BMC Infectious Diseases

RESEARCH

Open Access

Efficacy and safety of polymyxin B sulfate versus colistin sulfate in ICU patients with nosocomial pneumonia caused by *carbapenem-resistant Acinetobacter baumannii*: a multicenter, propensity score-matched, real-world cohort study

Wei Bu[1,2], Chengyu Wang[1], Yuan Wu[3], Peng Zhang[4], Nengfang Zhang[5], Ying Han[6], Xiaona Xu[1], Sha Li[1] and Yan Cai[1*]

Abstract

Background Despite the widespread use of colistin sulfate (CS) in clinical settings in China over recent years, supported by several studies demonstrating its clinical efficacy, there remains a lack of comparative data on the efficacy and safety of polymyxin B sulfate (PMB) versus CS, specifically for *carbapenem-resistant Acinetobacter baumannii* (CRAB)-caused nosocomial pneumonia.

Objective To compare the efficacy and safety of PMB and CS in intensive care unit (ICU) patients with nosocomial pneumonia caused by CRAB.

Methods We conducted a multicenter retrospective cohort study, including patients diagnosed with CRAB-caused nosocomial pneumonia and treated with intravenous PMB or CS in the ICU of the study hospitals between January 1, 2020, and June 30, 2024. Propensity score matching (PSM) was employed to adjust for potential baseline confounders between cohorts. Multivariate logistic regression analysis and Cox logistic regression analyses were performed to identify for factors potentially influencing the clinical outcomes and adverse events.

Results Following matching, a total of 190 patients were analyzed. There was no statistical significance in the rates of clinical success, microbiological eradication and 28-day mortality between the PMB and CS cohorts. While the incidence of acute kidney injury (AKI) and hepatotoxicity were comparable in both cohorts, but dermal toxicity was significantly higher in patients receiving PMB compared to those receiving CS (18.9% vs. 0%, $P < 0.05$). Among all the patients, hypertension, baseline renal insufficiency, usage of vasoactive drugs and in combination with three or more antibiotics were independent risk factors associated with AKI; while age, duration of polymyxins ≤ 7 days and Sequential Organ Failure Assessment (SOFA) score were risk factors associated with 28-day all-cause mortality.

*Correspondence:
Yan Cai
caiyan029@163.com

Full list of author information is available at the end of the article

Conclusion This study establishes that PMB and CS have similar efficacy in treating CRAB induced nosocomial pneumonia in the ICU settings. The incidence of AKI and hepatotoxicity of both polymyxins are comparable for both polymyxins, although PMB is associated with a significantly higher incidence of skin toxicity. Ensuring adequate therapy duration is key to better outcomes in the treatment of CRAB-induced nosocomial pneumonia in ICU patients, regardless of the type of polymyxins.

Keywords Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Nosocomial pneumonia, Polymyxin, Propensity score matching

Introduction

Antimicrobial resistance has become a global public health threat. In particular, the management of infections caused by carbapenem-resistant Gram-negative bacilli (CR-GNBs) poses a significant challenge for healthcare professionals due to the limited availability of drugs that remain effective against CR-GNBs. Among these CR-GNBs, CRAB has been identified as one of the critical threats by the WHO (World Health Organization) [1].

CRAB is one of the most predominant causative agents of nosocomial infections, especially in the ICU patients [2]. Limited antimicrobials are effective against CRAB. Data from the China Antimicrobial Surveillance Network (CHINET) in 2023 indicated that only tigecycline and polymyxins exhibited low resistance rates to CRAB (2.3% and 1.1%, respectively) [3]. The Infectious Diseases Society of America (IDSA) guidelines recommend the combination use of susceptible antibacterial agents, including polymyxins or tetracycline derivatives, for the treatment of CRAB caused infections [4].

Polymyxins, derived from *Paenibacillus polymyxa*, are a class of bactericidal antibiotics with diverse chemical structures [5]. In recent years, the increasing prevalence of CR-GNBs, has necessitated a reconsideration of polymyxins. Currently, three distinct polymyxins are available in China: PMB, CS and colistimethate sodium (CMS) [6]. CMS acts as a pro-drug metabolized to colistin in the kidney, while PMB and CS serve as active forms and are primarily excreted through non-renal pathways. PMB predominantly consists of polymyxin B1 and B2, whereas CS, the active component of CMS, consists mainly of polymyxin E1 and E2.

IDSA guidelines suggest the use of PMB in polymyxin-based treatment regimens for CRAB infections, owing to its superior PK profile compared to CMS. Despite the widespread use of CS in clinical settings in China over recent years, supported by several studies demonstrating its clinical efficacy [6–10], there remains a lack of comparative data on the efficacy and safety of PMB versus CS, specifically for CRAB-caused nosocomial pneumonia. This multicenter, retrospective cohort study, employing PSM, aims to compare the clinical effectiveness and safety of PMB and CS in treating nosocomial pneumonia caused by CRAB and to identify risk factors associated with clinical failure and adverse events.

Materials and methods

Study design

This multicenter retrospective study included ICU patients receiving PMB or CS due to CRAB-caused nosocomial pneumonia admitted to 5 hospitals in 2 different provinces in China (Shanxi and Guizhou). We obtained healthcare data retrospectively from five hospitals, namely the Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, Shaanxi), Affiliated Hospital of Zunyi Medical University (Zunyi, Guizhou), Xi'an TCM Hospital of Encephalopathy Affiliated to Shaanxi University of Chinese Medicine (Xi'an, Shaanxi), International Medical Xi'an Gaoxin Hospital (Xi'an, Shaanxi) and Chang'an Hospital (Xi'an, Shaanxi). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (No. 2024 – 185) and by the ethics committees at each participating site. Patients were screened if they received regular PMB (Shanghai No.1 Biochemical & Pharmaceutical Co., Ltd, China) or CS (Shanghai SPH New Asia Pharmaceutical Co. Ltd., Shanghai, China) treatment as recommended in current guidelines. Informed consent was waived by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University due to the retrospective nature of the study.

Population and data collection

Patients diagnosed with nosocomial pneumonia caused by CRAB and treated with intravenous PMB or CS in the ICU of the study hospitals between January 1,2020, and June 30, 2024 were included. Patients were excluded if they: (i) were age < 18 years; (ii) had continuous intravenous use of PMB or CS < 3 days; (iii) received intravenous PMB and CS sequentially within the same hospitalization; (iv) used a different type of polymyxin for aerosol than for intravenous use; (v) died within 48 h of ICU admission; (vi) key data were missing. If a patient experienced multiple hospitalizations, only the initial one was considered.

Patient information was extracted from electrical records, which included (i) demographic details: gender, age, admission and discharge dates, admission and discharge diagnoses, severity of disease, and comorbidities; (ii) infection status: infection site, pathogenic bacteria, and susceptibility results, in particular the minimum

inhibitory concentration (MIC) of polymyxins; (iii) therapeutic regimens: dosage, frequency, route, and duration of polymyxins and other antimicrobials; (iv) clinical outcome, mainly clinical and microbiological responses and adverse events of polymyxins. All the data collected were anonymized.

