ORIGINAL RESEARCH

Efficacy and Safety Factors Related to Plasma Concentration-Optimized Polymyxin B Therapy in Treating Carbapenem-Resistant Gram-Negative Bacterial Infections in China

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Background: Polymyxin B (PMB)-based combination therapies are used to treat severe carbapenem-resistant gram-negative bacterial (CR-GNB) infections. This observational study investigated the relationship between clinical factors, including PMB concentration, and clinical efficacy and safety.

Patients and Methods: Polymyxin B regimens were optimized through therapeutic drug monitoring (TDM) and area under the concentration-time curve (AUC). In all, 382 samples were tested from 130 patients. Logistic regression was used to analyze the relationships between variables with clinical efficacy and 30-day mortality factors were analyzed by Cox regression. The sensitivity and specificity of C_{min} and AUC for the occurrence of acute kidney injury (AKI) were determined by ROC curve analysis.

Results: The clinical effectiveness of PMB was 65.4%. Multivariate logistic regression analysis revealed that lung infection, continuous renal replacement therapy, and C-reactive protein were independent factors significantly associated with efficacy. AKI occurred in 14.6% of the patients during treatment; age > 73 years (OR: 3.63; 95% CI: 1.035–12.727; P = 0.044), C_{min} greater than 2.3 µg/mL (OR: 7.37; 95% CI: 1.571–34.580; P = 0.011), combined vancomycin (OR: 9.47; 95% CI: 1.732–51.731; P = 0.009), and combined piperacillin-tazobactam (OR: 21.87; 95% CI: 3.139–152.324; P = 0.002) were independent risk factors. The identified PMB cut-offs for predicting AKI were C_{min} = 2.3 µg/mL and AUC = 82.0 mg h/L.

Conclusion: Polymyxin B-based combination regimens are effective in treating CR-GNB infections, particularly bloodstream infections, but have shown unsatisfactory for lung infections. $C_{min} \geq 2.3$ µg /mL and AUC ≥ 82.0 mg h/L may increase PMB-associated AKI incidence. PMB dose should be adjusted based on TDM to ensure efficacy.

Keywords: Polymyxin B, PMB therapeutic drug monitoring, TDM, carbapenem-resistant gram-negative bacteria, CR-GNB, clinical efficacy, acute kidney injury, AKI

Introduction

Carbapenem-resistant Gram-negative bacterial (CR-GNB) infections are an urgent global public health threat with a high mortality rate[1] and are mainly caused by *carbapenem-resistant Enterobacteriaceae* (CRE), *Pseudomonas aeruginosa* (CRPA), *Acinetobacter baumannii* (CRAB), and *Klebsiella pneumoniae* (CRKP).[2] The emergence of these bacteria is a great challenge to clinical anti-infective therapy, and rational selection of antimicrobial drugs has become an important method to prevent and treat CR-GNB infections.

Polymyxin B (PMB) is one of the treatment options used for CR-GNB infections. Intravenous PMB is used to treat serious infections caused by a variety of pathogens, such as bacteremia, postoperative wound infections, and abdominal infections.[3–6] Previous studies have shown that PMB might be ineffective against pneumonia because of its large molecular structure and difficulty penetrating the pleura.[7] Recent findings suggested that aerosol inhalation delivery may have a positive effect on pneumonia when intravenous PMB fails.[8,9]

Administration of intravenous polymyxin B may lead to significant adverse effects in patients, such as nephrotoxicity, neurotoxicity, and skin darkening. Acute kidney injury (AKI) is the most concerning PMB toxicity issue that tends to limit its clinical application. Pharmacokinetic/toxicodynamic (PK/PD) data for PMB are scarce, and direct quantitative data establishing exposure-toxicity relationships are lacking. International consensus guidelines[9] recommend a daily dose of 1.25–1.50 mg/kg (q12h) for PMB, with a recommended loading dose of 2.0–2.5 mg/kg; however, high doses can cause nephrotoxicity. In a study by Elias,[10] doses of PMB greater than 200 mg/day increased the risk of nephrotoxicity while decreasing in-hospital mortality. From a safety perspective, clinicians are usually reluctant to select higher doses of PMB to avoid aggravating renal impairment; however, whether reducing the dose of PMB results in reduced in vivo antimicrobial activity at therapeutic blood levels is unknown. Because of this, there is an urgent need to understand the effective concentration range and renal toxicity concentration of PMB in patients with CR-GNB infections with high mortality rates, especially those with abnormal renal function.

Area under the concentration-time curve (AUC) thresholds of 50–100 mg h /L have been reported to reduce nephrotoxicity while ensuring clinical efficacy.[11] In a prospective study, the AUC/Minimal Inhibitory Concentration (MIC) threshold for the efficacy of PMB in patients with pneumonia was 66.9.[12] Despite the recognized value of PMB in treating CR-GNB infections, many questions regarding its optimal use, efficacy, and safety remain unanswered, including which factors are associated with the efficacy and safety of PMB. As PMB is increasingly being used to treat CR-GNB-induced infections, more studies are urgently needed to guide rational clinical use. In this study, we adjusted the PMB regimens by therapeutic drug monitoring (TDM) and estimated AUC, exploring the clinical efficacy and safety monitoring indices of PMB combination therapy. The results can help to develop a more rational clinical dosing regimen to improve antimicrobial efficacy and reduce nephrotoxicity.

Materials and Methods
Ethical Approval of the Study Protocol
The study was approved by the Ethics Committees of Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University (No. XHEC-D-2024-014). It was carried out by the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study, the study had no impact on the existed treatment. No biospecimens were collected from patients in this study. The confidentiality of patients' privacy and identity information was guaranteed, and there was no commercial interest involved, so that this research met the conditions for exemption from informed consent.

