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ORIGINAL RESEARCH

Clinical Effectiveness and Safety of Colistin Sulphate in Treating Infections Caused by Carbapenem-Resistant Organisms and Analysis of Influencing Factors

Ying-Chao Ma[1], Ya-Qing Sun[2], Xia Wu[1], Yong-Jing Wang[1], Xiu-Ling Yang[1], Jian-Jun Gu[3]

[1]Department of Pharmacy, Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, 050000, People's Republic of China; [2]College of Pharmacy, Hebei Medical University, Shijiazhuang, Hebei Province, 050000, People's Republic of China; [3]Department of Cardiac Surgery, Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, 050000, People's Republic of China

Correspondence: Jian-Jun Gu, Department of Cardiac Surgery, Second Hospital of Hebei Medical University, No. 215 of Heping West Road, Xinhua District, Shijiazhuang, 050000, Hebei Province, People's Republic of China, Tel +8631166002991, Email jianjungu62@126.com; Xiu-Ling Yang, Department of Pharmacy, Second Hospital of Hebei Medical University, No. 215 of Heping West Road, Xinhua District, Shijiazhuang, Hebei Province, 050000, People's Republic of China, Tel +8631166002712, Email yangxuilingyxl0d@126.com

Objective: To assess the efficacy and safety of colistin sulfate in treating infections caused by carbapenem-resistant organisms (CRO) and to analyze potential factors impacting its effectiveness.

Methods: In this retrospective study, medical records of CRO-infected patients from June 2020 to June 2023 were analyzed, divided into effective and ineffective treatment groups, and compared for clinical outcomes and adverse reactions. Multifactorial logistic regression and ROC curve analysis were used to identify influencing factors.

Results: The study included 226 patients, with 124 in the effective treatment group and 102 in the ineffective group. A total of 293 CRO strains were cultured. The clinical efficacy rate of colistin sulfate was 54.87%, the microbiological efficacy rate 46.46%, and the hospital mortality rate 20.80%, with nephrotoxicity observed in 11.50% of patients. Multifactorial analysis identified APACHE II scores and vasoactive drug use as independent predictors of ineffective treatment, while treatment duration and albumin levels predicted effective treatment. ROC analysis indicated that albumin levels >34 g/L, APACHE II scores <13, and treatment duration >10 days correlated with better clinical efficacy.

Conclusion: Colistin sulfate is both safe and effective in clinical settings. Factors such as treatment duration, albumin levels, APACHE II scores, and vasoactive drug use independently affect its clinical efficacy, providing valuable guidance for its informed clinical application.

Keywords: colistin sulphate, carbapenem-resistant organism, clinical efficacy, influencing factors, safety evaluation

Introduction

With the escalating utilization of carbapenems and the rapid proliferation of carbapenem-resistant organisms (CRO), the issue of CRO infections has intensified within clinical contexts. Both the World Health Organization and the US Centers for Disease Control and Prevention have categorized these organisms as priority bacteria with the highest risk level.[1] Despite this, the majority of CRO strains are susceptible to colistin, positioning it as the final recourse in CRO infection treatment. Colistin sulphate, a drug like colistin, has been independently developed in China and is presently exclusively available within the country due to its earlier listing and absence of modern drug development processes. However, its usage has declined in recent years, with limited domestic and international research conducted on its efficacy. Currently, there are only a handful of studies evaluating the clinical efficacy of colistin sulphate, indicating a paucity of adequate evidence regarding its therapeutic efficacy.[2–5] This study endeavors to explore the clinical effectiveness of colistin sulphate in managing CRO infections and elucidate its influencing factors through retrospective analysis. The objective

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of the study is to have a better understanding of the practical application of colistin sulphate in clinical diagnosis and treatment.

Materials, Subjects, and Methods

Case Selection

The retrospective collection of medical records included patients admitted to the Second Hospital of Hebei Medical University between June 2020 and June 2023, diagnosed with CRO infection. The diagnosis of CRO infection was established by two clinicians through an assessment of the patients' clinical symptoms, signs, and examination outcomes (such as fever patterns and inflammation markers), coupled with the findings from validated pathogenic cultures. Approval for data usage in this study was obtained from the Ethics Committee of the Second Hospital of Hebei Medical University (Ethics Approval Number: 2020-R551).

Diagnosis and Inclusion Criteria

(1) Patients were confirmed to have CRO infection based on etiological and drug sensitivity testing. (2) Intravenous colistin sulphate was administered according to the prescribed dosage regimen. (3) Patients received intravenous colistin sulphate treatment for a minimum of 3 days. (4) Patients were aged 18 years or older. (5) For patients with multiple occurrences of CRO infection, only data from the initial occurrence were included in the analysis.

Exclusion Criteria

(1) pregnancy, lactation; (2) incomplete medical record data; (3) death occurring within 3 days post-administration of colistin sulphate treatment.

Drugs

Colistin sulphate injection, with a strength of 500,000 IU per vial (approved by the Shanghai SPH New ASIA Pharmaceutical Co., Ltd., with approval number H31020822).