CRAB was identified using the VITEK-II-COMPACT (BioMérieux, France) and MALDI-TOF MS system (BioMerieux, France), and susceptibility to various antimicrobials was assessed through Broth microdilution, with results interpreted in accordance with the Clinical and Laboratory Standards Institute 2023 criteria (CLSI 2023) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) criteria, which classified a MIC of less than 2 mg/L as susceptible to polymyxins. Pulmonary CRAB infection was assessed rigorously, defined by the presence of new pulmonary imaging changes, increased sputum production, or other infection-related abnormalities in patients with confirmed detection of pulmonary CRAB [11]. Disease severity was quantified using Acute Physiology and Chronic Health Evaluation II (APACHE II) score and SOFA score, while comorbidities were evaluated using the age-adjusted Charlson Co-morbidity Index (age-adjusted CCI).

The outcomes included both clinical and microbiological responses to therapy. Clinical responses were categorized as follows: (i) success: defined as either the resolution or partial resolution of infection symptoms at the end of therapy, (ii) failure, which was characterized by the persistence of symptoms and signs for >3 days, necessitating additional antibiotic treatment. Clinical success was determined through a collaborative assessment involving clinicians and pharmacists to ensure a holistic assessment of the patient's response to treatment. Furthermore, 14-day (attributable) and 28-day (all-cause) mortality were analyzed. Attributable or CRAB-related mortality was defined as death during the treatment period that could be directly associated with septic shock due to CRAB infection. Microbiological responses included eradication and suppression, with eradication defined by no growth of CRAB isolates in subsequent tests and suppression as a 2-log reduction or greater in colony counts [12].

Adverse events were monitored throughout the hospitalization period and were assessed by the specialist physicians and clinical pharmacists using the Naranjo adverse drug reaction probability scale [13]. AKI diagnosis and staging were assessed according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, while drug-induced liver injury (DILI) was evaluated per the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines [14–15]. Dermal toxicity involves drug-induced skin reactions, such as skin rashes and skin pigmentation.

Statistical analysis

All statistical analyses were performed using SPSS (version 22.0, Chicago, IL, USA). The distribution of continuous variables was assessed by the Shapiro test. Data were presented as mean ± standard deviation (SD) for normally distributed variables or as median (interquartile range, IQR) if skewed distribution. Categorical data was expressed as frequencies and percentages. Comparisons between the PMB and CS cohorts were performed using the unpaired Student's t-test or non-parametric Mann-Whitney test for continuous and chi-square (or Fisher's exact) tests for categorical variables.

To mitigate baseline covariate bias between the PMB and CS cohorts, we employed PSM analysis [16]. The propensity score was determined using a logistic regression model that included covariates of great clinical importance or those showing differences relevant to PSM, including SOFA scores, APACHE II scores, septic shock, renal insufficiency and age-adjusted CCI. In this analysis, PSM models were estimated using 1-to-1 nearest-neighbor matching techniques without replacement, with a caliper level set at 0.2. In addition, multivariate logistic regression analysis and Cox logistic regression analyses were performed to identify factors that potentially influencing the clinical outcomes and adverse events. Survival analysis was performed by the Kaplan-Meier method, with pairwise comparisons assessed by the log-rank test. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 890 ICU patients were treated with either PMB or CS for CRAB-caused nosocomial pneumonia. After screening, only 232 individuals fulfilled the criteria. Of these, 132 (56.9%) received PMB, while 100 (43.1%) received CS treatment (Fig. 1). Before matching, no significant differences were noted between the two cohorts, except for differences in baseline renal function. To adjust for potential baseline confounders between cohorts, the 1-to-1 PSM was used, resulting in 95 pairs of patients with comparable characteristics (Table 1). In both cohorts, the majority of the patients were elderly males, with a median length of hospital stay of 31 days in the PMB cohort and 26 days in the CS cohort. The SOFA scores, APACHE II scores and age-adjusted CCI were similar in both cohorts. The majority of patients received mechanical ventilation (91.6% vs. 92.6%). Renal insufficiency was present in 15.8% of patients in both cohorts. Overall, the patients' baseline characteristics were well-balanced.

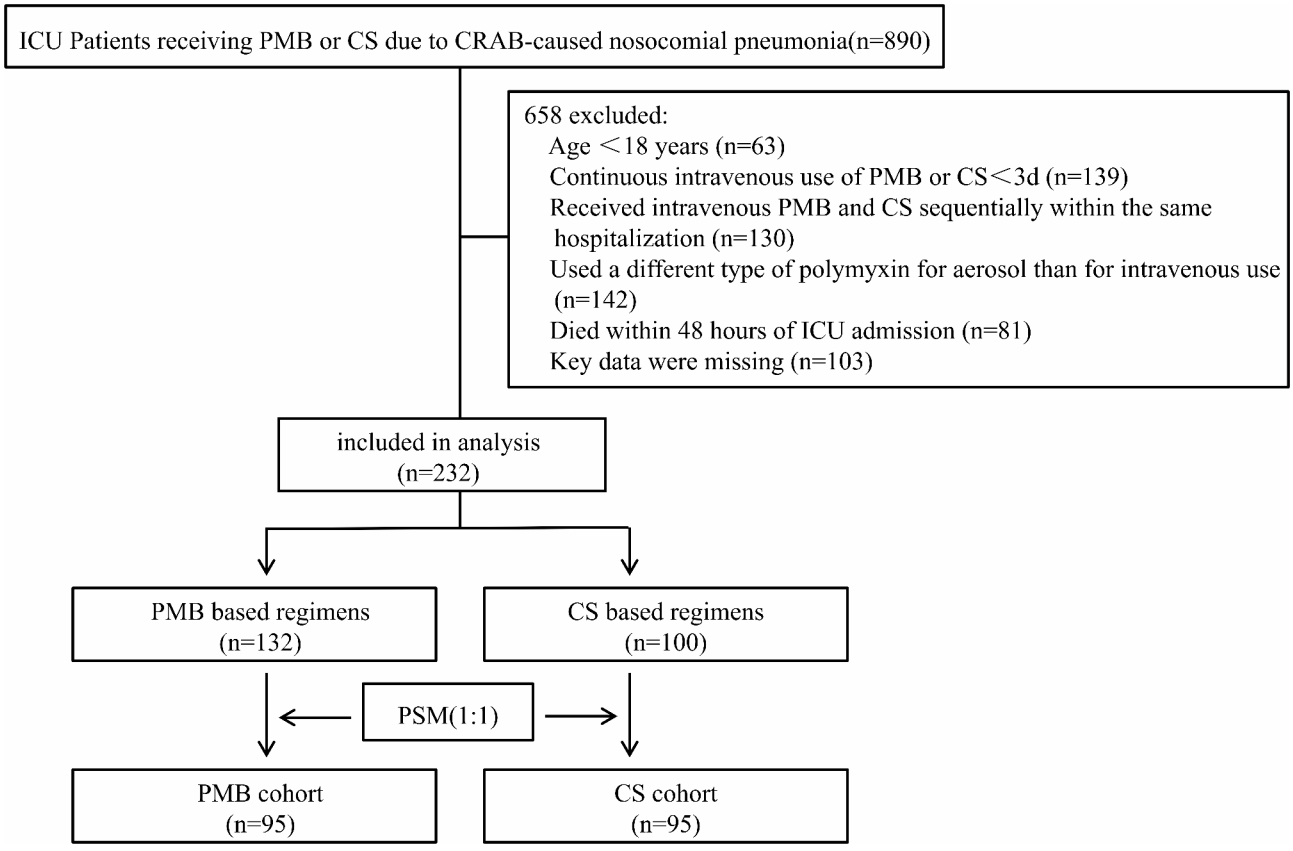

Fig. 1 Patient selection. PMB: polymyxin B sulfate; CS: colistin sulfate. PSM: propensity score matching

