < 0.1$ were included in the multivariate logistic regression. The results showed that the increase in CRP was associated with the increase in 28-day mortality (P= 0.042), that is, for every 1 mg/L increase in CRP, the mortality rate increased approximately 0.01-fold (95% confidence interval [CI]: 1.001–1.021). Other characteristic factors showed no statistical differences (Table 7).

Furthermore, a survival analysis was conducted according to the 28-day mortality situation of the three groups drug combination therapy. The P-value of Kaplan–Meier test was 0.094, which showed that there was no statistical significance among the three. However, the survival time of the C/M group was significantly longer than that of the C/C group (P=0.022), suggesting that C/M group has an advantage in extending survival time of patients (Figure 3).

Discussion

This study focuses on evaluating the efficacy of combined antibiotic treatment strategies for CR-GNB infections. The research results indicate that the C/C treatment regimen demonstrates the most outstanding performance in the 7-day microbial clearance rate, reaching 64.7%, which is significantly superior to other treatment regimens. However, no significant differences are observed in the 14-day and 28-day all-cause mortality rates. Additionally, the C/C group shows significant advantages in the improvement of inflammatory indicators and the reduction of severe illness-related scores. These findings suggest that the C/C treatment regimen may be an effective strategy for treating CR-GNB infections.

In treating CR-GNB infections, monotherapy often has limited efficacy. COL, a polypeptide antibiotic with broad Gram-negative activity, faces reduced effectiveness due to rising resistance.[24] CAZ/AVI, a novel β-lactam/β-lactamase inhibitor combination, demonstrates high efficacy against multidrug-resistant strains.[25] With the increase in bacterial resistance, the combination of antibiotics can, to a certain extent, reduce bacterial resistance, expand the antibacterial spectrum and exert a synergistic effect. Currently, there are few clinical studies on C/C. Recently, our team explored a new treatment regimen for CR-GNB infections–C/C regimen. The results of 31 patients showed that compared with before treatment, the inflammatory indicators of patients after combined treatment decreased significantly, the 28-day survival rate reached 71%, and the 7-day microbial clearance rate reached 69%.[19] After data update, the efficacy of the combined treatment in this study is similar to the previous one. Compared with the efficacy of the other two combined treatment regimens, the 7-day microbial clearance rate is significantly higher than the other two groups. Kara EM et al[26] performed an in vitro analysis of the efficacy of C/C regime on OXA-48-producing *Enterobacteriaceae* isolated from ICU, and the results suggested that the regime also had good efficacy against OXA-48-producing *Enterobacteriaceae* infection. However, the combination therapy is not recommended in most in vitro trials, and it is even considered that the efficacy of combination therapy is not better than that of CAZ/AVI monotherapy. Wu Y et al[27] tested the in-vitro efficacy

