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ORIGINAL RESEARCH

Factors Associated with Successful Treatment of Carbapenem-Resistant Gram-Negative Bacilli Infections Using Intravenous Colistin Sulfate in China: A Real-World Retrospective Study

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Objective: To evaluate the efficacy of intravenous colistin sulfate (CS) in the treatment of carbapenem-resistant Gram-negative bacilli (CR-GNB) infections in real-world clinical settings and to identify factors influencing its therapeutic outcomes, with the aim of promoting the rational use of CS.

Methods: A retrospective analysis was conducted on the clinical characteristics and treatment outcomes of 174 patients diagnosed with CR-GNB infection who received intravenous CS at our center between January 2021 and December 2023. The study evaluated both clinical efficacy and adverse drug reactions (ADRs).

Results: Among the 174 patients, 118 cases (67.8%) demonstrated clinical improvement, and the bacterial clearance rate was 53.9%. Multivariate logistic regression analysis identified several factors significantly associated with treatment efficacy: neurological disease (OR [95% CI]: 0.100 [0.019–0.541]; $p = 0.006$), admission to a surgical ward (OR [95% CI]: 0.136 [0.023–0.801]; $p = 0.027$), septic shock (OR [95% CI]: 5.147 [1.901–14.096]; $p = 0.001$), and empirical use of CS (OR [95% CI]: 4.250 [1.109–16.291]; $p = 0.035$). Additionally, 10 cases (5.8%) of acute kidney injury (AKI) were attributed to nephrotoxicity from CS, with 2 cases recovering after discontinuation of the drug.

Conclusion: Our findings suggest that intravenous colistin sulfate may be an effective treatment option for CR-GNB infections when used appropriately. However, further studies are required to better understand its real-world efficacy and safety profile.

Keywords: polymyxin, colistin, colistin sulfate, real world, carbapenem-resistant gram-negative bacilli, infection, efficacy, nephrotoxicity

Introduction

Antibiotic resistance poses the most serious threat to human health globally. Without proactive solutions to combat widespread antibiotic resistance, it is estimated that by 2050 around 10 million people will die each year from antimicrobial-resistant infections, more than from any other type of disease.[1] The World Health Organization (WHO) is urging all government sectors and society to take action on antibiotic resistance. More and more attention has been received on carbapenem-resistant gram-negative bacilli (CR-GNB), as shown in the WHO priority pathogen list, because effective treatment options for life-threatening infections caused by these pathogens are rapidly diminishing.[2] CR-GNB can confer resistance to almost all major classes of antibiotics (except for colistin, tigecycline, and certain aminoglycosides) through multiple mechanisms.[3]

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Polymyxins, which include polymyxin B and colistin (also known as polymyxin E), are a class of cyclic lipopeptide antibiotics that exert their antibacterial effects by binding to the lipid A component of lipopolysaccharide (LPS) on the outer membrane of Gram-negative bacteria, leading to the disruption of cell membrane integrity.[4] Although polymyxins were approved for clinical use in the late 1950s, their use declined in the 1970s due to concerns about nephrotoxicity and neurotoxicity, as well as the availability of more effective antibiotics, particularly cephalosporins and carbapenems.[5] However, since the 2000s, with the emergence of CR-GNB, polymyxins have become one of the few remaining therapeutic options for multidrug-resistant Gram-negative pathogens.[6,7]

Due to the fact that polymyxins have been off-patent for many years and were not widely utilized between the 1970s and 1990s, research on colistin and colistin sulfate (CS) remained limited.[8,9] However, in response to the increasing need for these antibiotics to combat resistant Gram-negative "superbugs" over the past two decades, significant advancements have been made in the fields of pharmacology, toxicology, and pharmacokinetics.[10,11]

CS was approved in 2018 and launched in July 2019 on the Chinese market, and the clinical data of CS in Chinese patients have gradually increased. In 2019, American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP) issued an international consensus guidelines on the clinical application of Polymyxins, but there were few Chinese clinical data cited in it.[12] Due to the lack of clinical research, there are relatively few real-world studies of CS in the Chinese population.[13,14] Therefore, we report a single-center retrospective real-world study to investigate the clinical outcomes and safety of intravenous CS treatment in patients with CR-GNB infections.