The infection sites, pathogens, and antibacterial agents usage

The infection sites and pathogens of all the patients are shown in Table 2. The vast majority had single CRAB lung infections while a small percentage of patients had multi-site infections including bloodstream infections or co-infection with CRAB and other CR-GNBs. Importantly, all CRAB were susceptible to polymyxins according to the EUCAST criteria, with MIC values ranging from 0.50 to 2 mg/L, and over half of the isolates had an MIC of 0.5 mg/L or less. The concomitant antibacterial drugs differed between cohorts. The combination of three antibacterial drugs (including polymyxins), especially carbapenems, was more common in the PMB cohort. Loading dose and inhaled polymyxins were infrequent across both cohorts. The antimicrobial regimens of all the patients are shown in Table S1.

Clinical outcomes and adverse events

The clinical outcomes of patients treated with PMB or CS are summarized in Table 3. After matching, the clinical responses in both cohorts were comparable, revealing a clinical success rate of 72.6% in the PMB cohort compared to 73.7% in the CS cohort. The rates of microbial eradication and inhibition were identical in both cohorts at 21.1% (20/95) and 52.6% (50/95), respectively. No statistically significant differences were observed in 14-day mortality (16.8% vs. 14.7%, $P=0.691$) and 28-day mortality (32.6% vs. 24.2%, $P=0.198$) between the two cohorts. Furthermore, the Kaplan-Meier survival analysis indicated no significant difference in mortality between the cohorts (Fig. 2). Notably, the dermal toxicity, including skin rashes and skin pigmentation, was significantly more prevalent in the PMB cohort compared to the CS cohort (18.9% vs. 0.0%, $P<0.001$). Although the incidence of AKI appeared to be higher in patients treated with PMB compared to those in CS, this difference was not statistically significant (28.4% vs. 18.9%, $P=0.125$). Conversely, the rate of hepatotoxicity in the PMB cohort was close to that in the CS cohort (6.4% vs. 4.3%, $P=0.516$) (Table 3).

Risk factors associated with clinical failure and adverse events

To identify factors associated with clinical outcomes and adverse events, we performed univariate and multivariable analysis on patients before and after matching (Table S2-S9 and Fig. 3). Patients were divided into clinical failure and success groups, and their demographic and clinical characteristics were compared to find the potential risk factors associated with clinical failure. The results

Table 1 Characteristics of ICU patients receiving PMB or CS for CRAB-caused nosocomial pneumonia

Demographics and clinical characteristics	Before PSM[a]				After PSM			
	Total (*N* = 232)	PMB (*n* = 132)	CS (*n* = 100)	*P* value	Total (*N* = 190)	PMB (*n* = 95)	CS (*n* = 95)	*P* value
Demographic characteristics								
Male	163(70.3%)	87(65.9%)	76(76.0%)	0.096	134(70.5%)	62(65.3%)	72(75.8%)	0.112
Age(years), median (IQR)	67.0(53.0–76.0)	67.0(52.0-74.8)	69.0(55.0-78.8)	0.295	67.0(52.8–76.0)	67.0(52.0–74.0)	69.0(54.0–79.0)	0.395
Hospitalization day(days), median (IQR)	27.0(19.0-46.8)	29.0(19.0-49.8)	26.0(19.0-42.8)	0.670	27.0(19.0-46.3)	31.0(20.0–52.0)	26.0(19–42.0)	0.977
Duration of polymyxins (days), median (IQR)	9.0(6.0–14.0)	9.0(6.0–13.0)	9.0(6.0–14.0)	0.308	9.0(6.0–14.0)	10.0(6.0–14.0)	9.0(6.0–14.0)	0.479
APACHE II score(scores), median (IQR)	21.0(16.25-26.0)	21.0(17.0–25.0)	22.0(16.0–26.0)	0.603	21.0(16.0–26.0)	21.0(16.0–25.0)	22.0(16.0–26.0)	0.724
SOFA score(scores), median (IQR)	9.0(7.0-10.8)	9.0(7.0–10.0)	9.0(7.0–10.0)	0.865	9.0(7.0–10.0)	9.0(7.0–10.0)	8.0(7.0–10.0)	0.978
Comorbidities								
Electrolyte disturbance	122(52.9%)	66(50.0%)	56(56.0%)	0.365	102(53.7%)	47(49.5%)	55(57.9%)	0.244
Respiratory failure	142(61.2%)	79(59.8%)	63(63.0%)	0.626	115(60.5%)	55(57.9%)	60(63.2%)	0.458
Septic shock	99(42.7%)	58(43.9%)	41(41.0%)	0.654	75(39.5%)	37(38.9%)	38(40.0%)	0.882
Hypertension	92(39.7%)	57(43.2%)	35(35.0%)	0.207	73(38.4%)	39(41.1%)	34(35.8%)	0.456
Type 2 diabetes	61(26.3%)	38(28.8%)	23(23.0%)	0.321	48(25.3%)	26(27.4%)	22(23.2%)	0.504
Cardiac insufficiency	144(62.1%)	83(62.9%)	61(61.0%)	0.770	116(61.1%)	58(61.1%)	58(61.1%)	1.000
Hepatic insufficiency	111(47.8%)	63(47.7%)	48(48.0%)	0.967	84(44.2%)	38(40.0%)	46(48.4%)	0.243
Renal insufficiency	49(21.1%)	34(25.8%)	15(15.0%)	**0.047**	30(15. 8%)	15(15.8%)	15(15.8%)	1.000
Tumor	33(14.2%)	18(13.6%)	15(15.0%)	0.768	27(14.2%)	15(15.8%)	12(12.6%)	0.533
Age-adjusted CCI(scores), median (IQR)	6.0(5.0–8.0)	6.0(5.0–8.0)	6.0(4.3-8.0)	0.721	6.0(4.0–8.00)	6.0(4.0–8.0)	6.0(4.0–8.0)	0.915
Supportive therapy								
Mechanical ventilation	215(92.7%)	122(92.4%)	93(93.0%)	0.868	175(92.1%)	87(91.6%)	88(92.6%)	0.788
Non-invasive	68(29.3%)	41(31.1%)	27(27.0%)	0.501	56(29.5%)	30(31.6%)	26(27.4%)	0.524
Invasive	147(63.4%)	82(62.1%)	65(65.0%)	0.652	119(62.6%)	58(61.1%)	61(64.2%)	0.653
Extracorporeal membrane oxygenation	10(4.3%)	6(4.5%)	4(4.0%)	1.000	8(4.2%)	4(4.2%)	4(4.2%)	1.000
Vasoactive drugs	184(79.3%)	110(83.3%)	74(74.0%)	0.082	148(77.9%)	79(83.2%)	69(72.6%)	0.080

a. PSM: propensity score matching

Table 2 The infection sites, pathogens and antibacterial agents of ICU patients receiving PMB or CS for CRAB-caused nosocomial pneumonia