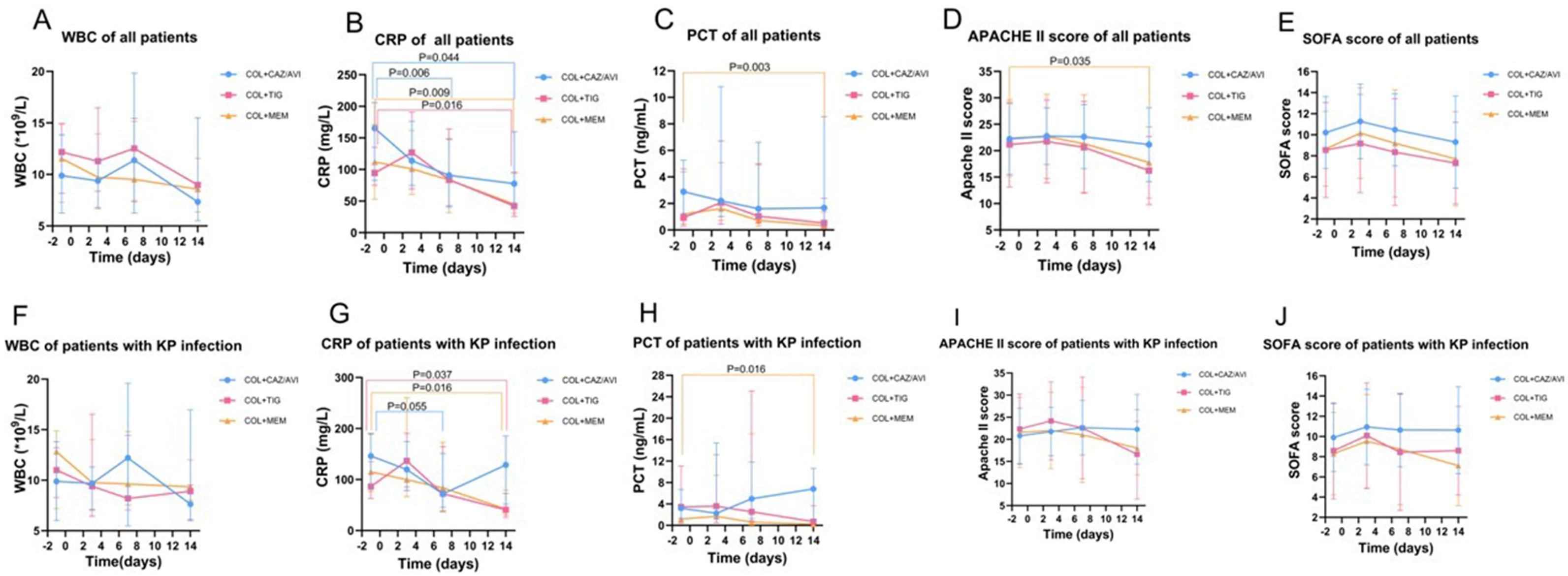

Figure 2 Dynamic changes of inflammatory markers and severe illness scores in CR-GNB patients and KP infectious patients. Changes in inflammatory markers and ICU-associated scores, including 1 day before and 3, 7, and 14 days after start of combination therapy. (**A**–**E**) WBC, CRP, PCT, APACHE II and SOFA score of all patients (*n* = 95); (**F**–**J**) WBC, CRP, PCT, APACHE II and SOFA score of patients with KP infection (*n* = 48).

Abbreviations: CR-GNB, Carbapenem-resistant Gram-negative bacteria; COL, colistin; CAZ/AVI, ceftazidime/avibactam; TIG, tigecycline; MEM, meropenem. WBC, white blood cell; PCT, procalcitonin; CRP, c-reactive protein; KP, *Klebsiella pneumoniae*; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

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Table 5 Outcome Indicators for Patients Treated with Different Type of Antibiotics for *Klebsiella pneumoniae* Infection

Characteristic	C/C (n=19)	C/T (n=12)	C/M (n=17)	*P*-Value
Primary outcome				
Microbial clearance within seven days, n (%)	11 (57.9)	3 (25.0)	5 (29.4)	0.122
Secondary outcomes				
Length of hospital stay (days)	34.0 (22.0–49.0)	26.5 (15.8–68.0)	28.0 (15.5–56.5)	0.919
Length of ICU stay (days)	12.0 (7.0–22.0)	8.5 (6.3–35.0)	17.0 (10.5–37.5)	0.338
14-day mortality, n (%)	3 (15.8)	4 (33.3)	5 (29.4)	0.482
28-day mortality, n (%)	4 (21.1)	4 (33.3)	6 (35.3)	0.663
APACHE II score day 7	21.63±6.09	18.80±11.17	19.33±8.16	0.879
APACHE II score day 14	22.25±7.92	16.60±10.11	18.00±6.06	0.384
SOFA score day 7	10.63±3.11	6.20±5.26	8.44±5.55	0.491
SOFA score day 14	10.63±4.31	8.60±4.39	7.11±3.95	0.248
Safety evaluation, n (%)				
AKI	5 (26.3)	3 (25.0)	1 (5.9)	0.228
Epilepsy	0 (0.0)	0 (0.0)	1 (5.9)	0.604
Diarrhea	0 (0.0)	3 (17.6)	3 (20.0)	0.222

Abbreviations: C/C, colistin combined with ceftazidime/avibactam; C/T, colistin combined with tigecycline; C/M, colistin combined with meropenem; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury.