Patient Enrollment and Data Collection
An observational study on hospitalized patients treated with intravenous PMB was conducted at the Xinhua Hospital School of Medicine (Shanghai Jiao Tong University, Shanghai, China) from January 2021 to September 2023. Inclusion criteria were that patients (i) who had a PMB medication history (Shanghai First Biochemical Pharmaceutical Co., Ltd., Shanghai, China), (ii) were infected with CR-GNB based on bacterial culture results, and (iii) had complete medical data and basic information. The exclusion criteria were (i) PMB was administered for less than 72 hours (ii) the C_{min} and C_{max} of PMB were not monitored (iii) Patients who had received chemotherapy drugs for anti-tumor treatment before or during PMB treatment. Data were extracted from electronic medical records including demographics, comorbidities, causative organisms, medications, physiologic parameters, and laboratory values for the day of initiation of PMB as well as during treatment.

Definitions

On the day of drug administration, Sequential Organ Failure Assessment (SOFA) and biochemical markers of infection, such as white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT), along with liver and kidney function indicators, were established as baseline measures. Subsequently, these markers were assessed twice weekly for evaluating therapeutic efficacy. Infections were diagnosed by two physicians based on clinical symptoms, microbiological cultures, and radiological findings. The identification of pathogenic bacteria was carefully differentiated from colonization and contamination in the absence of infection. Surgery was defined as any invasive procedures documented in the surgical record in the electronic medical records. The use of vasoactive drugs was characterized by the administration of agents such as dobutamine, norepinephrine, and dopamine, which are commonly employed in anti-shock therapy. The susceptibility of the causative Gram-negative bacilli (GNB) to carbapenems was determined following the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The EUCAST breakpoints for PMB against the mentioned bacterial strains were defined as 2 mg/L or lower for susceptibility and greater than 2 mg/L for resistance. Patients were monitored for two weeks following PMB discontinuation.

Polymyxin B Administration and Therapeutic Drug Monitoring

Therapeutic management was determined by the physician, including dosage, infusion schedule, timing of administration, adjustment of therapy, and concomitant use of antibiotics. Peak and trough concentrations of PMB were monitored after 4–5 doses. Blood samples were collected twice, before (C0.5 hours) and 2 hours after (C2 hours) the start of the infusion. Plasma concentrations of PMB were determined using a previously published validated ultra-high performance liquid chromatography-tandem mass spectrometry method.[13] The two concentrations (peak and trough) and a simple analytical equation were used to estimate AUC values.[14] AUC of 50–100 mg· h/L was recommended for the treatment of CR-GNB.[9] Clinical pharmacists provided PMB adjustment regimen reports based on estimated AUC values. Clinicians adjusted the PMB regimens based on the TDM report. Specific methods included increasing the single dose of PMB if the AUC did not reach the target value, and decreasing the dose of PMB or reducing the dosing frequency if the AUC target value was exceeded.

Outcome Measurement

The primary endpoints were clinical efficiency and incidence of AKI associated with PMB. The efficacy criteria were treatment success (including normalization or improvement of clinical symptoms, signs, laboratory test results, and imaging tests after treatment) or failure (with no significant improvement of the above, deterioration of the condition, or a switch to other treatment options). Creatinine clearance (Clcr) in adults was calculated using the Cockcroft Gault formula; the pediatric estimation glomerular filtration rate (eGFR) was used with a creatinine-based formula (creatinine - blood urea nitrogen).[15] Clcr $\geq$ 90 mL/min indicated normal renal function. AKI was defined as an increase in serum creatinine of 0.3 mg/L (26.5 μmol/L) and 50% from baseline on two consecutive occasions during the treatment period. The two creatinine values in this study were measured on the day of drug administration and 7 days after PMB administration.

Secondary endpoints were 30-day all-cause mortality, bacterial clearance of PMB, and skin pigmentation. The 30-day all-cause mortality was recorded from the start of PMB treatment. Pathogenic microbiological cultures were conducted twice weekly, with bacterial clearance evaluations at 7 and 14 days post-treatment. Bacterial clearance was evaluated as clearance with two consecutive bacterial cultures showing negative results or two consecutive bacterial cultures showing growth of other bacteria and disappearance of the original pathogen; non-clearance was defined as bacterial cultures still showing the original pathogen.

Statistical Analyses

Statistical analyses were performed using SPSS v21.0. Data were expressed as median and interquartile range (IQR) for continuous variables and as frequency / percentage (%) for categorical variables. Logistic regression was used to analyze the relationships between variables with clinical efficacy, bacterial clearance rate, and adverse drug reaction (ADR), and reported as estimated as odds ratios (ORs). In addition, 30-day mortality factors were analyzed by Cox regression and estimated by

hazard ratios (HRs). In the univariate analysis, variables with a p-value less than 0.1 were selected for inclusion in the multivariate regression model. The backward elimination method was then applied in SPSS to identify the significant factors associated with the outcome. The sensitivity and specificity of C_{min} and AUC for the occurrence of AKI were determined by ROC curve analysis and AKI occurrence as the outcome, finding high sensitivity and specificity index became the best entry point. Chi-square test analyzed categorical variables. All results were considered significant at $P < 0.05$.