Clinical characteristics	Before PSM[a]				After PSM			
	Total (*N* = 232)	PMB (*n* = 132)	CS (*n* = 100)	*P* value	Total (*N* = 190)	PMB (*n* = 95)	CS (*n* = 95)	*P* value
Infection sites								
Lung only	172(74.1%)	92(69.7%)	80(80.0%)	0.076	143(75.3%)	66(69.5%)	77(81.1%)	0.064
lung + bloodstream	41(17.7%)	27(20.5%)	14(14.0%)	0.202	31(16.3%)	19(20.0%)	12(12.6%)	0.169
Lung + other sites[b]	19(8.2%)	13(9.8%)	6(6.0%)	0.290	16(8.4%)	10(10.5%)	6(6.3%)	0.296
Pathogens								
CRAB only	183(78.9%)	108(81.8%)	75(75.0%)	0.444	144(75.8%)	70(73.7%)	74(77.9%)	0.752
CRAB + CRKP[c]	22(9.5%)	10(7.6%)	12(12.0%)		21(11.1%)	10(10.5%)	10(11.6%)	
CRAB + CRPA[d]	34(14.7%)	21(15.9%)	13(13.0%)		27(14.2%)	15(15.8%)	11(12.6%)	
Polymyxins MIC distribution(μg/ml)								
≤ 0.5	145(62.5%)	87(65.9%)	58(58.0%)	0.470	117(61.6%)	63(66.3%)	54(56.8%)	0.369
= 1	55(23.7%)	28(21.2%)	27(27.0%)		45(23.7%)	19(20.0%)	26(27.4%)	
= 2	32(13.8%)	17(12.9%)	15(15.0%)		28(14.7%)	13(13.7%)	15(15.8%)	
Polymyxin regimens								
loading dose	29(12.5%)	21(15.9%)	8(8.0%)	0.008	22(11.6%)	15(15.8%)	7(7.4%)	0.070
Intravenous plus inhalation	53(22.8%)	25(18.9%)	28(28.0%)	0.625	48(25.3%)	20(21.1%)	28(29.5%)	0.182
Polymyxin ≥ 7d	168(72.4%)	97(73.5%)	71(71.0%)	0.675	136(71.6%)	69(72.6%)	67(70.5%)	0.748
No. of antibacterial drugs in combination								
1	14(6.0%)	1(0.8%)	13(13.0%)	0.000	13(6.8%)	1(1.1%)	12(12.6%)	0.001
2	154(66.4%)	86(65.2%)	68(68.0%)		128(67.4%)	63(66.3%)	65(68.4%)	
3	64(27.6%)	45(34.1%)	19(19.0%)		49(25.8%)	31(32.6%)	18(18.9%)	
Concomitant antibacterial drugs								
Carbapenems[e]	121(52.2%)	82(62.1%)	39(39.0%)	0.000	94(49.5%)	57(60.0%)	37(38.9%)	0.004
Tetracyclines[f]	76(32.8%)	45(34.1%)	31(31.0%)	0.619	64(33.7%)	35(36.8%)	29(30.5%)	0.357
Cefoperazone-sulbactam	47(20.3%)	29(23.0%)	18(18.0%)	0.456	38(20.0%)	20(21.1%)	18(18.9%)	0.717
Quinolones[g]	16(6.9%)	11(8.3%)	5(5.0%)	0.321	13(6.8%)	8(8.4%)	5(5.3%)	0.389
Aminoglycosides[h]	13(5.6%)	6(4.6%)	7(7.0%)	0.421	11(5.8%)	4(4.2%)	7(7.4%)	0.351

(a) PSM: propensity score matching; (b) not including bloodstream; (c) CRKP: Carbapenem-resistant *Klebsiella pneumonia*; (d) CRPA: carbapenem-resistant *Pseudomonas aeruginosa*, (e) Carbapenems including meropenem and imipenem-cilastatin; (f) Tetracyclines including minocycline and tigecycline; (g) Quinolones including levofloxacin and ciprofloxacin; (h) Aminoglycosides including amikacin and tobramycin

showed that age[OR = 1.025 (1.001–1.049), *P* = 0.044], the treatment duration of polymyxins ≤ 7d [OR = 2.431 (1.150–5.136), *P* = 0.020], SOFA score[OR = 1.211 (1.042–1.407), *P* = 0.013] were independent risk factors for clinical failure (Table S3 and Fig. 3). Likewise, risk factors associated with microbiological failure or AKI were identified. The results showed that the treatment duration of polymyxins ≤ 7d[OR = 2.178 (1.023–4.635), *P* = 0.043] and SOFA score[OR = 1.210 (1.040–1.409), *P* = 0.014] were independent risk factors for microbiological failure; whereas hypertension[OR = 2.768 (1.254–6.109), *P* = 0.012], renal insufficiency[OR = 6.839 (2.728–17.148), *P* < 0.001], the use of vasoactive drugs[OR = 6.621 (1.388–31.590), *P* = 0.018], and in combination with three or more antibiotics [OR = 2.440 (1.052–5.660), *P* = 0.038], were independent risk factors for AKI (Table S5, S7 and Fig. 3).

Cox regression analysis was used to identify risk factors associated with 28-day all-cause mortality. The results showed that age[HR = 1.020 (1.001–1.039), *P* = 0.037], polymyxins administered for ≤ 7 days[HR = 2.530 (1.437–4.456), *P* = 0.001] and SOFA score[HR = 1.193 (1.066–1.334), *P* = 0.002], were risk factors for 28-day all-cause mortality (Table S9 and Fig. 3).

Discussion

CRAB infections pose significant challenges in healthcare settings, especially in ICU patients [2]. Nosocomial pneumonia is one of the most common type of healthcare-associated infection, and CRAB plays an important role in hospital-acquired pneumonia or ventilator-associated pneumonia [2, 17, 18]. Although novel antibiotics emerged in recent years, notably new β-lactam-β-lactamase inhibitors like ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam and imipenem- cilastatin-relabactam, all these agents are ineffective against CRAB [4]. Other novel alternatives, including cefiderocol, sulbactam-durlobactam and tetracycline derivatives (tigecycline and eravacycline) provide additional options for managing CRAB infections. The IDSA guidelines recommend a combination of sulbactam-durlobactam and carbapenems as the first-line

Table 3 The clinical outcomes and adverse events of patients receiving PMB or CS for CRAB nosocomial pneumonia