Observation Indicators and Efficacy Determination

Patient data were retrieved from the hospital's electronic medical record system, which included demographic information such as gender and age, clinical details such as infection site and laboratory indicators, results of pathogen cultures, clinical outcomes, and details of colistin sulphate administration. The main outcome assessed was the clinical efficacy observed at the conclusion of the colistin sulphate treatment. Secondary outcome measures comprised microbiological efficacy, in-hospital mortality, and occurrence of adverse drug reactions.

Clinical efficacy was evaluated based on the Technical Guidelines for Clinical Trials of Antimicrobial Drugs.[6] Patients were categorized as follows: cured, when symptoms, signs of infection, and laboratory indicators normalized; significantly improved, when there was notable improvement but not complete normalization in one of the above indicators; progress, when symptoms improved but laboratory tests remained abnormal and pathogen tests continued to be positive; ineffective, when patients did not meet the criteria for cure, improvement, or progress, or when infection symptoms persisted or led to death. Cured, significantly improved, and progress were collectively considered clinically effective outcomes. Drug sensitivity was assessed using the broth microdilution method, with colistin sulphate sensitivity interpreted according to guidelines from CLSI, EUCAST, and USCAST.[7–9] A minimum inhibitory concentration (MIC) $\leq$ 2 mg/L was deemed sensitive, while $\geq$ 4 mg/L was considered resistant. Patients treated empirically without positive culture results were excluded from microbiological efficacy analysis. Bacterial clearance was defined as two consecutive negative culture results from the infected site post-treatment. Effective microbial therapy was defined as either bacterial clearance or a reduction in bacterial load.

Colistin sulphate-associated acute kidney injury (AKI) is defined as AKI occurring during or within 72 hours after completing treatment with colistin sulphate. The baseline serum creatinine (SCr) value, obtained prior to colistin sulphate administration, serves as the reference point. Diagnostic criteria for AKI align with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline: an increase in SCr of $\geq$ 0.3 mg/dL (> 26.5 μmol/L) within 48

hours; or an increase in SCr of ≥ 1.5 times the baseline value within 7 days; or urine output < 0.5 mL/kg/h for 6 hours.[10] Patients with pre-existing chronic kidney disease (CKD), baseline creatinine clearance (CrCL) < 80 mL/min, or those undergoing chronic renal replacement therapy (CRRT) before colistin sulphate administration were excluded from analysis.

Statistical Processing

SPSS 25.0 software was utilized for statistical analysis. Normally distributed variables were presented as Mean ± SD. Intergroup comparisons were performed using *t*-tests and ANOVA tests. Non-normally distributed variables were expressed as Median (Q1, Q3), and intergroup comparisons were conducted using the Mann–Whitney *U*-test. Changes in continuous variables before and after treatment were analyzed using the paired-sample Wilcoxon signed-rank sum test. Categorical data were presented as frequency (%), and intergroup comparisons were made using the chi-square test with Fisher's exact test. Multivariate logistic regression models were employed to identify potential independent predictors of colistin sulphate's clinical efficacy. Variables with a P-value less than 0.1 in the analytical comparison between the treatment-effective and treatment-ineffective groups were included in the multivariate logistic regression model analysis, after controlling for confounding factors such as covariance. Odds ratios (ORs) and 95% confidence intervals were calculated, where an OR < 1 indicated a risk factor and an OR > 1 indicated a protective factor.

Results

General Data

According to data retrieved from the hospital's electronic medical record information system, a total of 280 patients received treatment with colistin sulphate between June 2020 and June 2023. After applying the inclusion criteria, 226 patients were ultimately included in the study (see Figure 1). Table 1 summarizes the primary demographic and clinical characteristics of these patients. The median age of the cohort was 68.00 (64.00, 73.00) years, with 147 male patients. The median BMI was 23.66 (20.20, 26.04) kg/m2, the median length of hospital stay was 47.00 (27.00, 64.00) days, and the median APACHE II score was 17.00 (12.00, 22.00) points. The most prevalent underlying condition was cardiovascular disease (40.27%), followed by hypertension (34.96%) and chronic respiratory disease (26.55%). Mechanical ventilation was required for 152 (67.26%) patients, vasoactive drugs were administered to 117 (51.77%) patients, and 29 (12.83%) patients underwent continuous renal replacement therapy (CRRT). Pulmonary infections were the most common, affecting 86.28% of the patients, with 94 (41.59%) patients experiencing multisite CRO infections.