Table 6 Patient Characteristics and Outcome Indicator Between Survivors and Non-Survivors

Characteristic	All Patients (n=95)	Survivors (n=66)	Non-Survivors (n=29)	OR (95% CI)	*P*-Value
Demographic variables					
Male, n (%)	75 (78.9)	54 (81.8)	21 (72.4)	1.71 (0.64, 4.57)	0.412
Age (years)	67.99±16.57	66.06±16.27	72.38±16.70		0.087
Body mass index (kg/m^2)	23.51±5.50	22.96±4.30	24.76±7.51		0.236
Smoke, n (%)	20 (21.1)	14 (21.2)	6 (20.7)	1.03 (0.35, 3.05)	1.000
Drink, n (%)	13 (13.7)	11 (16.7)	2 (6.9)	2.72 (0.56, 13.24)	0.332
APACHE II score	21.95±7.25	20.41±6.74	25.45±7.26		0.001
SOFA score	9.18±3.87	8.47±3.90	10.79±3.32		0.006
WBC (×10^9/L)	11.08 (7.32–14.63)	10.91 (6.75–14.72)	11.08 (8.12–14.00)		0.856
PCT (ng/mL)	1.89 (0.53–4.87)	1.07 (0.35–3.94)	3.40 (1.72–9.00)		0.001
CRP (mg/L)	115.40 (80.70–171.80)	105.10 (67.63–164.93)	161.40 (90.25–209.65)		0.017
Respiratory support way, n (%)					
Mechanical ventilation	81 (85.3)	54 (81.8)	27 (93.1)	0.33 (0.07, 1.58)	0.214
High-Flow oxygen therapy	13 (13.7)	12 (18.2)	1 (3.4)	6.29 (0.77, 51.30)	0.101
Others	1 (1.1)	0 (0.0)	1 (3.4)	7.00 (0.27, 181.93)	0.305
Underlying disease, n (%)					
Hypertension	53 (55.8)	36 (55.4)	17 (58.6)	0.88 (0.37, 2.09)	0.825
Diabetes	26 (27.4)	18 (27.3)	8 (27.6)	0.98 (0.37, 2.63)	1.000
Atrial fibrillation	3 (3.2)	1 (1.5)	2 (6.9)	0.21 (0.02, 2.45)	0.220
Clinical presentation, n (%)					
Sepsis	55 (57.9)	33 (50.0)	22 (75.9)	3.14 (1.16, 8.48)	0.024
Septic shock	45 (47.4)	27 (40.9)	18 (62.1)	2.36 (0.96, 5.80)	0.075
Comorbidities, n (%)					
Severe pneumonia	62 (65.3)	44 (66.7)	18 (62.1)	1.22 (0.51, 2.92)	0.815
Respiratory failure	43 (45.3)	32 (48.5)	11 (37.9)	1.55 (0.64, 3.77)	0.378
Renal insufficiency	36 (37.9)	21 (31.8)	15 (51.7)	2.30 (0.94, 5.60)	0.072
Use of sedatives, n (%)	66 (69.5)	46 (69.7)	20 (69.0)	1.03 (0.39, 2.72)	1.000

(*Continued*)

Table 6 (Continued).

Characteristic	All Patients (n=95)	Survivors (n=66)	Non-Survivors (n=29)	OR (95% CI)	*P*-Value
Use of a vasopressor, n (%)					
Norepinephrine	47 (49.5)	30 (45.5)	17 (58.6)	0.58 (0.24, 1.42)	0.271
Aramine	18 (18.9)	12 (18.2)	6 (20.7)	0.85 (0.28, 2.59)	0.781
Hypophysin	14 (14.7)	7 (10.6)	7 (24.1)	0.38 (0.12, 1.24)	0.117
Type of infection, n (%)					
Respiratory tract	89 (93.7)	65 (98.5)	24 (82.8)	8.12 (1.50, 43.97)	0.010
Bloodstream	10 (10.5)	6 (9.1)	4 (13.8)	0.62 (0.16, 2.44)	0.488
Urinary tract	4 (4.2)	3 (4.5)	1 (3.4)	0.75 (0.07, 7.95)	1.000
Pathogen, n (%)					
CRKP	48 50.5)	34 (51.5)	14 (48.3)	1.14 (0.42, 2.76)	0.826
CRAB	48 (50.5)	33 (50.0)	15 (51.7)	0.93 (0.39, 2.24)	1.000
CRPA	18 (18.9)	14 (21.2)	4 (13.8)	1.68 (0.50, 5.63)	0.571
Other antibiotics, n (%)					
Caspofungin	24 (25.3)	14 (21.2)	10 (34.5)	1.95 (0.73, 5.24)	0.203
Voriconazole	6 (6.3)	4 (6.1)	2 (6.9)	1.15 (0.19, 7.07)	1.000
Linezolid	11 (11.6)	7 (10.6)	4 (13.8)	1.35 (0.35, 5.22)	0.731
Vancomycin	6 (6.3)	4 (6.1)	2 (6.9)	1.15 (0.19, 7.07)	1.000
Teicoplanin	4 (4.2)	2 (3.0)	2 (6.9)	2.37 (0.29, 19.47)	0.583
Daptomycin	6 (6.3)	3 (4.5)	3 (10.3)	2.42 (0.44, 13.39)	0.365
Renal replacement therapy, n (%)	48 (50.5)	28 (42.4)	20 (69.0)	0.33 (0.13, 0.85)	0.025
Days of combination therapy (days)	8.84±4.73	9.48±4.91	7.38±3.99		0.031
Primary outcome					
Microbial clearance within seven days, n (%)	37 (38.9)	32 (48.5)	5 (17.2)		0.006
Secondary outcomes					
Length of hospital stay (days)	34.0 (22.0–53.0)	40.5 (26.8–55.5)	22.0 (14.0–37.5)		0.001
Length of ICU stay (days)	14.0 (8.0–29.0)	19.0 (11.0–37.0)	9.0 (7.0–12.5)		<0.001
APACHE II score day 7	21.61±8.01	20.13±7.33	27.13±8.28		0.002
APACHE II score day 14	18.58±6.99	18.82±7.23	16.25±3.78		0.490
SOFA score day 7	9.41±4.58	8.50±4.51	12.80±3.08		0.001
SOFA score day 14	8.07±4.25	7.85±4.30	10.25±3.50		0.287
Safety evaluation, n (%)					
AKI	12 (12.6)	11 (16.7)	1 (3.4)		0.098
Epilepsy	7 (7.4)	7 (10.6)	0 (0.0)		0.097
Diarrhea	15 (15.8)	12 (18.2)	3 (10.3)		0.542