Characteristics	Before PSM [a]				After PSM			
	Total (*N* = 232)	PMB (*n* = 132)	CS (*n* = 100)	*P* value	Total (*N* = 190)	PMB (*n* = 95)	CS (*n* = 95)	*P* value
Clinical responses								
Success	162(69.8%)	89(67.4%)	73(73.0%)	0.360	139(73.2%)	69(72.6%)	70(73.7%)	0.871
Failure	70(30.2%)	43(32.6%)	27(27.0%)		51(26.8%)	26 (27.4%)	25(26.3%)	
Microbiological responses								
Eradication	45(19.4%)	24(18.2%)	21(21.0%)	0.771	40(21.1%)	20 (21.1%)	20 (21.1%)	1.000
Suppression	119(51.3%)	67(50.8%)	52(52.0%)		100(52.6%)	50(52.6%)	50 (52.6%)	
Failure	68(29.3%)	41(31.0%)	27(27.0%)		50(26.3%)	25(26.3%)	25 (26.3%)	
Mortality								
14-days	40(17.2%)	25(18.9%)	15(15.0%)	0.431	30(15.8%)	16 (16.8%)	14 (14.7%)	0.691
28-days	71(30.6%)	47(35.6%)	24(24.0%)	0.057	54(28.4%)	31 (32.6%)	23(24.2%)	0.198
Adverse events								
Overall AKI[b]	54(23.3%)	35(26.5%)	19(19.0%)	0.180	45(23.7%)	27(28.4%)	18(18.9%)	0.125
KDIGO 1	25(10.8%)	16(12.1%)	9(9.0%)	0.953	21(11.1%)	13(13.7%)	8(8.4%)	0.635
KDIGO 2	15(6.8%)	10(7.6%)	5(5.0%)		14(7.4%)	9(9.5%)	5(5.3%)	
KDIGO 3	14(6.0%)	9(6.8%)	5(5.0%)		10(5.3%)	5(5.3%)	5(5.3%)	
Hepatotoxicity[c]	12(5.2%)	8(6.0%)	4(4.0%)	0.483	10(5.3%)	6 (6.4%)	4(4.3%)	0.516
Mild	7(3.0%)	4(3.0%)	3(3.0%)	0.428	6(3.2%)	3(3.2%)	3(3.2%)	0.453
Moderate	5(2.2%)	4(3.0%)	1(1.0%)		4(2.1%)	3 (3.2%)	1 (1.1%)	
Dermal toxicity[d]	21(9.1%)	21(15.9%)	0(0.0%)	**< 0.001**	18(9.5%)	18 (18.9%)	0 (0.0%)	**< 0.001**

a. PSM, propensity score matching

b. According to the KDIGO criteria, staging of acute kidney injury(AKI) as follows: (i) stage 1, serum creatinine 1.5 to 1.9 times baseline or ≥ 0.3 mg/dl (≥ 26.5μmol/l) increase; (ii) stage 2, serum creatinine 2.0 to 2.9 times baseline; (iii) stage 3, serum creatinine serum creatinine 3.0 times baseline or ≥ 4.0 mg/dl (≥ 353.6 μmol/l) increase or initiation of renal replacement therapy

c. DILI severity classifications: i) mild: alanine transaminase (ALT) ≥ 5 or alkaline phosphatase (ALP) ≥ 2 and Total bilirubin (TBL) < 2 upper limit of normal (ULN); ii) Moderate: ALT ≥ 5 or ALP ≥ 2 and TBL ≥ 2 ULN, or symptomatic hepatitis; iii) Severe: ALT ≥ 5 or ALP ≥ 2 and TBL ≥ 2 ULN, or symptomatic hepatitis and 1 of the following criteria: international normalized ratio (INR) ≥ 1.5; ascites and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis; Other organ failure due to DILI; iiii) Fetal/transplantation: death or liver transplantation due to DILI

d. 5 case of skin rashes and 13 with skin pigmentation in the PMB cohort

Definition of skin hyperpigmentation: A disorder characterized by darkening of the skin due to excessive melanin deposition.

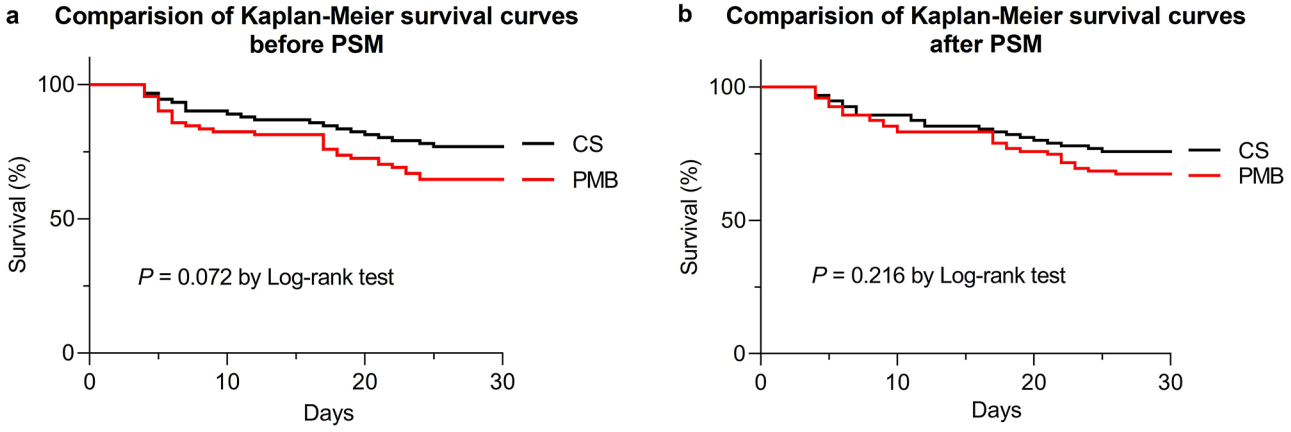

Fig. 2 Survival curves of patients receiving PMB or CS for CRAB-caused nosocomial pneumonia. PMB: polymyxin B sulfate; CS: colistin sulfate. PSM: propensity score matching

treatment. Alternatively, high dose of ampicillin-sulbactam plus polymyxins or minocycline/tigecycline or cefiderocol [4, 19]. However, in China, CRAB exhibited significant resistance to ampicillin-sulbactam (90.6%) [3]; in addition, newer agents such as cefiderocol and sulbactam-durlobactam are either not commonly available or are restricted by the health insurance policies, leaving antimicrobials against CRAB remain extremely limited in China. Consequently, polymyxins, including CMS, PMB and CS, have become important options for treating CRAB infections due to their remarkable susceptibility to this pathogen.