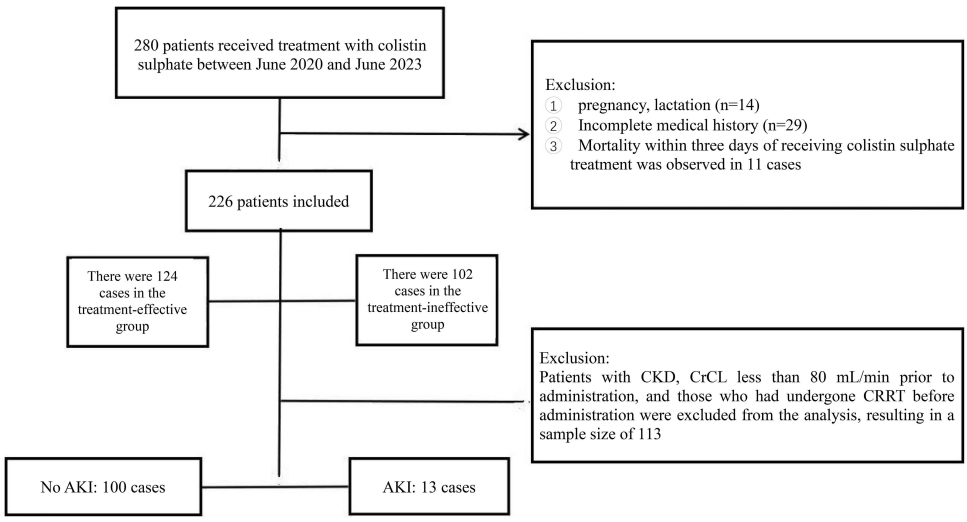

Figure 1 Flowchart of study subgroups.

Table 1 Clinical Features of Patients Diagnosed with CRO Infection

Item	Result (n=226)
Male (n%)	147 (65.04%)
Age (years)	68.00 (64.00, 73.00)
BMI (kg/m^2)	23.66 (20.20, 26.04)
APACHE II Scoring	20.00 (14.00, 22.00)
ICU (n%)	181 (80.09%)
Mechanical ventilation (n%)	152 (67.26%)
Vasoactive agent (n%)	117 (51.77%)
ECMO (n%)	10 (4.42%)
CRRT (n%)	29 (12.83%)
Length of stay (n%)	47.00 (27.00, 64.00)
Underlying disease (n%)	
Hypertension	79 (34.96%)
Diabetes	47 (20.80%)
Chronic respiratory disease	60 (26.55%)
Chronic kidney disease	16 (7.08%)
Angiocardiopathy	91 (40.27%)
Cerebrovascular disease	29 (12.83%)
Malignant solid tumor	19 (8.41%)
Hematological malignancies	18 (7.96%)
Autoimmune disease	14 (6.19%)
Trauma	16 (7.08%)
Chronic liver disease	33 (14.60%)
Infection site (n%)	
Pulmonary infection	195 (86.28%)
Bloodstream infection	57 (25.22%)
Central nervous system infection	10 (4.42%)
Skin soft-tissue infection	7 (3.10%)
Abdominal infection	12 (5.31%)
Urinary system infection	12 (5.31%)
Multisite infection	94 (41.59%)
Pathogenic bacteria (n%)	
CRAB	143 (63.27%)
CRKP	92 (40.71%)
CRPA	34 (15.04%)
CREC	21 (9.29%)
Other CREs	13 (5.75%)
Number of pathogens ≥ 2	60 (26.55%)
MIC (n%)	
MIC=0.25mg/L	74 (32.74%)
MIC=0.5mg/L	95 (42.04%)
MIC=1mg/L	114 (50.44%)
MIC=2mg/L	10 (4.42%)
Baseline condition	
Scr (μmol/L)	73.00 (49.00, 111.00)
CrCL (mL/min)	80.10 (42.90, 126.01)
ALB (g/L)	33.90 (30.50, 36.40)
Medication of colistin sulfate	
Loading dose (n%)	119 (52.65%)
Maintenance dose (MIU)	1.00 (1.00, 1.50)
Integral dose (MIU)	12.00 (8.00, 19.50)

(*Continued*)

Table 1 (Continued).

Item	Result (n=226)
Daily dose/Weight (MIU/kg)	1.82 (1.54, 2.13)
Course of treatment (d)	10.00 (7.00, 14.00)
Drug combination (n%)	
Tigecycline	121 (53.54%)
Carbapenems	49 (21.68%)
Cefoperazone-Sulbactam	23 (10.18%)
Tigecycline+Cefoperazone-Sulbactam	15 (6.64%)

(*Continued*)

Pathogenicity

A total of 293 strains of carbapenem-resistant organism (CRO) pathogens were identified, with the highest detection rate observed for carbapenem-resistant *Acinetobacter baumannii* (CRAB) (143 strains, 63.27%), followed by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) (92 strains, 40.71%), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) (34 strains, 15.04%), and carbapenem-resistant *Escherichia coli* (CREC) (21 strains, 9.29%). Additionally, 60 patients (26.55%) were found to be co-infected with two or more types of CROs. It's worth noting that all identified CROs exhibited sensitivity to colistin sulphate.

Medication Administration

All patients received targeted treatment following the identification of the pathogenic organisms. A combination regimen centered on colistin sulphate was employed across all cases, with 119 cases (52.65%) receiving a loading dose, primarily 100 mg. Among these, a combination of two antimicrobial drugs was utilized in 193 cases (85.40%). The primary combination drugs included tigecycline in 121 cases (53.54%), carbapenems in 49 cases (21.68%), and sulbactam and cefoperazone in 23 cases (10.18%). A combination regimen involving three or more antimicrobial drugs was administered in 33 cases (14.60%), with the specific combinations detailed in Table 1. The duration of colistin sulphate administration ranged from 3 to 34 days for all patients, with a median treatment course of 10.00 (7.00, 14.00) days and a cumulative dose of 12.00 (8.00, 19.50) MIU.