Methods

Study Design and Subjects

This single-center, real-world, retrospective study was conducted on 174 adult patients who were treated with intravenous CS and hospitalized at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China between January 2021 and December 2023. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee and informed consent was waived due to the retrospective nature of the study (Code TJ-IRB202308134). All patient data were de-identified prior to analysis, with strict measures implemented to protect confidentiality. No personally identifiable information was accessible during or after the study, ensuring full compliance with privacy protection standards.

Inclusion Criteria

The study enrolled patients who met the following inclusion criteria: (1) patients confirmed positive culture of CR-GNB or highly suspected CR-GNB infections (which were defined as follows: Non-response to carbapenem therapy after 72 hours; history of colonization with CR-GNB; current infection site shows a large number of Gram-negative bacteria under microscopic examination, or the patient is from an ICU ward with a high prevalence of CR-GNB); (2) underwent continuous anti-infective treatment for more than three days with intravenous CS (colistin sulfate for injection, Shanghai SPH New Asia Pharmaceutical Co. Ltd., Shanghai, China). Cases with less than three days of CS therapy were excluded from this study to ensure that the drug has sufficient time to exert its effect and to reduce interference from non-drug factors; (3) considering the potential impact of the COVID-19 pandemic on the patterns of colistin antibiotic use and clinical outcomes in this study, we excluded all cases of COVID-19 infection.

The inclusion and evaluation of all cases were carried out collaboratively by infection experts, microbiologist, and clinical pharmacists from the research team.

Data Collection

Data were collected through electronic medical records, and variables included: gender, age, Charlson Comorbidity Index (CCI), comorbidities, inpatient ward, pre-infection variables, infection variables, infection site, pathogens, treatment duration, and treatment regimen. The CCI was scored according to the Charlson Comorbidity Index, version 2016.[15]

Patient Screening Procedure

The diagnosis of infection is mainly based on the patient's laboratory test results, microbial culture results and the clinician's experience. Comorbidities included diabetes, chronic obstructive pulmonary disease (COPD), hematological malignancies, solid tumors, chronic hepatitis, cardiovascular disease (confirmed coronary artery disease, chronic heart failure, arrhythmias, and peripheral arterial disease), neurological disease (cerebrovascular diseases, neurodegenerative diseases, epilepsy, and sequelae of traumatic brain injury), chronic kidney disease, human immunodeficiency virus (HIV) infection, endocrine disease, gastrointestinal disease, solid organ transplantation, and others. The disease classification is based on ICD-10 codes and verified by medical record review.[16]

Microbiology

All CR-GNB were identified in the microbiology laboratory, including *Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumannii* and other strains. Bio-samples included blood, venous catheter samples, urine, perianal swabs, sputum, tracheal secretions, bronchoalveolar lavage fluid, intraperitoneal fluid, and pleural drainage fluid. Bacterial identification and drug susceptibility were performed using the Vitek®2 automated system (Biomerieux, France). Drug susceptibility was interpreted according to the criteria of the Clinical and Laboratory Standards Institute criteria.[17] *Enterobacteriaceae* with a minimum inhibitory concentration (MIC) $\geq$ 4 μg/mL were considered carbapenem-resistant, while *P. aeruginosa* and *Acinetobacter* spp. were considered resistant if their MIC was $\geq$ 8 μg/mL.[17] Strains isolated with CS MIC values of $\leq$ 2 μg/mL were deemed susceptible to CS (colistin breakpoint for *Enterobacteriaceae*).[18] Clinicians assessed the pathogenicity of the pathogens based on their professional judgment and the distribution of pathogens within the healthcare facility.

Treatment Regimen Evaluation

All included patients received intravenous CS, either in combination with other anti-CR-GNB agents or monotherapy. According to the guidelines and relevant expert consensus, CS monotherapy was not recommended, most in combination with another or more CR-GNB-sensitive antibacterial drugs; If there are no drugs that exhibit true sensitivity, the non-sensitive drugs with the lowest relative breakpoint MIC can be considered for combination therapy. In some cases, the duration of CS treatment was too short, and the recommended treatment days were 14 days.[12] All patients in this study were treated with intravenous CS at a dose of 1.0–1.5 million IU per day. The appropriateness of the CS regimen used in the study population was evaluated. Empirical treatment was defined as the administration of CS before receiving bacterial culture results.