Results
Patient Demographics and Clinical Outcomes

A cohort of 168 patients was administered PMB and underwent TDM during the study period. After excluding 38 patients who met the exclusion criteria, 130 patients were included in the final analysis. The median age was 67 years (IQR: 51–78 years). The age distribution included 18.5% of patients < 18 years and 20% > 80 years, with a male predominance of 67.7%. The most prevalent site of infection was the lung, accounting for 64.6% of cases (84/130), followed by bloodstream (40%, 52/130) and abdominal infections (15.4%, 20/130). Notably, 20.8% of the patients (27/130) presented with multi-site infections. Adverse drug reactions during medication included 14.6% of AKI cases (19/130) and 50.8% of skin pigmentation cases (66/130). Detailed information regarding patient demographics and clinical outcomes is presented in Table 1.

Table 1 Patients Demographics and Clinical Outcomes

Parameters	Variable
Demographics	
Age, years, median (IQR)	67 (51.3, 78.0)
<18, n (%)	24 (18.5)
18~64, n (%)	32 (24.6)
65~80, n (%)	48 (36.9)
>80, n (%)	26 (20.0)
Male, n (%)	88 (67.7)
Weight, kg, median (IQR)	60.0 (50.0, 67.5)
SOFA score, median (IQR)	6.0 (3.0, 10.0)
Postoperative patients, n (%)	70 (53.8)
CRRT, n (%)	16 (12.3)
ICU, n (%)	114 (87.7)
Length of ICU stay, days, median (IQR)	28 (16, 45)
Total length of hospital stays, days, median (IQR)	43 (28, 70)
Infection types, n (%)	
Lung infection	84 (64.6)
Bloodstream infection	52 (40.0)
Abdominal infection	20 (15.4)
Other infections[a]	6 (4.6)
Comorbidities, n (%)	
Diabetes	31 (23.8)
Cardiovascular diseases	77 (59.2)
Neoplastic disease	22 (16.9)
Chronic digestive diseases	40 (30.8)
Kidney disease	19 (14.6)
COVID-19	15 (11.5)

(Continued)

Table 1 (Continued).

Parameters	Variable
Pathogenic bacteria species, n (%)	
CR Klebsiella Pneumoniae	67 (51.5)
CR Acinetobacter baumannii	61 (46.9)
CR Pseudomonas aeruginosa	17 (13.1)
Stenotrophomonas maltophilia	5 (3.8)
Escherichia coli	5 (3.8)
Klebsiella oxytoca	3 (2.3)
Others[b]	5 (3.8)
PMB MIC, μg/mL	
≤0.5, n (%)	57(43.9)
1, n (%)	54(41.5)
≥2, n (%)	19(14.6)
PMB administration duration, days, median (IQR)	13 (7, 17)
3~7, n (%)	35 (26.9)
8–14, n (%)	54 (41.5)
15~21, n (%)	22 (16.9)
22–30, n (%)	9 (6.9)
≥31, n (%)	9 (6.9)
Concomitant antibiotics, n (%)	
Carbapenems	86 (66.2)
Cefoperazone-sulbactam	21 (16.2)
Piperacillin-tazobactam	7 (5.4)
Cefepime	6 (4.6)
Tigecycline	17 (13.1)
Fosfomycin	30 (23.1)
Amikacin	3 (2.3)
Vancomycin	18 (13.8)
Amikacin	3 (2.3)
Others[c]	33 (25.4)
Outcomes	
Total clinical effective rate, n (%)	85 (65.4)
Clinical effective rate in 7 days, n (%)	31 (23.8)
Total bacterial clearance, n (%)	70 (53.9)
Bacterial clearance in 7 days, n (%)	35 (26.9)
Time of bacterial clearance, days, median (IQR)	9 (6, 12)
30-day mortality, n (%)	39 (30.0)

Notes: Bacterial names are in italics. [a]Intracranial infection; Biliary tract infection; Wound infection. [b]*Enterobacter cloacae; Klebsiella aerogenes.* [C]Ceftazidime avibactam; Ceftazidime; Levofloxacin; Teicolanin; Linezolid; Voriconazole; Fluconazole.
Abbreviations: IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MIC, Minimal Inhibitory Concentration; COVID-19, Coronavirus Disease 2019; *CR, Carbapenem-resistant.*

Polymyxin B Exposure and Drug Concentration Monitoring results

For adults, the loading dose of PMB was 1.7 mg/kg (IQR: 1.5–2.0 mg/kg), while the maintenance dose was 0.9 mg/kg (IQR: 0.8–1.0 mg/kg); in children, these doses were 1.6 mg/kg (IQR: 1.5–2.0 mg/kg) and 1.1 mg/kg (IQR: 1.0–1.3 mg/kg), respectively. PMB was administered by aerosol inhalation in 33 cases, and intrathecal injection was used in two.

Out of the 130 patients in the study, 107 were adults and 23 were children. Among them, 83 patients underwent blood sample testing once, with 2 samples taken each time to measure trough and peak concentrations. Additionally, 47 patients had their blood samples tested more than 2 times, resulting in a total of 382 blood samples being tested 191 times. The C_{min} observed was 2.4 μg/mL (IQR: 1.8–3.5 μg/mL) in adults and 0.8 μg/mL (IQR: 0.6–1.3 μg/mL) in children. The

C_{max} was 5.4 μg/mL (IQR: 4.3–7.0 μg/mL) for adults and 4.4 μg/mL (IQR: 3.4–6.3 μg/mL) for children. The AUC values were 91.8 mg h/L (IQR: 70.8–119.6 mg h/L) in adults and 55.8 mg h/L (IQR: 44.5–77.9 mg h/L in children. Detailed data of 191 times of PMB drug concentration monitoring are presented in Table S1. Out of the total 43 patients, the PMB regimens were modified based on AUC estimation. The initial concentrations of PMB in the patients were used in several studies to analyze factors affecting the clinical efficacy of PMB, bacterial clearance rate, 30-day all-cause mortality, AKI, skin pigmentation, and ROC curve analysis.