Clinical Efficacy and Outcome

At the conclusion of the treatment, significant reductions were observed in the patients' body temperature, white blood cell count, C-reactive protein, and procalcitonin levels, with the differences being statistically significant ($P < 0.05$, Table 2). Of the patients treated with colistin sulphate, 124 were classified as having had effective treatment, while 102 were deemed to have had ineffective treatment, resulting in a clinical efficacy rate of 54.87%. Among the patients, 105 exhibited bacterial clearance or had a reduced bacterial load by the end of the treatment, yielding a microbial treatment efficacy rate of 46.46%. Regrettably, 47 patients succumbed to their conditions, leading to an in-hospital mortality rate of 20.80%.

Table 2 Changes in Infection Markers Pre- and Post-Administration[a]

Item	Before treatment	Post treatment	P value
Temperature (°C)	38.15 (37.60, 38.40)	36.75 (36.50, 37.50)	<0.001
WBC ($\times 10^9$ /L)	9.45 (4.80, 13.90)	8.57 (6.00, 10.40)	0.024
NE (%)	80.50 (68.70, 89.10)	77.65 (68.10, 86.20)	0.352
CRP (mg/L)	86.60 (49.20, 148.40)	37.10 (23.10, 82.90)	<0.001
PCT (μg/L)	0.57 (0.20, 1.98)	0.40 (0.11, 1.05)	<0.001

Note: a. Analyzed using the paired-sample Wilcoxon signed-rank test.

Analysis of Factors Influencing Clinical Efficacy

Patients were categorized into either the treatment-effective or treatment-ineffective groups based on clinical efficacy, comprising 124 cases and 102 cases, respectively. There were no statistically significant differences between the two groups concerning gender, age, BMI, ICU admission, mechanical ventilation, ECMO application, CRRT administration, length of hospital stay, underlying diseases, presence of CRO strains, baseline renal function, administration of a loading dose of colistin sulphate, maintenance dose, daily dose/body weight, and use of combination medications ($P > 0.05$). In contrast, compared to the treatment-ineffective group, patients in the treatment-effective group exhibited lower APACHE II scores and PCTs, less use of vasoactive medications, higher albumin levels, longer courses of colistin sulphate, higher cumulative doses, fewer multisite infections, lower in-hospital mortality, and higher microbiologic efficacy, with statistically significant differences ($P < 0.05$, Table 3).

Variables with a P-value < 0.1 in the aforementioned univariate analysis underwent multicollinearity testing and were subsequently included in the multifactorial logistic regression model. The results revealed that patients' APACHE II scores, use of vasoactive drugs, duration of colistin sulphate use, and albumin levels were independently associated with clinical outcomes. Among these variables, a high APACHE II score (OR = 1.148; 95% CI: 1.075–1.227; $P < 0.001$) and the use of vasoactive drugs (OR = 3.110; 95% CI: 1.486–6.509; $P = 0.003$) were identified as independent risk factors for clinical treatment failure. Conversely, a prolonged course of colistin sulphate use (OR = 0.848; 95% CI: 0.781–0.920; $P < 0.001$) and an increase in patients' albumin levels (OR = 0.835; 95% CI: 0.771–0.903; $P < 0.001$) were associated with a reduced clinical treatment failure rate, as indicated in Table 4.

Table 3 Comparison of the Clinical Features Between the Two Groups of Patient[b,c,d]

Item	Effective (n=124)	Ineffective (n=102)	*P*
Male (n%)	78 (62.90%)	69 (67.65%)	0.457
Age (years)	65.00 (46.00, 69.00)	67.00 (55.00, 70.00)	0.314
BMI (kg/m^2)	24.05 (20.20, 25.34)	23.66 (21.22, 26.12)	0.759
APACHE II Scoring*	16.00 (10.25, 20.00)	21.50 (15.75, 24.00)	<0.001
ICU (n%)	96 (77.42%)	85 (83.33%)	0.268
Mechanical ventilation (n%)	78 (62.90%)	74 (72.55%)	0.124
Vasoactive agent (n%)*	44 (35.48%)	73 (71.57%)	<0.001
ECMO (n%)	4 (3.23%)	6 (5.88%)	0.353
CRRT (n%)	14 (11.29%)	15 (14.71%)	0.445
Length of stay (n%)	50.00 (27.00, 73.00)	44.00 (30.00, 61.00)	0.291
Underlying disease (n%)			
Hypertension	43 (34.68%)	36 (35.29%)	0.923
Diabetes	24 (19.35%)	23 (22.55%)	0.556
Chronic respiratory disease	32 (25.81%)	28 (27.45%)	0.781
Chronic kidney diseases	10 (8.06%)	6 (5.88%)	0.524
Angiocardiopathy	49 (39.52%)	42 (41.18%)	0.800
Cerebrovascular disease	17 (13.71%)	12 (11.76%)	0.664
Malignant solid tumor	9 (7.26%)	10 (9.80%)	0.493
Hematological malignancies	12 (9.68%)	6 (5.88%)	0.294
Autoimmune disease	8 (6.45%)	6 (5.88%)	0.860
Trauma	10 (8.06%)	6 (5.88%)	0.524
Chronic liver disease	14 (12.90%)	19 (18.63%)	0.120
Infection site (n%)			
Pulmonary infection	105 (84.68%)	90 (88.24%)	0.439
Bloodstream infection	29 (23.39%)	28 (27.45%)	0.484
Central nervous system infection	4 (3.23%)	6 (5.88%)	0.353
Skin soft-tissue infection	3 (2.42%)	4 (3.92%)	0.704