Outcomes

For this analysis, the primary outcome was the clinical response; the secondary outcomes included factors associated with microbiological response and the occurrence of ARDs during CS treatment. Clinical response was defined as survival, improvement in infection indicators, or complete symptom resolution. Clinical failure was defined as: (1) death due to all causes during treatment with CS; (2) persistence or deterioration of symptoms or infection indicators. The microbiological response, only for patients in the microbiologically evaluable analysis set, was based on results of the baseline and post-treatment cultures, and the clinical response assigned by the investigator. Bacteria eradication rate was defined as the rate that the causative pathogens were eliminated during the course of CS treatment. The AKI was defined using Improving Global Outcomes criteria.[19] Available safety laboratory data were graded using the Common Terminology Criteria for Adverse Events.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics, Version 24.0 (IBM Corporation, Armonk, NY, USA). Fisher test was used to compare the clinical efficacy of patients with different comorbidities, inpatient wards, pre-infection variables, infection variables, infection sites, empirical and target treatments, CS monotherapy and combination therapy, and other factors. A p-value of $\leq$ 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 174 patients treated with intravenous CS were enrolled in the analysis, of whom 122 (70.1%) were male, with a mean age of 50.6 ± 17.3 years. Among these patients, 88 (50.6%) were from medical wards, 54 (31.0%) were from surgical wards, and 32 (18.4%) were from the Intensive Care Unit. A total of 60 patients (34.5%) had a Charlson Comorbidity Index (CCI) score of ≥ 3. Cardiovascular disease was present in 62 patients (35.6%), 42 patients (24.1%) had undergone solid organ transplantation, and 36 patients (20.7%) had hematological malignancies. Endoscopic procedures were performed on 100 patients (57.5%), while 76 patients (43.7%) required mechanical ventilation. The most common site of infection was the lungs, with pulmonary infections accounting for 112 cases (64.4%). The predominant CR-GNB identified was *Acinetobacter baumannii* (98 cases, 56.3%), followed by *Klebsiella pneumoniae* (82 cases, 47.1%). A total of 34 patients (19.5%) suffered from septic shock. The mean duration of drug treatment was 15.1 ± 10.2 days, and 22 patients (12.6%) received empirical treatment. The demographic and clinical characteristics of the patients treated with intravenous CS are summarized in Table 1.

Table 1 Patient Demographic and Clinical Characteristics

Characteristic	Values
Age (year, mean ± SD)	50.6 ± 17.3
Male, n (%)	122 (70.1)
Female, n (%)	52 (29.9)
Charlson's Comorbidity Index ≥ 3, n (%)	60 (34.5)
Comorbidities, n (%)	
Diabetes	28 (16.1)
COPD	14 (8.0)
Hematological malignancies	36 (20.7)
Solid tumors	4 (2.3)
Chronic hepatitis	22 (12.6)
Cardiovascular disease	62 (35.6)
Neurological disease	14 (8.0)
Chronic kidney disease	20 (11.5)
HIV	0 (0)
Neutropenia	4 (2.3)
Endocrine	12 (6.9)
Gastrointestinal disease	10 (5.7)
Solid organ transplantation	42 (24.1)
Other	30 (17.2)
Inpatient wards, n (%)	
ICU	32 (18.4)
Surgical	54 (31.0)
Medical	88 (50.6)
Pre-infection variables, n (%)	
Central venous catheter	64 (36.8)
Nasogastric tube	20 (11.5)
Surgical drainage	38 (21.8)
Bladder catheter	4 (2.3)
Endoscopy	100 (57.5)
Mechanical ventilation	76 (43.7)
Continuous veno-venous hemodialysis	52 (29.9)
Steroid therapy	32 (18.4)
Immunosuppressive therapy	46 (26.4)
Previous surgery	70 (40.2)

(*Continued*)

Table 1 (Continued).

Characteristic	Values
Infection variables, n (%)	
Nosocomial infection	6 (3.4)
Polymicrobial infection	12 (6.9)
Septic shock	34 (19.5)
Sites of infection, n (%)	
Pulmonary	112 (64.4)
Urinary tract	16 (9.2)
Incision	4 (1.1)
Intraperitoneal	8 (4.6)
Bloodstream	28 (16.1)
Central nervous system	2 (1.1)
Abdominal infection	8 (4.6)
Pathogens, n (%)	
KP	82 (47.1)
PA	30 (17.2)
EC	34 (19.5)
AB	98 (56.3)
Others	28 (16.1)
Treatment, n (%)	
Empirical use	22 (12.6)
Days of antibiotic therapy (mean ± SD)	15.1 ± 10.2
Intravenous	174 (100)
Inhalation	102 (58.6)
Intrathecal injection	2 (1.1)
Loading dose (IU)	1 million
Daily dose (IU)	1.5 million
Combination antibiotic therapy, n (%)	138 (79.3)
Carbapenem	74 (42.5)
Tigecycline	58 (33.3)
Cephalosporin	4 (2.3)
Ceftazidime-avibactam	29 (16.7)
Others	12 (6.9)