Analysis of Factors Affecting Clinical Efficacy of Polymyxin B

The overall clinical response rate to PMB was 65.4% (85/130). Univariate logistic regression analysis identified several factors influencing the clinical efficacy of PMB, including bloodstream infection (OR: 4.10; 95% CI: 1.759–9.535; P = 0.001), lung infection (OR: 0.22; 95% CI: 0.087–0.541; P = 0.001), CRRT (OR: 0.27; 95% CI: 0.090–0.789; P = 0.017), CRP (OR: 0.32; 95% CI: 0.140–0.725; P = 0.006), and Coronavirus Disease 2019 (COVID-19) (OR: 0.30; 95% CI: 0.101–0.918; P = 0.035). Multivariate logistic regression analysis revealed that lung infection, CRRT, and CRP were independent factors significantly associated with the clinical efficacy of PMB (Table 2). The study included 84 patients with lung infection, with 16 cases in the effective group and 17 cases in the ineffective group receiving PMB atomization treatment. The chi-square test yielded a p-value of 0.352, suggesting that there was no statistically significant difference between the two groups.

Table 2 Univariate and Multivariate Analysis of Clinical Efficacy of Polymyxin B

Parameters	Efficacious n=85	Non-Efficacious n=45	OR (95% CI)	*P* value
Univariate analysis				
Age, years, median (IQR)	65 (40,76)	72 (63,83)		0.169
<18 vs >80, n (%)	18 (21.2)/ 13 (15.3)	6 (13.3)/13 (28.9)	3.00 (0.902–9.980)	0.073
18~64 vs >80, n (%)	24 (28.2)	8 (17.8)	3.00 (0.989–9.100)	0.052
65~80 vs >80, n (%)	30 (35.3)	18 (40.0)	1.67 (0.635–4.377)	0.300
Comorbidities, n (%)				
Cardiovascular diseases	44 (51.8)	33 (73.3)	0.39 (0.178–0.856)	**0.019**
COVID-19	6 (7.1)	9 (20.0)	0.30 (0.101–0.918)	**0.035**
Test index before PMB treatment				
WBC, X10⁹/L, median (IQR)	12.1 (7.9,16.4)	12.1 (7.4,17.2)	0.99 (0.941–1.040)	0.680
CRP, mg /L, median (IQR)	82.0 (40.0.131.0)	130.5 (62.8.160.0)		
<160 vs ≥160, n (%)	15 (17.6)	19 (42.2)	0.32 (0.140–0.725)	**0.006**
PCT, ng /mL, median (IQR)	1.1 (0.3,6.8)	1.1 (0.4,5.0)	1.00 (0.984–1.018)	0.908
eGFR, mL /min, median (IQR)	87.1 (49.4.134.1)	61.7 (27.5,93.3)	1.01 (0.999–1.010)	0.101
SOFA, median (IQR)	6.0 (3.0,9.0)	6.0 (3.0,12.0)	0.97 (0.902–1.048)	0.460
Mechanical ventilation, n (%)	45 (52.9)	24 (53.3)	0.95 (0.477–2.031)	0.966
CRRT, n (%)	6 (7.1)	10 (22.2)	0.27 (0.090–0.789)	**0.017**
Surgery, n (%)	51 (60.0)	19 (42.2)	2.05 (0.986–4.275)	0.055
Vasopressors, n (%)	25 (29.4)	20 (44.4)	0.52 (0.246–1.103)	0.089
Infection type, n (%)				
Bloodstream infection	43 (50.6)	9 (20.0)	4.10 (1.759–9.535)	**0.001**
Lung infection	46 (54.1)	38 (84.4)	0.22 (0.087–0.541)	**0.001**
Abdominal infection	16 (18.8)	4 (8.9)	2.38 (0.744–7.596)	0.144
PMB Therapeutic regimen				
Loading dose, n (%)	69 (81.2)	36 (80.0)	1.08 (0.434–2.680)	0.871
Loading dose, mg /kg, median (IQR)	1.7 (1.4,2.0)	1.8 (1.7,2.0)	1.14 (0.718–1.819)	0.573
Maintenance dose, mg/kg, median (IQR)	1.0 (0.8,1.1)	0.9 (0.8,1.0)	1.85 (0.433–7.872)	0.407
Daily dose, mg /kg, median (IQR)	1.9 (1.6,2.3)	1.9 (1.5,2.0)	1.51 (0.702–3.256)	0.291

(*Continued*)

Table 2 (Continued).

Parameters	Efficacious n=85	Non-Efficacious n=45	OR (95% CI)	*P* value
Concomitant antibiotics, n (%)				
Carbapenems	53 (62.4)	32 (71.1)	0.67 (0.309–1.467)	0.319
Cefoperazone Sodium Sulbactam	16 (18.8)	5 (11.1)	1.86 (0.632–5.447)	0.261
Tigecycline	11 (12.9)	6 (13.3)	0.97 (0.332–2.810)	0.950
Fosfomycin	20 (23.5)	10 (22.2)	1.08 (0.454–2.553)	0.866
TDM, median (IQR)				
C_{min} /MIC	2.1 (1.3,3.9)	2.7 (2.1,4.7)	0.95 (0.853–1.064)	0.392
C_{max} /MIC	6.2 (3.8,9.3)	7.4 (4.6,10.2)	0.99 (0.935–1.055)	0.828
AUC /MIC	96.2 (57.7.160.9)	109.7 (76.3.182.1)	1.00 (0.996–1.002)	0.573
Pathogenic bacteria species, n (%)				
CR Klebsiella Pneumoniae	46 (54.1)	20 (44.4)	1.47 (0.713–3.049)	0.295
CR Acinetobacter baumannii	40 (47.1)	22 (48.9)	0.93 (0.451–1.915)	0.842
CR Pseudomonas aeruginosa	13 (15.3)	8 (17.8)	0.84 (0.318–2.194)	0.715
Multivariate analysis				
Lung infection			0.23 (0.083–0.653)	**0.006**
CRRT			0.16 (0.037–0.663)	**0.012**
CRP, mg/L				
<160 vs ≥160			0.31 (0.123–0.780)	**0.013**

Note: *P* values<0.05 are in bold; Bacterial names are in italics.
Abbreviations: WBC, White Blood Cells; CRP, C-reactive protein; PCT, Procalcitonin; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; MIC, Minimal Inhibitory Concentration; *CR, Carbapenem-resistant*.