(*Continued*)

Table 3 (Continued).

Item	Effective (n=124)	Ineffective (n=102)	*P*
Abdominal infection	5 (4.03%)	7 (6.86%)	0.345
Urinary system infection	7 (5.65%)	5 (4.90%)	0.804
Multisite infection*	35 (28.23%)	59 (57.84%)	<0.001
Treatment indicators			
Temperature (°C)	38.10 (37.70, 38.40)	38.30 (37.10, 38.40)	0.499
WBC ($\times 10^9$ /L)	9.60 (7.40, 11.21)	9.70 (7.28, 13.92)	0.793
NE% (%)	82.72 (76.66, 87.42)	80.90 (74.90, 89.40)	0.646
PCT (μg/L)*	0.50 (0.16, 1.60)	0.89 (0.27, 2.17)	0.028
CRP (mg/L)	89.50 (47.90, 151.90)	81.10 (51.40, 143.00)	0.883
Baseline condition			
Scr (μmol/L)	71.50 (49.00, 120.00)	69.00 (48.00, 93.75)	0.454
CrCL (mL/min)	81.88 (43.34, 142.16)	94.35 (56.43, 139.20)	0.548
ALB (g/L)*	34.50 (30.50, 36.90)	32.00 (29.10, 33.90)	<0.001
Pathogenic bacteria (n%)			
CRAB	75 (60.48%)	58 (56.86%)	0.582
CRKP	51 (41.13%)	41 (40.20%)	0.887
CRPA	15 (12.10%)	19 (18.63%)	0.172
CREC	9 (7.26%)	12 (11.76%)	0.246
Other CREs	5 (4.03%)	8 (7.84%)	0.221
Number of pathogens ≥ 2	30 (24.19%)	30 (29.41%)	0.377
MIC (n%)			0.349
MIC=0.25mg/L	42 (33.87%)	32 (31.37%)	
MIC=0.5mg/L	53 (42.74%)	42 (41.18%)	
MIC=1mg/L	57 (45.97%)	57 (55.88%)	
MIC=2mg/L	3 (2.42%)	7 (6.87%)	
Medication of colistin sulfate			
Loading dose (n%)	64 (51.61%)	55 (53.92%)	0.729
Maintenance dose (MIU)	1.00 (1.00, 1.50)	1.00 (1.00, 1.50)	0.431
Integral dose (MIU)*	14.50 (10.75, 22.69)	8.75 (6.88, 15.13)	<0.001
Daily dose/Weight (MIU/kg)	1.74 (1.50, 2.27)	1.82 (1.54, 2.14)	0.834
Course of treatment (d)*	13.00 (9.00, 17.00)	8.00 (5.75, 12.50)	<0.001
Drug combination (n%)			0.644
Tigecycline	64 (51.61%)	57 (55.88%)	
Carbapenems	27 (21.77%)	22 (21.57%)	
Cefoperazone-Sulbactam	16 (12.90%)	7 (6.86%)	
Tigecycline+Cefoperazone-Sulbactam	9 (7.26%)	6 (5.88%)	
Tigecycline+Carbapenems	5 (4.03%)	5 (4.90%)	
Cefoperazone-Sulbactam+Sulbactam	3 (2.42%)	5 (4.90%)	
Outcome (%)			
In-hospital mortality*	19 (15.32%)	28 (27.45%)	<0.001
Patients occurred with AKI	6 (8.11%)	7 (14.29%)	0.275
Valid microbiological response*	74 (59.68%)	31 (30.39%)	0.025

Additional analysis of the ROC curves determined critical values for the APACHE II score (13.5), duration of treatment (10.5 days), and albumin level (34.2 g/L). These findings suggest that a treatment duration exceeding 10 days is necessary for the effective use of colistin sulphate. Furthermore, patients exhibited improved clinical efficacy when their albumin levels exceeded 34 g/L and their APACHE II score was below 13, as depicted in Figure 2.