Abbreviations: WBC, white blood cell; PCT, procalcitonin; CRP, c-reactive protein; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; CI, credibility interval.

Table 7 Multivariate Analysis of the Patients Between Survivors and Non-Survivors

Variable	Odds Ratio	95% CI	*P*-Value
Age (each 1-year increment)	1.033	0.990–1.077	0.135
Apache II score (each 1 increment)	0.985	0.878–1.104	0.794
SOFA score (each 1 increment)	1.163	0.959–1.410	0.126
Sepsis	5.937	0.826–42.677	0.077
Septic shock	0.367	0.057–2.379	0.293
PCT (each 1-ng/mL increment)	1.015	0.955–1.091	0.537
CRP (each 1-mg/L increment)	1.010	1.001–1.021	0.042
Renal insufficiency	1.508	0.449–5.062	0.507
Respiratory tract	0.104	0.008–1.431	0.091
Renal replacement therapy	1.244	0.330–4.685	0.747
Days of combination therapy (each 1-day increment)	0.899	0.787–1.027	0.116

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; CRP, c-reactive protein; CI, credibility interval.

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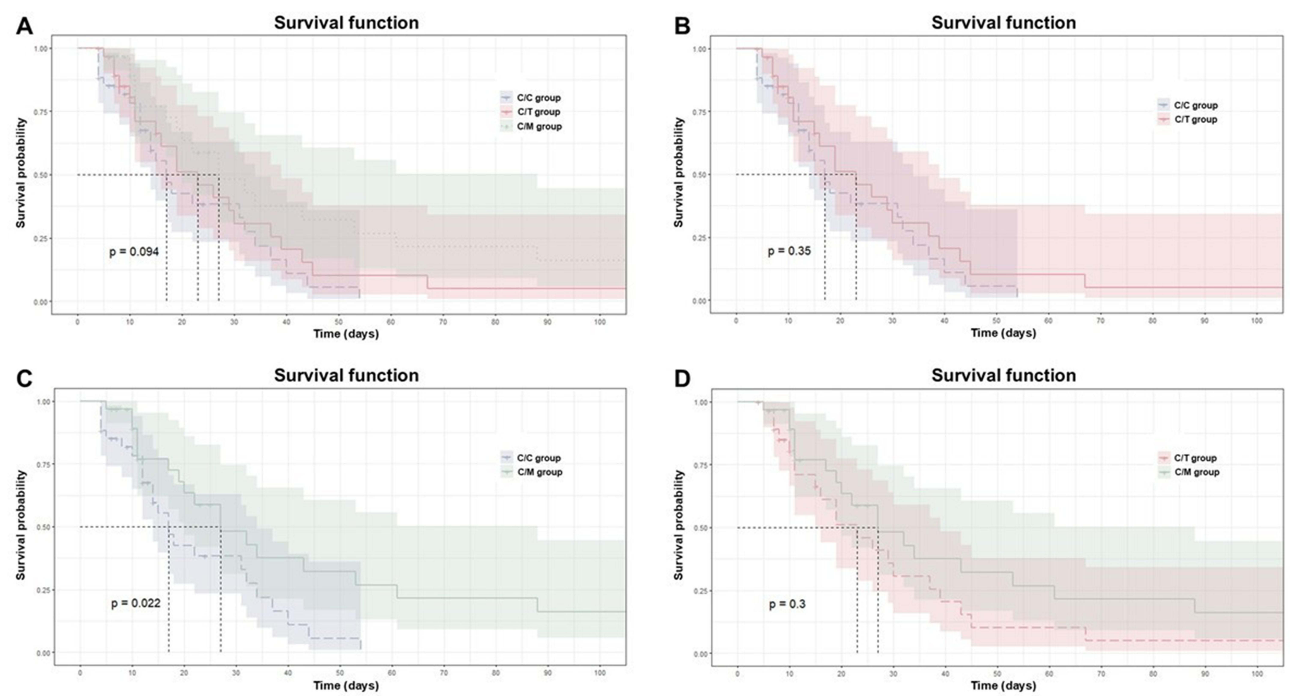