Analysis of Factors Influencing 30-Day All-Cause Mortality

The 30-day all-cause mortality rate was found to be 30% (39/130). Univariate Cox regression analysis showed that age, bloodstream infection, lung infection, CRP, use of vasopressors, CRRT, and combined COVID-19 were the main influencing factors. Bloodstream infection (HR: 0.30; 95% CI: 0.122–0.713; P = 0.007), use of vasopressors (HR: 2.12; 95% CI: 1.086–4.138; P = 0.028), CRP (HR: 3.45; 95% CI: 1.752–6.803; P = 0.000), and COVID-19 (HR: 2.48; 95% CI: 1.151–5.354; P = 0.020) were identified as independent risk factors for 30-day all-cause mortality (Table 3). Kaplan–Meier survival estimates for 30-day all-cause mortality are illustrated in Figure 1.

Table 3 Univariate and Multivariate Analysis of 30-Day All-Cause Mortality

Parameters	Univariate Analysis		
	HR	95% CI	*P* value
Univariate analysis			
Age, years			**0.042**
<18 vs >80	0.17	0.038–0.784	**0.023**
18~64 vs >80	0.46	0.177–1.177	0.104
65~80 vs >80	0.98	0.468–2.069	0.966
Comorbidities			
Diabetes	2.23	1.168–4.257	**0.015**
Cardiovascular diseases	2.24	1.090–4.569	**0.028**
COVID-19	3.21	1.518–6.782	**0.002**

(*Continued*)

Table 3 (Continued).

Parameters	Univariate Analysis		
	HR	**95% CI**	**P value**
Test index before PMB treatment			
WBC, X10^9/L	0.10	0.951–1.048	0.948
CRP, mg/L			
<160 vs ≥160	3.92	2.058–7.450	**0.000**
PCT, ng/mL	1.00	0.987–1.015	0.904
SOFA score, 1-point increments	1.06	0.998–1.128	0.060
Surgery operation	0.56	0.298–1.067	0.055
CRRT	2.27	1.040–4.942	**0.039**
Mechanical ventilation	1.36	0.718–2.574	0.345
Vasopressors	2.15	1.144–4.022	**0.017**
Infection type			
Bloodstream infection	0.29	0.129–0.661	**0.003**
Lung infection	3.40	1.422–8.113	**0.006**
Abdominal infection	0.43	0.132–1.391	0.158
TDM			
C$_{min}$ /MIC	1.05	0.982–1.126	0.150
C$_{max}$ /MIC	1.02	0.976–1.061	0.413
AUC /MIC	1.00	0.999–1.004	0.229
Multivariate analysis			
Bloodstream infection	0.30	0.122–0.713	**0.007**
Vasopressors	2.12	1.086–4.138	**0.028**
CRP, mg/L			
<160 vs ≥160	3.45	1.752–6.803	**0.000**
COVID-19	2.48	1.151–5.354	**0.020**

Note: *P* values<0.05 are in bold.
Abbreviations: WBC, White Blood Cells; CRP, C-reactive protein; PCT, Procalcitonin; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; MIC, Minimal Inhibitory Concentration; COVID-19, Coronavirus Disease 2019.

Analysis of Factors Affecting Bacterial Clearance

The total bacterial clearance rate was 53.9% (70/130), occurring within 7 days in 26.9% of cases (35/130). Univariate logistic analysis identified four statistically significant factors: mechanical ventilation, bloodstream infection, lung infection, and surgery. Multivariate logistic regression analysis revealed that bloodstream infection (OR: 5.58; 95% CI: 2.45–12.71; P < 0.001) and surgery (OR: 2.29; 95% CI: 1.06–4.97; P = 0.035) were independent factors significantly affecting bacterial clearance. Detailed statistical data can be found in Table S2.

Analysis of Factors Influencing Acute Kidney Injury and Skin Pigmentation During Polymyxin B Treatment