Table 4 Multivariate Logistic Regression Analysis Was Performed to Assess the Factors Associated with the Favorable Clinical Efficacy of Colistin Sulphate

Item	*OR*	95% CI	*P*
APACHE II Scoring	1.148	1.075–1.227	<0.001
Vasoactive agent (n%)	3.110	1.486–6.509	0.003
Multisite infection	1.528	0.732–3.186	0. 259
Course of treatment (d)	0.848	0.781–0.920	<0.001
PCT (μg/L)	0.949	0.814–1.107	0.508
ALB (g/L)	0.835	0.771–0.903	<0.001
In-hospital mortality	0.594	0.197–1.792	0.355
Valid microbiological response	0.690	0.298–1.247	0.116

Adverse Reactions

To mitigate the influence of pre-existing renal issues and prior to CRRT treatments on AKI assessment, a subset of 113 patients was analyzed specifically for colistin sulphate-associated AKI, excluding those with these pre-existing conditions. Among this subset, 13 patients (11.50%) developed AKI. The onset of AKI varied, with two patients experiencing it 4–7 days post-administration, 4 patients between 7–14 days, and 7 patients after 14 days. Following discontinuation of colistin sulphate, creatinine levels decreased in 7 patients; however, regrettably, 3 patients eventually succumbed. AKI incidence was 8.11% in the treatment-effective group and 14.29% in the treatment-ineffective group. Notably, there was no statistically significant difference in colistin sulphate-associated AKI incidence between the two groups ($P > 0.05$). Moreover, no other adverse reactions, such as neurotoxicity or skin pigmentation, were observed in any of the patients.

Discussion

The rise in CRO infections resulting from carbapenem overuse presents a significant global health challenge, exacerbated by the limited availability of effective antimicrobial agents. Colistin sulphate exhibits robust antibacterial efficacy against carbapenem-resistant strains such as *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacteriaceae*.[11] Given its considerable potential in CRO therapy, the need to enhance its clinical utilization is pressing, particularly considering the current scarcity of comprehensive clinical studies on colistin sulphate.[12]

In this investigation with 226 cases, the therapeutic efficacy of colistin sulphate in managing CRO infections was evaluated. Following treatment with colistin sulphate, notable improvements were observed in patients' clinical symptoms, evidenced by significant reductions in body temperature, white blood cell count, C-reactive protein, and procalcitonin levels. The microbial treatment effectiveness rate stood at 46.46% (105 out of 226 cases), while the clinical effectiveness rate was 54.87% (124 out of 226 cases). These outcomes align with findings from previous studies by Lu,

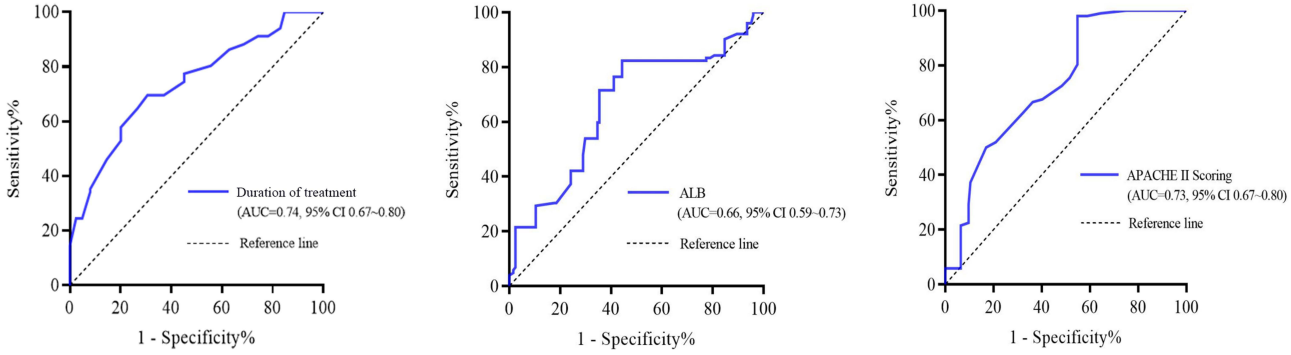

Figure 2 ROC curves were generated to evaluate the clinical efficacy based on the duration of treatment, ALB levels, and APACHE II scores.
Notes: The sensitivity was 69.4%, the specificity was 69.6%, and the Youden's index was 0.39.

Jin, and Yu.[2–4] Remarkably, the in-hospital mortality rate recorded in this study was 20.80%, which was comparatively lower than findings reported in other recent investigations.

This study delved deeper into the determinants influencing the clinical efficacy of colistin sulphate. The comparative analysis between groups confirmed that patients exhibiting poorer efficacy tended to present with elevated APACHE II scores and PCT levels. Moreover, multisite infections and the utilization of vasoactive drugs were more prevalent among these individuals. Conversely, clinically effective patients displayed higher albumin (ALB) levels, longer durations of colistin sulphate treatment, higher cumulative doses, and achieved greater bacterial clearance. Subsequent logistic regression analysis, after eliminating confounding factors, revealed that the duration of colistin sulphate use (OR = 0.848; 95% CI: 0.781–0.920; P < 0.001) and ALB levels (OR = 0.835; 95% CI: 0.771–0.903; P < 0.001) were predictive of treatment effectiveness. Conversely, elevated APACHE II scores (OR = 1.148; 95% CI: 1.075 to 1.227; P < 0.001) and the use of vasoactive drugs (OR = 3.110; 95% CI: 1.486 to 6.509; P = 0.003) were identified as independent risk factors for unfavorable clinical outcomes.