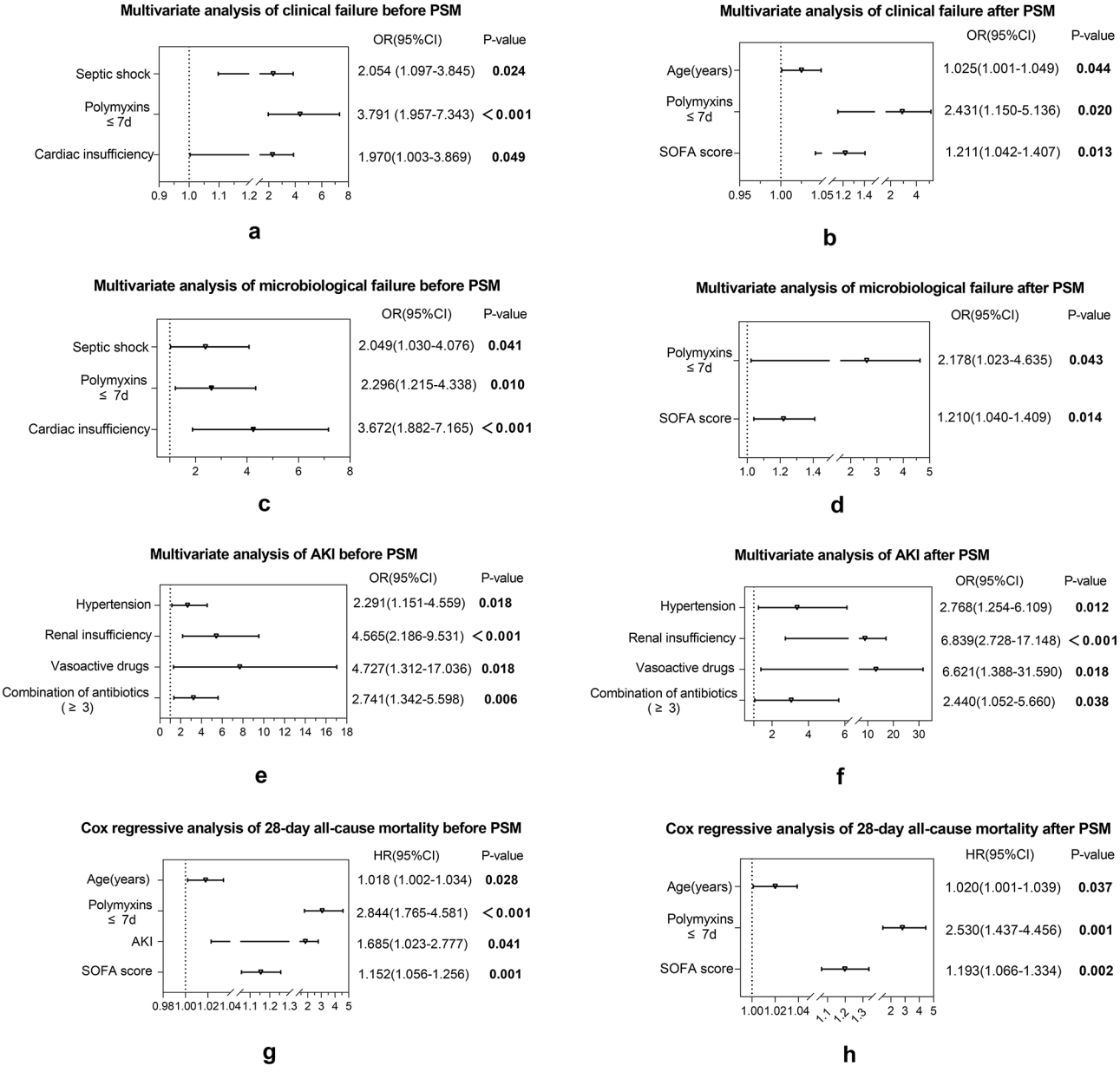

Fig. 3 Forest plots of risk factors associated with clinical outcomes and adverse events. (**a**, **b**): Multivariate analysis of factors associated with clinical failure in ICU patients with CRAB-caused nosocomial pneumonia before (**a**) and after (**b**) PSM; (**c**, **d**): Multivariate analysis of factors associated with microbiological failure in ICU patients with CRAB-caused nosocomial pneumonia before (**c**) and after (**d**) PSM; (**e**, **f**): Multivariate analysis of factors associated with AKI in ICU patients with CRAB-caused nosocomial pneumonia before (**e**) and after (**f**) PSM; (**g**, **h**): COX multivariate analysis of factors associated with 28-day all-cause mortality in ICU patients with CRAB-caused nosocomial pneumonia before (**g**) and after (**h**) PSM. PSM: propensity score matching; AKI, acute kidney injury

To our knowledge, four studies have compared the efficacy or safety of PMB and CS[6–7, 21–22]. Two of them evaluated the effectiveness of PMB and CS in treating CR-GNBs-caused infections while two others compared the adverse events of the two polymyxins [6–7, 20–21]. Nevertheless, there are currently no data comparing different polymyxins in treating CRAB-induced nosocomial pneumonia; furthermore, multicenter study about comparation of PMB and CS has not been found. Therefore, we conducted this multicenter PSM-based study to evaluate the clinical effectiveness and safety of PMB and CS in the treatment of CRAB-caused nosocomial pneumonia in ICU patients.

In this study, after employing PSM to adjust for potential baseline confounders between groups, we found that there was no significant difference in the rate of clinical success, microbial eradication and mortality between the PMB and CS cohorts when treating CRAB caused

nosocomial pneumonia in ICU patients. Survival analysis also showed that there was no significant difference in the mortality between patients treated with these two regimens. These results of clinical outcome were in accordance with the previous findings in CR-GNBs caused infections. Wang et al. found that although the microbial efficacy was higher in the CS cohort (57.1%) than in the PMB cohort (30.8%), no significant difference was seen in clinical success, as well as mortality [6]. Liu et al. also reported similar clinical response rates, bacterial clearances and 28-day mortality between the CS and PMB groups [7]. We further explored the risk factors associated with clinical failure, microbiological failure and mortality. The results showed that age, duration of anti-infection therapy (polymyxins ≤ 7 days) and SOFA scores were independent risk factors for both clinical failure and 28-day all-cause mortality, with a duration of polymyxins ≤ 7 days also being a potential risk factor for microbiological failure. Consistent with our findings, two other studies also found that longer antimicrobial therapy leads to better outcomes [22–23]. Another study prompted that cancer patients who received a long course (≥ 14 days) of colistin therapy presented greater clinical and microbiological responses and lower 30-day mortality, compared to those receiving a short course (< 14 days) [24–25]. Therefore, a longer course of polymyxin therapy should be considered for management of CRAB-caused infections. However, prolonged antibiotic exposure may increase the likelihood of bacterial resistance [22–23]. Therefore, the duration of antimicrobial treatment needs to be carefully determined according to the patient's condition, immunity and bacterial clearance. Furthermore, in our study, only a few patients received aerosolized polymyxins, with 20 patients in the PMB cohort and 26 patients in CS cohort. Multivariate logistic regression analysis and Cox logistic regression analyses showed that inhaled polymyxins were not associated with the clinical responses, microbial results and mortality. Inhaled polymyxins could improve the antibiotics exposure in the lung theoretically, however, it still lacks high-level clinical evidence. The Infectious Diseases Society of America (IDSA) 2024 Guidance did not suggest the use of nebulized antibiotics for the treatment of respiratory infections caused by CRAB [4].