Acute kidney injury was observed in 14.6% of patients (16/130) during PMB treatment. Univariate logistic analysis identified age, C$_{min}$, AUC, combined carbapenem use, and combined piperacillin-tazobactam as factors with significant differences between those who developed AKI and those who did not. Multivariate analysis revealed that age > 73 years (OR: 3.63; 95% CI: 1.035–12.727; P = 0.044), C$_{min}$ greater than 2.3 μg/mL (OR: 7.37; 95% CI: 1.571–34.580; P = 0.011), combined vancomycin (OR: 9.47; 95% CI: 1.732–51.731; P = 0.009), and combined piperacillin-tazobactam (OR: 21.87; 95% CI: 3.139–152.324; P = 0.002) were independent risk factors for AKI (Table 4).
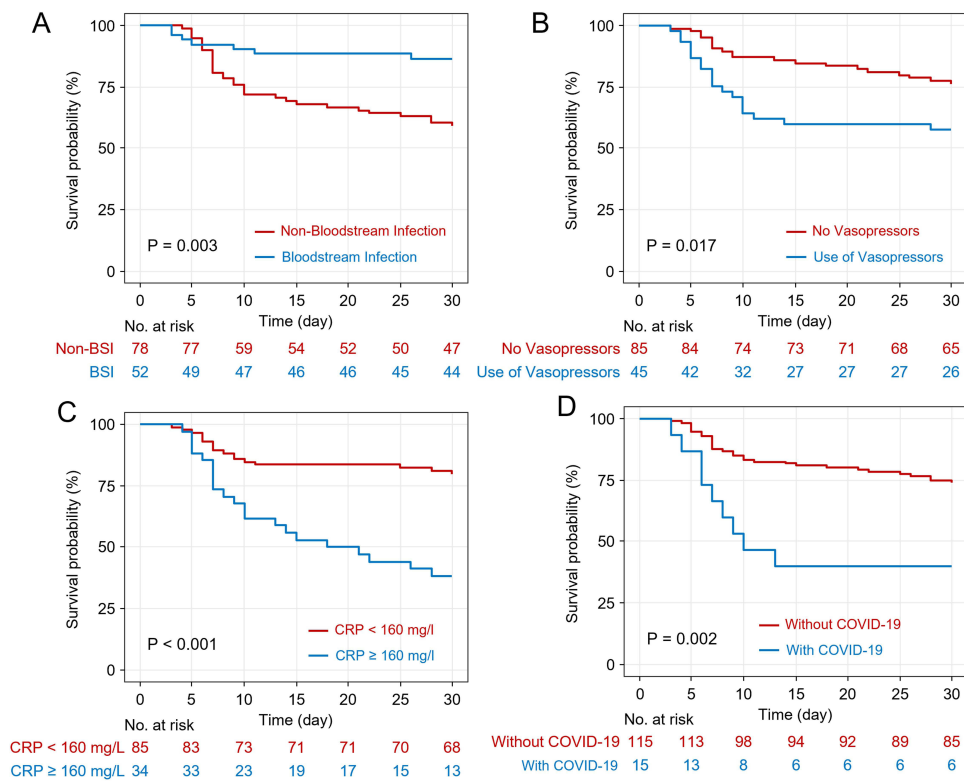
Figure 1 Kaplan–Meier survival estimates for 30-day all-cause mortality.
Notes: (**A**) Bloodstream infection and Non- Bloodstream infection (P < 0.01). (**B**) Use of Vasopressors and No Vasopressors (P < 0.01). (**C**) CRP<160 mg/L and ≥160 mg/L (P < 0.01). (**D**) With COVID-19 and Without COVID-19 (P < 0.01).
Abbreviations: CRP, C-reactive protein; COVID-19, Coronavirus Disease 2019.

In the analysis of skin pigmentation, PMB treatment duration and age were identified as independently associated risk factors, with odds ratios of 44.788 (95% CI: 13.724–146.162; P < 0.001) and 163 (95% CI: 0.042–0.642; P = 0.009), respectively (Table S3).

Table 4 Analysis of Factors Influencing Acute Kidney Injury During Polymyxin B Treatment

Parameters	AKI n=19	Non- AKI n=111	OR (95% CI)	P value
Univariate analysis				
Age, years, median (IQR)	80 (70.5, 86.0)	65 (44.0, 75.0)	1.06 (1.016–1.097)	**0.005**
>73, n (%)	11(73.7)	32 (28.8)	6.91 (2.300–20.779)	**0.001**
Test index before PMB treatment				
Creatinine, μmol/L, median (IQR) (IQR)median(IQR) (IQR)	51.5 (35.1, 79.6)	56.0 (37.1, 116.4)	9.99 (0.985–1.003)	0.213
SOFA, median (IQR)	6.0 (3.0, 9.0)	6.0 (3.0, 10.0)	0.97 (0.873–1.077)	0.563
PMB therapeutic regimen, median (IQR)				
Loading dose, mg/kg	1.8 (1.5, 2.0)	1.7 (1.5, 2.0)	1.32 (0.663–2.638)	0.427
Maintenance dose, mg/kg	0.8 (0.8, 1.0)	1.0 (0.8, 1.1)	0.12 (0.012–1.219)	0.073
Daily dose, mg/kg	1.7 (1.5, 2.0)	2.0 (1.6, 2.3)	0.39 (0.123–1.225)	0.106
Accumulated dose, mg/kg	15.0 (10.4, 24.4)	20.5 (14.0,29.7)	0.98 (0.954–1.016)	0.326
Treatment duration, days	11.0 (7.0, 18.0)	13.0 (7.5, 16.0)	0.99 (0.958–1.029)	0.696

(Continued)

Table 4 (Continued).

Parameters	AKI n=19	Non- AKI n=111	OR (95% CI)	P value
TDM				
C_{min}, µg/mL, median (IQR)	2.9 (2.4,4.0)	1.9 (1.2,3.0)	1.43 (1.060–1.931)	**0.019**
>2.3, n (%)	14 (73.3)	38 (34.2)	5.38 (1.802–16.059)	**0.003**
C_{max}, µg/mL, median (IQR)	5.7 (4.7, 7.8)	5.1 (3.7, 6.7)	1.11 (0.944–1.315)	0.202
AUC, mg·h/L, median (IQR)	104.3(85.5, 136.0)	78.7 (56.5, 111.0)	1.01 (1.000–1.020)	**0.049**
>82, n (%)	16 (84.2)	53 (47.7)	5.84 (1.610–21.163)	**0.007**
Concomitant antibiotics, n (%)				
Carbapenem	7 (36.8)	79 (71.2)	0.25 (0.089–0.682)	**0.007**
Cefepime	1 (5.3)	5 (4.5)	1.18 (1.130–10.676)	0.884
Amikacin	1 (5.3)	2 (1.8)	3.03 (0.261–35.147)	0.376
Vancomycin	5 (26.3)	13 (11.7)	2.69 (0.833–8.706)	0.098
Piperacillin-tazobactam	5 (26.3)	2 (1.8)	19.65 (3.445–109.974)	**0.001**
Multivariate analysis				
Age, year, >73 vs ≤ 73			3.63 (1.04–12.73)	**0.044**
C_{min}, µg/mL, >2.3 vs ≤ 2.3			7.37 (1.57–34.58)	**0.011**
Vancomycin			9.47 (1.73–51.73)	**0.009**
Piperacillin-tazobactam			21.87 (3.14–152.3)	**0.002**