Notes: Polymicrobial infection: The isolation of ≥2 pathogens from the same infection site, or the isolation of different pathogens from different sites that are both considered active infections. Due to polymicrobial infections in some patients, the sum of pathogen proportions may exceed 100%; Inhalation: It refers to the administration of CS via nebulization devices for the treatment of respiratory infections.

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, Intensive Care Unit; KP, *Klebsiella pneumoniae*; PA, *Pseudomonas aeruginosa*; EC, *Escherichia coli*; AB, *Acinetobacter baumannii*.

Evaluation of the Rationality of the Clinical Application

For all patients, a loading dose of 1 million IU of CS was administered, followed by a daily dose of 1.5 million IU, divided into 2–3 doses, in accordance with standard dosing recommendations for CS. Additionally, for patients with pulmonary infections, inhalation of CS (250,000 IU every 12 hours) was used in combination with intravenous treatment. For patients with central nervous system infections, CS (50,000 IU every 24 hours) was administered via the intraventricular/intrathecal (IVT/IT) route in combination with systemic therapy. Instances of irrational use of CS included cases where combination therapy was not utilized (n = 36) and cases where CS treatment duration was less than 7 days (n = 6).

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Clinical Response Evaluation

A total of 118 cases were evaluated for clinical efficacy, yielding an overall clinical effectiveness rate of 67.8% (118/174). When comparing the clinical response and failure groups, several factors were found to influence clinical outcomes. Patients with neurological diseases exhibited a significantly lower clinical effectiveness rate (3.73% vs 17.86%, $p = 0.002$), while those with chronic kidney disease demonstrated a higher clinical effectiveness rate (16.78% vs 3.57%, $p = 0.023$). Additionally, patients in surgical wards had a higher clinical effectiveness rate (46.61% vs 7.14%, $p < 0.001$), whereas those in medical wards had a lower clinical effectiveness rate (46.61% vs 67.86%, $p = 0.002$).

Mechanical ventilation was associated with a lower clinical effectiveness rate (37.29% vs 64.29%, $p < 0.001$), and patients with septic shock also showed a reduced clinical effectiveness rate (11.19% vs 39.29%, $p < 0.001$). Patients with pulmonary infections had a lower clinical effectiveness rate compared to those without pulmonary infections (65.25% vs 75.0%, $p = 0.044$). Furthermore, patients receiving targeted therapy had a higher clinical effectiveness rate than those receiving empirical therapy (9.32% vs 21.32%, $p = 0.016$) (Table 2).

Table 2 Characteristics of Patients With Clinical Response or Clinical Failure

Characteristics	Clinical Response (n (%)/mean ± SD)	Clinical Failure (n (%)/mean ± SD)	*p*-value
Male	88 (74.58)	34 (60.71)	0.062
Female	30 (25.42)	22 (39.29)	
Age	50.2 ± 15.2	51.6 ± 21.3	0.633
CCI ≥ 3	46 (42.88)	14 (25.00)	0.070
Comorbidities			
Diabetes	18 (16.78)	10 (17.86)	0.662
COPD	10 (9.32)	4 (7.14)	0.763
Hematological malignancies	26 (24.24)	10 (17.86)	0.525
Solid tumors	4 (3.73)	0 (0)	0.394
Chronic hepatitis	16 (14.92)	6 (10.71)	0.598
Cardiovascular disease	40 (37.29)	22 (39.29)	0.488
Neurological disease	4 (3.73)	10 (17.86)	0.002
Chronic kidney disease	18 (16.78)	2 (3.57)	0.023
Neutropenia	4 (3.73)	0 (0)	0.394
Endocrine	10 (9.32)	2 (3.57)	0.342
Gastrointestinal disease	4 (3.73)	6 (10.71)	0.078
Solid organ transplantation	34 (31.69)	8 (14.29)	0.036
Other	20 (18.64)	10 (17.86)	0.882
Inpatient wards			
ICU	17 (15.85)	15 (26.79)	0.062
Surgical ward	50 (46.61)	4 (7.14)	<0.001
Medical ward	50 (46.61)	38 (67.86)	0.002
Pre-infection variables			
Central venous catheter	40 (37.29)	24 (42.86)	0.252
Nasogastric tube	18 (16.78)	2 (3.57)	0.023
Surgical drainage	28 (26.10)	10 (17.86)	0.381
Bladder catheter	2 (1.86)	2 (3.57)	0.595
Endoscopy	64 (59.66)	36 (64.29)	0.21
Mechanical ventilation	40 (37.29)	36 (64.29)	<0.001
Continuous veno-venous hemodialysis	32 (29.83)	20 (35.71)	0.247
Steroid therapy	20 (18.64)	12 (21.43)	0.476
Immunosuppressive therapy	36 (33.56)	10 (17.86)	0.077
Previous surgery	44 (41.02)	26 (46.42)	0.251