The adverse events of polymyxins, particularly AKI, are of the greatest concern. The incidence of polymyxin-associated AKI has been reported in the literature to range from 10–60% [22]. We found no significant difference of AKI and hepatotoxicity between the two polymyxin cohorts. However, the results of adverse events of polymyxins seemed controversial, especially the AKI. Two real-world, PSM-based studies revealed that the incidence of AKI was significantly higher in the PMB cohort compared with the CS cohort (21.1% vs. 7.0%, $P = 0.004$; 50.6% vs. 18.3%; $P < 0.001$) [20–21]; while findings from two other separate teams indicated comparable AKI between PMB and CS cohorts (14.6% vs. 15.0%, $P > 0.05$; 20.5% vs. 5.9%; $P > 0.05$) [6, 7]. In our study, despite the well-balanced baseline renal function post-PSM, the incidence of AKI appeared to be higher in the PMB cohort than the CS cohort but no significant difference was found (28.4% vs. 18.9%, $P = 0.125$). Different population of patients and sample size may contribute to this discrepancy. Furthermore, our study showed that hypertension, baseline renal insufficiency, the use of vasoactive drugs, and in combination with three or more antibiotics were independent risk factors for AKI. These results were in keeping with previous findings, which indicated that pre-existing renal dysfunction before polymyxin treatment (Papadimitriou-Olivgeris) and usage of vasoactive drugs (Yang QJ) were probably risk factors for AKI [20, 26–28]. Given that many antibiotics can cause AKI, the combined use of multiple antibiotics increases the risk of polymyxin-induced AKI, suggesting that combination of antibiotics should be used with caution and that renal function of patients should be carefully monitored [29]. The skin toxicity, including rashes or skin pigmentation seemed much higher in the PMB cohort than the CS cohort. Two retrospective case-control studies also reported polymyxin B induced skin pigmentation, with the incidence of 15% and 8%, respectively [30–31]. Skin pigmentation seems only occurred in patients receiving PMB which has a side chain of phenylalanine. Phenylalanine can be hydroxylated in vivo to produce tyrosine, which is the main raw material for the synthesis of melanin [32–33]. The possible mechanism is that polymyxin B can cause the release of histamine, which can stimulate the activity of melanocytes and increase the synthesis and secretion of melanin. In addition, histamine may further promote the proliferation of melanocytes and the production of melanin through synergistic action with other inflammatory factors, leading to the formation of post-inflammatory pigmentation [31].

Our study has several limitations. First, the definition of clinical success has an element of subjectivity that may introduce information bias, which is prong to produce information bias; therefore, objective measures, such as 28-day mortality, offer a more convincing assessment. Second, our study was a retrospective observational cohort study, and there might have been imbalances in baseline variables between cohorts. Although we used PSM to adjust for potential baseline confounders, unknown biases might inevitably exist. Third, although multicenter data were collected, the overall sample size was small which limits the generalizability of our findings. Hence, large randomized prospective clinical trials are required to better assess and understand the efficacy and safety profiles of different polymyxins.

Conclusion

In this study, both PMB and CS exhibited overall favorable clinical and bacterial responses. This suggests that both polymyxins are effective for nosocomial pneumonia caused by CRAB. The hepatotoxicity and AKI profiles of the two polymyxins were found to be comparable. However, patients receiving PMB should be vigilant for potential skin toxicity. Treatment of polymyxins ≤ 7 days was a risk factor associated with 28-day mortality, thus ensuring adequate therapy duration is key to better outcomes in ICU patients with CRAB-induced nosocomial pneumonia, regardless of the type of polymyxins.

Abbreviations

PMB	Polymyxin B sulfate
CS	Colistin sulfate
ICU	Intensive care unit
CRAB	*Carbapenem-resistant Acinetobacter baumannii*
PSM	Propensity score matching
AKI	Acute kidney injury
SOFA	Sequential Organ Failure Assessment
CR-GNB	Scarbapenem-resistant Gram-negative bacilli
WHO	World Health Organization
CHINET	China Antimicrobial Surveillance Network
IDSA	Infectious Diseases Society of America
CMS	Colistimethate sodium
MIC	Minimum inhibitory concentration
CLSI	Clinical and Laboratory Standards Institute
EUCAST	European Committee for Antimicrobial Susceptibility Testing
APACHE II	Acute Physiology and Chronic Health Evaluation II
Age-adjusted	CCI Age-adjusted Charlson Co-morbidity Index
KDIGO	Kidney Disease Improving Global Outcomes
DILI	Drug-induced liver injury
EASL	European Association for the Study of the Liver

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10773-1.

Supplementary Material 1

Author contributions

Y.C. conceived the study; W.B., C.W., Y.W., P.Z., N.Z., Y.H., X.X., and S.L. collected and analyzed the data; Y.C. and Y.W. validated the results; W.B., C.Y. drafted and revised the manuscript; All authors contributed to the study and have read and approved the final manuscript.

Funding

This work was supported by the Key Research and Development Program of Shaanxi (2021 KW-65) and the Science and Technology Bureau Program of Zun Yi, Guizhou Province [HZ (2020)251].

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and informed consent

This study was conducted following the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (No. 2024 – 185). Given the retrospective nature of this research, the requirement for written informed consent was also waived by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pharmacy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China
[2]Department of Pharmacy, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China
[3]Intensive Care Unit, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China
[4]Intensive Care Unit, Xi'an TCM Hospital of Encephalopathy, Shaanxi University of Chinese Medicine, Xi'an, Shaanxi, China
[5]Intensive Care Unit of Cardiac and Great Vessel Surgery, International Medical Xi'an Gaoxin Hospital, Xi'an, Shaanxi, China
[6]Intensive Care Unit, Chang'an Hospital, Xi'an, Shaanxi, China

Received: 28 November 2024 / Accepted: 10 March 2025
Published online: 20 March 2025

References

1. Zeng M, Xia J, Zong Z, Shi Y, Ni Y, Hu F, et al. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. J Microbiol Immunol Infect. 2023;56(4):653–71. https://doi.org/10.1016/j.jmii.2023.01.017.
2. Sun K, Peng F, Xu K, Liu Y, Zhou X, Shang N, Li C. A novel multivariate logistic model for predicting risk factors of failed treatment with carbapenem-resistant acinetobacter baumannii ventilator-associated pneumonia. Front Public Health. 2024;12:1385118. https://doi.org/10.3389/fpubh.2024.1385118.
3. CHINET. Results of bacterial resistance surveillance in 2023 [updated 2024-03-05. https://www.chinets.com/Document/Index?pageIndex=0#
4. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious diseases society of America 2024 guidance on the treatment of Antimicrobial-Resistant Gram-Negative infections. Clin Infect Dis. 2024;ciae403. https://doi.org/10.1093/cid/ciae403.
5. Rabanal F, Cajal Y. Recent advances and perspectives in the design and development of polymyxins. Nat Prod Rep. 2017;34(7):886–908. https://doi.org/10.1039/c7np00023e.
6. Wang J, Shah BK, Zhao J, Xiong J, Wang C, Xie S. Comparative study of polymyxin B and colistin sulfate in the treatment of severe comorbid patients infected with CR-GNB. BMC Infect Dis. 2023;23(1):351. https://doi.org/10.1186/s12879-023-08339-0.
7. Liu D, Jie F, Ding Y, Qu H, Chen D, Huang J. Real-world data on the effects of colistin sulfate and polymyxin B sulfate in the treatment of pneumonia induced by CR-GNB. J Infect Dev Ctries. 2024;18(7):1050–7. https://doi.org/10.3855/jidc.18887.
8. Yang X, Wang T, Zhang B, Zhang W, Wu G, Xu D, et al. Clinical outcome assessment of colistin sulphate in children with carbapenem-resistant organism infections: first data from China. Int J Antimicrob Agents. 2024;64(3):107273. https://doi.org/10.1016/j.ijantimicag.2024.107273.
9. Wu Y, Jiang S, Li D, Wu Y, Li Q, Wang X, et al. Clinical efficacy and safety of colistin sulfate in the treatment of Carbapenem-Resistant organism infections in patients with hematological diseases. Infect Dis Ther. 2024;13(1):141–54. https://doi.org/10.1007/s40121-023-00909-8.
10. Ma YC, Sun YQ, Wu X, Wang YJ, Yang XL, Gu JJ. Clinical effectiveness and safety of colistin sulphate in treating infections caused by Carbapenem-Resistant organisms and analysis of influencing factors. Infect Drug Resist. 2024;17:3793–804. https://doi.org/10.2147/IDR.S473200.
11. Zhang R, Wu Y, Deng G, Deng J. Value of sputum gram stain, sputum culture, and Bronchoalveolar lavage fluid gram stain in predicting single bacterial pathogen among children with community-acquired pneumonia. BMC Pulm Med. 2022;22(1):427. https://doi.org/10.1186/s12890-022-02234-1.
12. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant acinetobacter baumannii ventilator-associated pneumonia. J Infect. 2008;56(6):432–6. https://doi.org/10.1016/j.jinf.2008.04.002.