Note: *P* values<0.05 are in bold.
Abbreviations: SOFA, Sequential Organ Failure Assessment; TDM, Therapeutic drug concentration monitoring; C_{min}, Trough concentration; C_{max}, Peak concentration; AUC, Area Under the concentration-time Curve.

Determining the Polymyxin B Cut-off Values of C_{min} and AUC_{24} for Predicting Acute Kidney Injury During Polymyxin B Treatment

In this study, we attempted to use ROC curve analysis to establish the cut-off values for the C_{min} and AUC_{24} of PMB that predicted the occurrence of AKI. The identified cut-off values were C_{min} at 2.3 µg/mL (sensitivity: 78.9%; specificity: 61.3%) and AUC_{24} at 82.0 mg· h/L (sensitivity: 84.2%; specificity: 52.3%). C_{min} demonstrated a superior predictive value compared with AUC_{24}, as evidenced by a larger area under the ROC curve (0.73 with 95% CI: 0.635–0.800 and 0.69 with 95% CI: 0.592–0.791, respectively) (Figure 2).
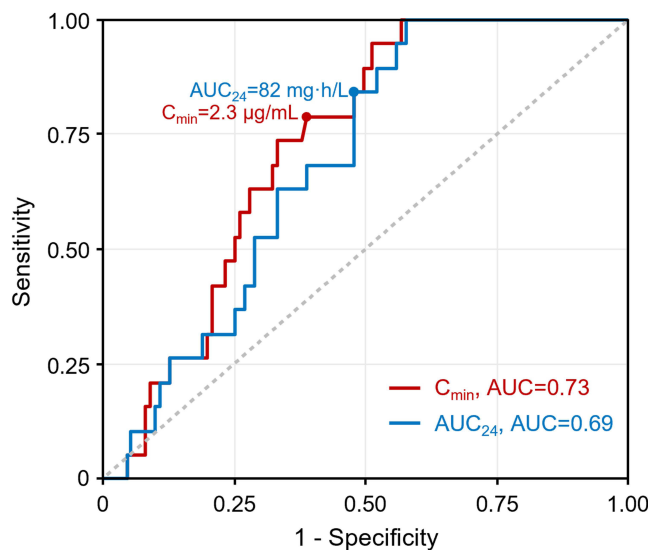

Figure 2 Receiver operating characteristic curve of the C_{min} and AUC_{24} of PMB for AKI.
Abbreviations: C_{min}, Trough concentration; AUC_{24}, Area Under the concentration-time Curve across 24 h.

Discussion

In this study, we analyzed the clinical efficacy of PMB-based combination regimens for the treatment of CR-GNB infections. Factors including lung infection and CRRT treatment were identified as unfavorable, while CRP levels <160 mg/L were considered favorable predictors of clinical efficacy with PMB combination therapy. Age > 73 years, C_{min} > 2.3 μg/mL, and combination therapy with either piperacillin-tazobactam or vancomycin were independent risk factors for AKI. C_{min} ≥ 2.3 μg/mL and AUC ≥ 82.0 mg h/L were the cutoff values for predicting PMB-associated AKI.

The clinical efficacy of PMB was 65.4%, and increasing PMB concentration did not affect efficacy. There was no correlation between clinical efficacy and PMB dose in this study, but many previous studies have shown that clinical efficacy was associated with high doses of PMB.[10,16,17] Here, the median daily dose of PMB was 1.0 mg/kg (q12h), which was lower than the guideline-recommended dose. C_{min}/MIC, C_{max}/MIC, and AUC/MIC were not associated with the clinical efficacy of PMB; however, the effective range of trough concentration and C_{min}/MIC of PMB in combination with other antibiotics still need to be studied and observed in large samples. In this study, PMB-based combination regimens were utilized for the treatment of CR-GNB infections, with carbapenems being the primary regimen. Other agents such as Cefoperazone Sodium Sulbactam, Tigecycline, and Fosfomycin were also included. There was no statistically significant difference in clinical efficacy between the various combined regimens. Several studies have demonstrated that for CR-GNB infections, PMB combination regimens containing carbapenems and other agents can lead to improved clinical efficacy and microbial response.[18–21]This study further confirmed that PMB-based combination regimens are effective in treating CR-GNB infections, resulting in better clinical outcomes and microbial responses.