(*Continued*)

Table 2 (Continued).

Characteristics	Clinical Response (n (%)/mean ± SD)	Clinical Failure (n (%)/mean ± SD)	*p*-value
Infection variables			
Nosocomial infection	6 (5.59)	0 (0)	0.215
Polymicrobial infection	6 (5.59)	6 (10.71)	0.171
Septic shock	12 (11.19)	22 (39.29)	<0.001
Sites of infection			
Pulmonary	70 (65.25)	42 (75.00)	0.044
Urinary tract	10 (9.32)	6 (10.71)	0.307
Incision	2 (1.86)	2 (3.57)	0.595
Intraperitoneal	4 (3.73)	4 (7.14)	0.595
Bloodstream	18 (16.78)	10 (17.86)	0.662
Central nervous system	2 (1.86)	0(0)	0.827
Abdominal infection	2 (1.86)	2 (3.57)	0.595
Pathogens			
KP	58 (54.07)	24 (42.86)	0.437
PA	22 (20.51)	8 (14.29)	0.477
EC	24 (22.37)	10 (17.86)	0.70
AB	68 (63.39)	30 (53.57)	0.614
Treatment			
Empirical use	10 (9.32)	12 (21.43)	0.016
Days of antibiotic therapy	16.1 ± 11.6	13.1 ± 6.2	0.089
Combination therapy	94 (87.63)	44 (78.57)	0.228

Abbreviations: CCI, Charlson's Comorbidity Index; COPD, chronic obstructive pulmonary disease; ICU, Intensive Care Unit; KP, *K. pneumoniae*; PA, *P. aeruginosa*; EC, *E. coli*; AB, *A. baumannii*.

Logistics Multivariate Regression Analysis

Significant variables with a *p*-value of <0.05 from the clinical response evaluation were included in the multivariate logistic regression analysis to identify independent risk factors for clinical response. The results indicated that neurological disease (OR [95% CI]: 0.100 [0.019 to 0.541]; $p = 0.006$), surgical ward (OR [95% CI]: 0.136 [0.023 to 0.801]; $p = 0.027$), septic shock (OR [95% CI]: 5.147 [1.901 to 14.096]; $p = 0.001$), and empirical use (OR [95% CI]: 4.250 [1.109 to 16.291]; $p = 0.035$) were identified as independent risk factors for clinical response (Table 3).

Microbiological Efficacy

The results of microbial culture showed that 152 patients had CR-GNB, and the microbial culture results were *K. pneumoniae* (70.7%, 58/82), *P. aeruginosa* (73.3%, 22/30), *E. coli* (70.6%, 24/34), and other mainly *A. baumannii* (69.4%, 68/98). Microbiological eradication occurred in 82 (53.9%) out of 152 patients with positive culture results.

Table 3 Multivariate Analyses to Identify the Risk Factors for Clinical Response

Characteristics	B	SE	Wald	*df*	*p*-value	OR (95CI)
Neurological disease	−2.305	0.834	7.608	1	0.006	0.100 (0.019–0.514)
Surgical ward	−1.991	0.903	4.866	1	0.027	0.136 (0.023–0.801)
Septic shock	1.644	0.511	10.349	1	0.001	5.177 (1.901–14.096)
Empirical use	1.447	0.686	4.456	1	0.035	4.250 (1.109–16.291)

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Safety Assessment

In this study, 10 cases (5.8%) of AKI were attributed to CS nephrotoxicity, of which 2 cases recovered after drug withdrawal. No neurological toxicity such as paresthesia, or skin pigmentation and any other ADRs were observed.