13. Murali M, Suppes SL, Feldman K, Goldman JL. Utilization of the Naranjo scale to evaluate adverse drug reactions at a free-standing children's hospital. PLoS ONE. 2021;16(1):e0245368. https://doi.org/10.1371/journal.pone.0245368.
14. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204. https://doi.org/10.1186/cc11454.
15. European Association for the Study of the Liver, Clinical Practice Guideline Panel. Chair, panel members, EASL governing board representative. EASL clinical practice guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222–61. https://doi.org/10.1016/j.jhep.2019.02.014.
16. Chen D, Qian Z, Su H, Meng Z, Lv J, Huang Y, et al. Invasive pulmonary aspergillosis in Acute-on-Chronic liver failure patients: Short-Term outcomes and antifungal options. Infect Dis Ther. 2021;10(4):2525–38. https://doi.org/10.1007/s40121-021-00524-5.
17. Groft LM, Claeys KC, Heil EL. An evaluation of meropenem/vaborbactam for the treatment of nosocomial pneumonia. Expert Opin Pharmacother. 2021;22(3):265–71. https://doi.org/10.1080/14656566.2020.1840552
18. Lu L, Yang C, Zhu H, Sun K, Liu L, Duan S, Tang J. Regularity of ventilator-associated pneumonia induced by three common pathogens. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2023;35(5):482–6. https://doi.org/10.3760/cma.j.cn121430-20220516-00483. Chinese.
19. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European society of clinical microbiology and infectious diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022;28(4):521–47. https://doi.org/10.1016/j.cmi.2021.11.025.
20. Yang QJ, Xiang BX, Song MH, Yang CY, Liang JH, Xie YL, Zuo XC. Acute kidney injury with intravenous colistin sulfate compared with polymyxin B in critically ill patients: A real-world, retrospective cohort study. Pharmacotherapy. 2024;44(8):631–41. https://doi.org/10.1002/phar.4601.
21. Zhang Y, Dong R, Huang Y, Ling X, Ye Z, Jiang S. Acute kidney injury associated with colistin sulfate vs. polymyxin B sulfate therapy: A real-world, retrospective cohort study. Int J Antimicrob Agents. 2024;63(1):107031. https://doi.org/10.1016/j.ijantimicag.2023.107031.
22. Zhuang HH, Qu Q, Long WM, Hu Q, Wu XL, Chen Y, et al. Ceftazidime/avibactam versus polymyxin B in carbapenem-resistant Klebsiella pneumoniae infections: a propensity score-matched multicenter real-world study. Infection. 2024. https://doi.org/10.1007/s15010-024-02324-8. Online ahead of print.
23. Zhou C, Jin L, Wang Q, Wang X, Chen F, Gao Y, et al. Bloodstream infections caused by Carbapenem-Resistant enterobacterales: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. Infect Drug Resist. 2021;14:731–42. https://doi.org/10.2147/IDR.S294282.
24. Katip W, Uitrakul S, Oberdorfer P. Short-Course versus Long-Course colistin for treatment of Carbapenem-Resistant A.baumannii in cancer patient. Antibiot (Basel). 2021;10(5):484. https://doi.org/10.3390/antibiotics10050484.
25. Katip W, Rayanakorn A, Oberdorfer P, Taruangsri P, Nampuan T. Short versus long course of colistin treatment for carbapenem-resistant A. baumannii in critically ill patients: A propensity score matching study. J Infect Public Health. 2023;16(8):1249–55. https://doi.org/10.1016/j.jiph.2023.05.024.
26. Papadimitriou-Olivgeris M, Assimakopoulos SF, Kolonitsiou F, Solomou A, Vamvakopoulou S, Spyropoulou A, et al. Risk factors for acute kidney injury in critically ill patients with bacteraemia by carbapenem non-susceptible gram negative bacteria. Infez Med. 2019;27(4):380–92.
27. Han L, Xu FM, Zhang XS, Zhang CH, Dai Y, Zhou ZY, et al. Trough polymyxin B plasma concentration is an independent risk factor for its nephrotoxicity. Br J Clin Pharmacol. 2022;88(3):1202–10. https://doi.org/10.1111/bcp.15061.
28. Song MH, Xiang BX, Yang CY, Lee CH, Yan YX, Yang QJ, et al. A pilot clinical risk model to predict polymyxin-induced nephrotoxicity: a real-world, retrospective cohort study. J Antimicrob Chemother. 2024;79(8):1919–28. https://doi.org/10.1093/jac/dkae185.
29. Li L, Huang X, Liu J, Li C, Lin Z, Ren R, et al. Efficacy and safety factors related to plasma Concentration-Optimized polymyxin B therapy in treating Carbapenem-Resistant Gram-Negative bacterial infections in China. Infect Drug Resist. 2024;17:3057–71. https://doi.org/10.2147/IDR.S468890.
30. Mattos KP, Lloret GR, Cintra ML, Gouvêa IR, Betoni TR, Mazzola PG, Moriel P. Acquired skin hyperpigmentation following intravenous polymyxin B treatment: a cohort study. Pigment Cell Melanoma Res. 2016;29(3):388–90. https://doi.org/10.1111/pcmr.12468.
31. Mattos KPH, Cintra ML, Gouvêa IR, Ferreira LÁ, Velho PENF, Moriel P. Skin hyperpigmentation following intravenous polymyxin B treatment associated with melanocyte activation and inflammatory process. J Clin Pharm Ther. 2017;42(5):573–8. https://doi.org/10.1111/jcpt.12543.
32. Kopple JD. Phenylalanine and tyrosine metabolism in chronic kidney failure. J Nutr. 2007;137(6 Suppl 1):1586. https://doi.org/10.1093/jn/137.6.1586S. S-1590S; discussion 1597S-1598S.
33. Rzepka Z, Buszman E, Beberok A, Wrześniok D. From tyrosine to melanin: signaling pathways and factors regulating melanogenesis. Postepy Hig Med Dosw (Online). 2016;70(0):695–708. https://doi.org/10.5604/17322693.1208033.

Publisher's note