The APACHE II score is recognized as a leading indicator of illness severity.[13] A higher score is indicative of a more severe condition, often correlating with a poorer prognosis, heightened morbidity, and increased mortality rates. It holds superior predictive value for assessing the prognosis of patients with severe infections. Previous studies have highlighted the superior predictive capability of the APACHE II score compared to other scoring systems like the PSI and SOFA scores.[14] In our study, we assessed the initial condition of patients by recording the highest APACHE II score before administering colistin sulphate. The findings revealed a significantly higher APACHE II score in the clinically ineffective group compared to the effective group [16.00 (10.25, 20.00) vs 21.50 (15.75, 24.00), P < 0.001]. Elevated APACHE II scores were associated with reduced clinical efficacy. The ROC curve analysis indicated that individuals with an APACHE II score exceeding 13 exhibited lower clinical effectiveness rates. These patients typically present with severe illnesses, accompanied by significant comorbidities and compromised immune systems. They often suffer from microcirculatory disturbances, hypoalbuminemia, hepatic and renal impairment, among other conditions. Consequently, they may exhibit altered pharmacokinetic profiles, affecting the distribution and metabolism of antimicrobial agents within the body.[15] Achieving optimal clinical efficacy with colistin sulphate can be challenging in such cases, despite its high sensitivity to CRO.

Vasoactive medications are commonly employed in clinical settings to address conditions like cardiac arrest, heart failure, and shock, aiming to improve the patient's blood pressure, cardiac output, and microcirculation. Their administration often signifies the severity of the patient's condition. Our research indicates that patients receiving vasoactive drugs not only exhibit inferior treatment effectiveness but also demonstrate reduced microbial clearance.

Hypoproteinemia is a prevalent condition in critically ill individuals, often leads to fluid balance shifts and capillary leakage syndrome. This phenomenon alters the apparent volume of distribution (Vd) of hydrophilic drugs, resulting in drug dilution and reduced concentrations in both plasma and tissues.[16,17] Conversely, polymyxins are primarily bound to proteins in the body.[18] When plasma protein levels decrease, the concentration of free drug increases, potentially enhancing efficacy. However, as the kidney and liver only clear free drug, decreased albumin levels elevate free drug concentrations, increasing overall drug clearance and diminishing effective concentrations in plasma and infection sites. Furthermore, poor nutritional status in hypoalbuminemic patients can compromise immunity, hindering recovery from infection.[19] A retrospective study by Qu et al affirmed that serum albumin levels are highly predictive of poorer clinical outcomes in patients with CRO infections.[20] In our study, albumin emerged as an independent predictor of clinical outcomes, with the ROC curve indicating improved outcomes when albumin levels exceeded 34 g/L. Notably, the treatment-effective group exhibited significantly higher albumin levels compared to the treatment-ineffective group. Thus, actively maintaining albumin levels and timely supplementing human albumin when necessary may mitigate the risk of treatment failure and adverse reactions.[21]

In this investigation, the administration methods of colistin sulphate adhered to guideline recommendations. Analysis revealed no significant association between the loading dose, maintenance dose, or combination therapy and clinical efficacy. However, the duration of colistin sulphate treatment demonstrated a close correlation with treatment effectiveness, consistent with prior studies by Lu Xin, Lu Xiong, and others.[2,22] Extending the duration of colistin sulphate therapy appropriately has been linked to enhanced clinical efficacy. The ROC curve analysis indicated that an effective

treatment course with colistin sulphate should exceed 10 days, underscoring the importance of completing the full treatment regimen for optimal therapeutic outcomes. Nonetheless, prolonged treatment and higher cumulative doses may heighten the risk of adverse reactions, although in this study, there was no notable disparity in the incidence of AKI between the treatment-effective and treatment-ineffective groups. It is essential to consider that prolonged hospital stays resulting from extended treatment durations can impose financial burdens on critically ill patients. Moreover, it is worth noting that the limited therapeutic efficacy observed in some patients with shorter treatment courses does not preclude the possibility that individuals with severe conditions may succumb to underlying disease progression early in the medication course.

Some studies have indicated that insufficient dosage of polymyxins may lead to treatment failure in critically ill patients.[23,24] However, this study found no correlation between the daily dose of administered colistin sulphate and its efficacy. Similarly, no association was found between the administered dose of colistin sulphate and efficacy when patients were segregated by body weight. According to the Chinese expert consensus on the clinical application of polymyxins, and in line with current viewpoints, it is imperative to further explore the optimal dosage of colistin sulphate.[25] Such adjustments should be based on the pharmacokinetic/pharmacodynamic profile of colistin sulphate.