Discussion

The results of this study demonstrated an overall clinical efficacy rate of 67.8%, with a microbiological eradication rate of 53.9%. Numerous studies have evaluated the clinical efficacy and safety of colistin methanesulfonate (CMS) and polymyxin B (PMB). According to previously reported data, the clinical efficacy of CMS ranged from 41% to 67%, with an AKI incidence ranging from 26% to 50%.[20,21] The incidence of nephrotoxicity associated with PMB has varied between 20% and 60% in prior studies.[22–24] However, data on colistin sulfate (CS) are more limited. A retrospective cohort study in China evaluating the clinical efficacy and nephrotoxicity of CS for treating carbapenem-resistant Gram-negative bacterial infections reported an overall favorable clinical response rate of 58%, a bacterial clearance rate of 40%, and a 28-day all-cause mortality rate of 44%.[25] In comparison, the clinical efficacy and bacterial clearance rates observed in our study were slightly higher than the averages reported in previous studies.

This study found that patients with different comorbidities exhibited varying clinical outcomes: patients with chronic kidney disease had higher clinical efficacy, while those with neurological diseases were more prone to clinical failure. Our current understanding of the PK/PD relationship of polymyxins remains limited.[26–28] A retrospective PK study of PMB in 32 adult patients with varying renal function (71.9% of whom were critically ill) found that creatinine clearance (CrCL) significantly impacted the PK of CS. Based on the therapeutic target area under the curve over 24 hours (50–100 mg*h/L) for PMB, an adjusted dosing regimen for PMB in patients with different renal functions was recommended. In patients with renal insufficiency, the dose of PMB should be reduced according to CrCL.[27] In our study, the dosage of CS was not adjusted according to CrCL in patients with chronic kidney disease, which may be one of the reasons for the nephrotoxicity of CS.

Previous research on polymyxins and nervous system diseases has primarily focused on two areas: the neurotoxicity of polymyxins and the use of intrathecal polymyxins for treating central nervous system infections.[29–31] The neurotoxicity of polymyxins can manifest as symptoms such as facial numbness, flushing, dizziness, ataxia, lethargy, peripheral paresthesia, and apnea. This neurotoxicity may be attributed to the induction of mitochondrial dysfunction, leading to reactive oxygen species (ROS)-induced apoptosis.[32] It may also result from the inhibition of acetylcholine release at the neuromuscular junction, prolongation of depolarization, and promotion of histamine release due to calcium ion depletion. However, recent literature rarely mentions neurotoxicity, as its incidence is less common than nephrotoxicity, typically occurring in less than 7% of cases.[33]

CS has limited ability to penetrate the blood-brain barrier. Clinical trials have shown that intravenous polymyxin achieves low concentrations in cerebrospinal fluid without significantly increasing the risk of meningitis. Animal studies have reported that the concentration of the drug in the cerebrospinal fluid of mice ranges from 5–11% of plasma levels.[22] In another study involving mice with meningitis, drug concentrations in the cerebrospinal fluid could reach up to 34–67% of plasma concentrations, but never exceeded 0.2 mg/L.[34] In this study, no clear relationship has been established between the effect of intravenous CS treatment and neurological disease complications.

A previous clinical study involving 181 patients with sepsis treated with intravenous PMB showed that: By the evaluation of time of PMB administration and efficacy, it was found that the effective rate (60.0% vs 37.6%, $p = 0.008$) and bacterial clearance rate (54.5% vs 34.4%, $p = 0.016$) in the group of time of PMB administration less than 24 hours before CR-GNB isolated were significantly higher than those in the group of time of PMB administration more than 24 hours. The found indicated that the earlier the targeted anti-infection administration of PMB, the better the clinical effect.[14] This study revealed that the clinical efficacy rate of CS in patients admitted to surgical wards surpassed that observed in patients admitted to medical wards. This discrepancy can potentially be attributed to several factors. Firstly, patients in surgical wards typically undergo continued hospitalization following surgery, enabling prompt administration of CS upon occurrence of CR-GNB infection. Conversely, some patients in medical wards are often hospitalized after the infection has progressed significantly, resulting in delayed initiation of anti-infective therapy. Secondly, it is plausible that

individuals hospitalized in surgical wards tend to exhibit milder symptoms of postoperative infection compared to those with severe infections who are frequently transferred for treatment at corresponding medical wards or ICU. Specific data related to the timing of medication of different wards should collected for further analysis.