Figure 3 Survival curve analysis. Kaplan-Meier survival curves according to different types of antibiotic treatment result. (**A**) Survival curves of the three groups of C/C, C/T, and C/M (*P*=0.094); (**B**) Survival curves of the C/C group and C/T group (*P*=0.35); (**C**) Survival curves of the C/C group and C/M group (*P*=0.022); (**D**) Survival curves of the C/T group and C/M group (*P*=0.3).

Abbreviations: C/C, colistin combined with ceftazidime/avibactam; C/T, colistin combined with tigecycline; C/M, colistin combined with meropenem.

of C/C in treating CRKP by the checkerboard method. Among 59 CRKP strains, most did not show synergy or antagonism to the C/C, and only 2 CRKP strains producing IMP enzymes had a synergistic effect; while the research results of Wang F et al[28] on 90 CRKP strains showed that partial synergy was observed in 43% of the isolates. In addition, Borjan J et al[29] suggested that, in view of the potential toxicity and lack of synergy, the CAZ/AVI-polymyxin B combination should be avoided. Similarly, a study of Shields RK et al found that COL failed to enhance the eradication effect of CAZ/AVI on carbapenem-resistant *Enterobacteriaceae* and failed to inhibit the emergence of CAZ/AVI resistance.[30] However, research on the clinical efficacy of the combination treatment of the two is still lacking at present, and it is inaccurate to evaluate only through in-vitro tests. Furthermore, the treatment regimens of C/M and C/T also showed certain efficacies. In the published literature, Yu L et al[31] observed through in-vitro tests that the C/M might be an effective treatment option for colistin-resistant CRKP isolates. Similarly, Daikos GL et al[15] observed the lowest mortality rate among patients with CRKP infections who received carbapenem-containing combination treatments through in-vivo studies. In addition, Tumbarello M et al[32] observed that combination therapy with COL and TIG, particularly when combined with MEM, was associated with a significantly lower mortality rate. However, the data of this combined treatment strategy in large-scale clinical trials are still limited, and the emergence of TIG- and COL-resistant bacteria also poses challenges to clinical treatment.

CAZ/AVI has been shown to effectively inhibit Ambler class A, C, and D β-lactamases, including ESBLs, KPC, and OXA-48 carbapenemases, as well as AmpC enzymes. However, its efficacy is limited against bacteria producing OXA-23 or class B carbapenemases.[33] Previous studies have indicated that in China, OXA-23 is the primary mechanism mediating carbapenem resistance in AB.[33,34] Consequently, CAZ/AVI exhibits limited effectiveness against CRAB infections. Nevertheless, CAZ/AVI remains effective against a small subset of CRAB strains producing OXA-48 or OXA-51 enzymes. TIG, a glycylcycline antibiotic, exerts its antibacterial effects by binding to the 30S ribosomal subunit, thereby inhibiting protein synthesis. This mechanism of action enables TIG to suppress the proliferation of various clinically relevant multidrug-resistant pathogens, making it a valuable therapeutic option for complex infections.[35] However, PA exhibits intrinsic resistance to TIG due to the expression of resistance-nodulation-division family efflux pumps (eg, MexXY-OprM, MexAB-OprM), which actively expel TIG from the bacterial cell. Additionally, the absence or reduced expression of outer membrane porins (eg, OprD) further limits TIG's intracellular accumulation, contributing to this intrinsic resistance.[36] In our study, 13 patients with CRAB infections, co-infected with CRKP and CRPA, were treated with the C/C regimen. Similarly, 4 patients with CRPA infections, co-infected with CRKP and CRAB, received the C/T regimen. In principle, these types of co-infections are not ideally suited for treatment with COL in combination with CAZ/AVI or TIG, as the therapeutic efficacy may be comparable to COL monotherapy. However, given the presence of CAZ/AVI- or TIG-susceptible pathogens in these co-infections, combination therapy was employed. Despite the potential influence of these factors, no significant differences were observed in outcome measures, such as mortality rate and length of hospital stay, between the C/C regimen and the other treatment groups. Therefore, subgroup analysis of treatment efficacy for CRAB and CRPA infections was not deemed appropriate in this study.