Optimizing the dosage regimen has the potential to enhance therapeutic efficacy while mitigating adverse effects.[4] Therapeutic drug monitoring (TDM) can serve as a valuable tool in guiding the dose adjustment of clinical colistin sulphate, representing an important avenue for future research. It is worth noting that polymyxin analogs are generally not recommended for monotherapy due to the risk of heterogeneous resistance. For CRO infections, the recommended approach involves utilizing polymyxins in combination with one or more drugs that exhibit sensitivity to pathogenic bacteria. Commonly employed combinations include tigecycline, carbapenems, and β-lactams and β-lactamase inhibitors.[26] In this study, no significant impact of different combination regimens on clinical efficacy was observed, consistent with the findings of Qu et al.[20] However, it is still advisable to consider combining colistin sulphate with other agents to reduce the risk of heterogeneous resistance and enhance clinical efficacy.

Adverse reactions associated with polymyxins encompass nephrotoxicity, neurotoxicity, skin pigmentation, among others, with nephrotoxicity being the most frequently encountered adverse event in clinical polymyxin therapy.[27] However, in this study, no instances of neurotoxicity or skin pigmentation were observed, and the nephrotoxicity incidence was 11.50%. Numerous studies on polymyxin B and colistimethate sodium have reported nephrotoxicity rates ranging from 20% to 50% at recommended therapeutic doses for both drugs.[28] Notably, the incidence of AKI associated with colistin sulphate was considerably lower compared to these two polymyxins.

This study excluded the effects of CRRT and baseline renal insufficiency, which are often confounding factors in other studies. Baseline renal insufficiency may stem from various causes. AKI occurred in 6 (8.11%) patients with treatment success and 7 (14.29%) patients with treatment failure. Although no significant difference in AKI incidence was noted between the two groups, it was observed that the majority of nephrotoxicity cases occurred after 14 days of treatment. This suggests that while extending the treatment duration may potentially enhance efficacy, it could also elevate the risk of nephrotoxicity. Furthermore, most patients who developed AKI experienced improved renal function after discontinuation of colistin sulphate compared to their pre-treatment status.

This study has several limitations that warrant consideration. Firstly, it is a single-center, retrospective study, which introduces the possibility of selection bias and limits the generalizability of the findings due to the influence of center-specific clinical practices. Secondly, the study's sample size was limited, lacked control groups, and did not conduct subgroup analyses or investigate the efficacy of colistin sulphate administered via non-intravenous routes. Additionally, the correlation between the timing of dosing and efficacy was not explored, nor was the incidence of adverse drug reactions examined in relation to drug dosage, duration of dosing, and other factors. Thirdly, the determination of therapeutic outcomes and nephrotoxicity related to colistin sulphate may lack objectivity. The study did not monitor plasma and tissue concentrations to confirm whether appropriate therapeutic drug levels were achieved.

Conclusion

This study delved into the clinical effectiveness and safety of colistin sulphate in treating patients with CRO infections. It identified that the duration of colistin sulphate treatment, patients' albumin levels, APACHE II scores, and the use of vasoactive drugs were key independent factors influencing its clinical efficacy. Notably, the incidence of nephrotoxicity was relatively low. These insights offer valuable guidance for the judicious application of colistin sulphate in clinical settings. Moving forward, there is a need for larger-scale, multicenter, prospective studies to comprehensively explore the factors impacting both efficacy and adverse reactions of colistin sulphate. Furthermore, investigating the pharmacokinetic properties of colistin sulphate through therapeutic drug monitoring (TDM) could facilitate personalized dosing strategies. Leveraging emerging technologies such as machine learning may further enhance our understanding and optimize the utilization of colistin sulphate.[29]

Abbreviations

CRO, carbapenem resistant organism); CLSI, clinical and laboratory standards institute); EUCAST, European committee on antimicrobial susceptibility testing); USCAST, United States committee on antimicrobial susceptibility testing); AKI, acute kidney injury); SCr, serum creatinine); KDIGO, kidney disease: improving global outcomes); CKD, chronic kidney diseases); CrCL, creatinine clearance); CRRT, chronic renal replacement therapy); OR, odds ratio); MIC, minimal inhibitory concentration); BMI, body mass index); ECMO, extracorporeal membrane oxygenation); CRAB, carbapenem-resistant Acinetobacter baumannii); CRPA, carbapenem-resistant pseudomonas aeruginosa); CRE, carbapenem-resistant enterobacterales); CRKP, carbapenem-resistant Klebsiella pneumoniae); CREC, carbapenem-resistant Escherichia coli); ALB, albumin); PCT, procalcitonin); CPR, cardiopulmonary resuscitation); WBC, white blood cell); NE, neutrophilic granulocyte percentage); ICU, intensive care unit); TDM, therapeutic drug monitoring); APACHE II, acute physiology and chronic health evaluation II).

Data Sharing Statement

The relevant supporting data are available from the author upon request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Ethics Committee of the Second Hospital of Hebei Medical University (No.2020-R551). Written informed consent was obtained from all participants.

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Disclosure

The authors declare no conflict of interest.

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