Our findings indicate that septic shock is associated with clinical treatment failure when using CS. Similarly, a previous study identified mechanical ventilation, septic shock, multiple-site infections, and total PMB cumulative dose as independent factors affecting treatment efficacy.[35] A multicenter, real-world retrospective study assessing the safety and efficacy of PMB for CR-GNB in 100 patients found that among those treated with intravenous PMB, fewer patients in the survival group were on mechanical ventilation (21% vs 30%, $p < 0.001$) or developed septic shock (17% vs 32%, $p < 0.001$) compared to those in the non-survival group. The 28-day mortality rate for patients on mechanical ventilation was 58.82%, compared to 20.41% for patients not on mechanical ventilation. Similarly, the 28-day mortality rate was 65.31% for patients with septic shock, versus 15.69% for those without septic shock.[13]

This study found that the clinical effectiveness of empirical treatment with CS was a key factor associated with successful outcomes. In contrast, a previous retrospective study reported higher mortality rates with empirical PMB treatment. The authors of that study emphasized the importance of rapid identification of CR-GNB infections and the prompt initiation of PMB therapy when CR-GNB infections are confirmed and PMB-susceptible, in order to prevent progression to mechanical ventilation or septic shock.[13] Additionally, their analysis suggested that the narrow antibacterial spectrum of CS, which specifically targets Gram-negative bacteria, may contribute to its potential inefficacy.[36,37] Furthermore, when bacterial culture results fail to isolate potential pathogens, etiological treatment becomes unfeasible, leading to suboptimal outcomes with empirical treatment.

In this study, 3.4% of cases were treated with CS for less than 7 days. Previous reports have indicated that, compared to the 3–7 day treatment group, patients in the 8–14 day and >14 day treatment groups had significantly higher rates of treatment efficacy and bacterial clearance ($p < 0.05$), with no significant difference between the latter two groups ($p > 0.05$). However, the >14 day treatment group experienced more ADRs. Some patients also developed resistance to PMB, suggesting that while the duration of PMB treatment is important, longer treatment is not always better. Prolonged treatment may increase the risk of bacterial resistance to PMB and lead to a higher incidence of ADRs.[14] Therefore, for patients infected with CS-sensitive CR-GNB, it is crucial to ensure an adequate duration of CS treatment to achieve optimal anti-infective effects.

The heteroresistance rate of polymyxins can be as high as 14%, which has led to recommendations for polymyxin-based combination therapies to reduce the risk of heteroresistance and improve microbial clearance, cure rates, and survival rates in patients.[36] For carbapenem-resistant *A. baumannii*, clinically available antibiotics include polymyxin, sulbactam and its combination formulations, and tigecycline, often used in combination therapy.[36,37] For carbapenem-resistant *Enterobacteriaceae*, treatment options primarily include polymyxin, tigecycline, and ceftazidime/avibactam, with a focus on selecting combinations of relatively sensitive agents.[36,38] In our study, among patients treated with CS, 20.7% received CS monotherapy, 33.3% were treated in combination with tigecycline, 42.5% with carbapenems, and 55.8% received two or more drugs, aligning with current guideline recommendations.

Achieving therapeutic concentrations of PMB in lung tissue is challenging when administered intravenously.[39,40] Therefore, for patients with severe pulmonary infections caused by CR-GNB, relevant guidelines recommend supplementing intravenous polymyxins treatment with aerosol inhalation of polymyxins.[12] In this study, patients with respiratory infections accounted for 64.4%, and 102 cases were assisted by aerosol inhalation.

Our study has several limitations. First, the sample size was small, and the study design was retrospective and conducted at a single center. As a result, certain issues could not be addressed with the available data, such as the lack of 28-day mortality data and the relationship between the use of CS in CRRT patients and the occurrence of nephrotoxicity. Larger, multi-center studies with broader sample sizes are needed to further evaluate the clinical effects of CS treatment in real-world settings.

Conclusions

In conclusion, it is essential to strengthen the monitoring of clinical CS use, including ensuring appropriate indications, treatment duration, consideration of comorbidities that may impact efficacy, as well as the rational use of empirical

treatment and combination therapy, to enhance its clinical effectiveness. Our findings demonstrate that CS has high clinical efficacy in the treatment of CR-GNB infections in a real-world setting.

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Disclosure

All authors declared no conflicts of interest in this work.

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