The results showed that the inflammatory indicators and severe illness-related scores of the three groups of patients changed during the treatment process, but the changing trends and amplitudes differed among the different treatment regimens. The CRP level and age in the C/C group were significantly higher than that in the other two groups at the initial stage of treatment (P=0.034 and P=0.015), and more patients in this group developed sepsis and septic shock, which might be related to the severity of infection in these patients. Compared with before treatment, the decrease in CRP after 14 days of treatment in the three groups was statistically significant, but the decrease in the C/C group was the greatest, suggesting that this regimen might be more effective in controlling the inflammatory response. This is consistent with our previous research results that the C/C treatment can significantly reduce the CRP level. Through subgroup analysis, we did not find any differences in the treatment of CRKP infections among the three groups of antibiotics, but due to the small sample size, the evaluation of the efficacy of the three groups of antibiotics still needs to be further explored. In addition, after including the indicators with a univariate analysis $P < 0.1$ for all patients in the multivariate analysis, the results showed that the increase in CRP level at the initial stage of treatment was associated with an increase in mortality, which is similar to the research results of Zhou Y et al.[37] According to the survival curve, the difference was not statistically significant among three regimens (P=0.094). However, the C/M group was better than the C/C group, while the other controls had no statistical significance. We posit that the survival time of the C/M group exceeds that of the C/C group for two primary reasons. First, the C/C group exhibited advanced age, higher comorbidity indices, and a higher incidence of sepsis and septic shock. Despite superior microbial clearance in the C/C subgroup, the overall disease severity in these patients markedly diminished their survival prospects. Figure 2 illustrates a statistically significant reduction in PCT, CRP, and APACHE II levels in the C/M group compared to the other groups after a 14-day treatment period. Second, this outcome might be influenced by the relatively small sample size, necessitating further expansion for validation. Consequently, while our findings imply a superior survival rate in the C/M group compared to the C/C group, the clinical significance of this observation remains uncertain. Therefore, caution is advised for clinicians considering the utilization of COL in combined with CAZ/AVI. In our research, the C/C regimen might be more effective in reducing inflammatory indicators and improving severe illness-related scores, but the impact on survival rate needs further study. Future studies should focus on the long-term effects of different antibiotic combination treatment regimens on patient prognosis and explore individualized treatment regimens to improve the therapeutic effect.

This study has several limitations. First, as this research is a retrospective, single-center observational design, the indication bias must be considered. Moreover, the small sample size prevented the inclusion of patients' comorbidities in the logistic regression analysis, which might have influenced the study results. Second, the concurrent use of anti-gram-positive bacteria and antifungal drugs might have an impact on the study results. Third, the bacterial susceptibility testing in our center does not include colistin, and some drug-resistant bacteria may have colistin resistance. Therefore, in future prospective studies, we will pay more attention to the susceptibility test of colistin and use it in combination under sensitive conditions.

Conclusion

The C/C treatment regimen appears to be more effective in achieving microbiological clearance and improving inflammatory parameters in patients with CR-GNB infections. While the impact on survival rates and survival duration requires further investigation, the C/C regimen warrants consideration as a potent therapeutic option for CR-GNB infections.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board and the Ethics Committee of the Zhejiang Provincial People's Hospital, which complies with the Declaration of Helsinki (ethics approval number: QT2024269, Date of approval: 3/12/2024). And individual consent for this retrospective analysis was waived.

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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 that they have no competing interests.

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