The clinical response rate of PMB for pneumonia was lower than for other sites of infection, and the 30-day all-cause mortality rate was higher for COVID-19 infection. It has been suggested that PMB combination therapy is effective for treating CRO pneumonia.[22–24] Here, lung infections accounted for 63.1% of the cases, and there were combinations of infections at other sites in some cases, which might be partly responsible for the poor outcome of lung infections. Pharmacodynamic studies have shown that even with the highest tolerated dose of polymyxin, lung concentrations of the drug may be lower than optimal for the infecting strains unless the MICs of these pathogens were well below the breakpoint;[25,26] inhaled polymyxins were recommended to overcome these drawbacks.[9,27] In this study, only 33 patients with lung infection were treated with PMB aerosol inhalation, showing no significant difference in efficacy compared to those who did not undergo aerosol treatment. Variations in aerosol inhalation regimens and devices may impact the effectiveness of PMB, possibly contributing to the observed low efficacy in treating lung infections. Severe COVID-19 infection may increase the level of immunosuppression, possibly leading to more deaths in the later stages of hospitalization.[28] The mortality rate in patients with COVID-19-MDR-GNB has been reported to be 68.6%.[29] Additionally, 15 cases of COVID-19 infection in this study were complicated by CR-GNB, which could explain the high treatment failure rate in lung infections. Further research and analysis are needed to determine if high-dose intravenous PMB and aerosolized PMB are necessary to achieve adequate pulmonary drug concentrations in COVID-19 patients.

Guidelines recommend that patients undergoing continuous renal replacement therapy (CRRT) should not adjust the dose of PMB.[9] Patients undergoing continuous veno-venous hemodiafiltration (CVVHDF) exhibit higher total clearance and a shorter terminal half-life of PMB.[30] Some clinical studies suggest that higher doses of PMB could potentially improve efficacy and reduce mortality in patients undergoing renal replacement therapy.[31,32] Our study involving 16 patients treated with CRRT and receiving the usual PMB dosage showed low clinical effectiveness. The pharmacokinetic changes in CRRT patients are intricate, with various factors influencing anti-infective efficacy. Further prospective studies focusing on different renal replacement therapy modalities will offer insights into safe and effective PMB dosing regimens for treatment. PMB demonstrates rapid, concentration-dependent bacterial killing in vitro against a variety of Gram-negative organisms.[33] Several reports indicated that PMB holds promise in the clinical treatment of bloodstream infections.[34–36] The study confirmed that blood cultures turned negative within 3 days of starting therapy in all patients assessed for microbiological efficacy.[37] Moreover, there was evidence suggesting that early administration of PMB may lower the mortality rate in cases of CRKP bloodstream infections.[38] The study also observed high bacterial clearance at the site of bloodstream infection across the range of drug concentrations tested, highlighting the clinical benefits of PMB in treating CR-GNB bloodstream infections.

The incidence of AKI was 14.6%, which was lower than the previously reported 20%-60%.[39–41] Although the clearance of PMB did not depend on the glomerular filtration rate, 90–95% of filtered PMB was reabsorbed by tubular cells in critically ill patients.[42,43] Because of reabsorption and intracellular accumulation, exposure of renal tubular cells to high concentrations of PMB can cause direct damage.[42,44] A meta-analysis showed that being elderly, high daily dosage, having an underlying disease such as diabetes, and concomitant use of nephrotoxic drugs were independent predictors of polymyxin-induced nephrotoxicity.[45] Our findings suggested that age > 73 years and the combined use of piperacillin-tazobactam or vancomycin were independent risk factors for AKI, consistent with the findings of the above-mentioned study. Regardless of initial renal function, routine adjustment of PMB dose by TDM avoided potential adverse outcomes, especially in elderly patients; this may also have contributed to the lower incidence of AKI. The AUC thresholds for PMB-associated AKI have been reported to be 99.4 mg h/L[11] and 97.72 mg h/L.[46] Maintaining PMB C_{min} < 3.13 mg/L may help to reduce the occurrence of PMB-associated nephrotoxicity.[47] Here, the risk of AKI was predicted to increase in combined PMB therapy when $C_{min} \geq 2.3$ μg / mL and AUC ≥ 82.0 mg h/L, much lower than the thresholds reported previously; this may be related to the higher proportion of older patients in our study population. C_{min} was the better threshold for AKI prediction. Further clinical studies with large sample sizes are needed to concretely determine the efficacy of TDM for PMB in preventing AKI risk.

The prevalence of skin pigmentation was 50.8%, which is considerably higher than the previously reported 8 to 15%[48,49] but it is reported that almost all patients treated with PMB developed hyperpigmentation on the head and neck.[50] Most patients with hyperpigmentation had dark skin on the face and neck with skin changes appearing approximately a week after starting PMB treatments, but the degree of hyperpigmentation varied widely. This higher incidence may have been because we adopted a more stringent standard: darker skin on the face or neck than before treatment was considered to be skin hyperpigmentation. The exact pathogenesis of PMB-induced skin pigmentation is still debated and may be multifactorial. The cumulative effect of PMB in neonates and infants may affect skin darkening, most likely because of immature renal function.[51] The cumulative effect of PMB in the body might also be a relevant factor. The present study confirms that younger patients have a greater likelihood of skin pigmentation, especially those < 50 years old. The risk of hyperpigmentation increased when the duration of PMB exceeded 10 days, indicating that a higher cumulative dose was more likely to cause hyperpigmentation.

There are several limitations in the present study. No separate analysis was performed to characterize the PK/PD of PMB in patients who were children. The poor outcome of lung infections was influenced by many factors which were not systematically analyzed and summarized. Additionally, there was no further analysis of bacterial species and site of infection. These shortcomings will be further improved in follow-up studies.

Conclusion

Polymyxin B-based combination regimens are effective in the treatment of CR-GNB infections, especially in blood-stream infections where bacteria are easily cleared, but they have shown unsatisfactory efficacy in treating lung infections. Increasing the concentration of PMB did not affect efficacy within the range of doses and concentrations currently administered. Age > 73 years, $C_{min} \geq 2.3$ μg/mL, AUC ≥ 82.0 mg·h/L, combined therapy with vancomycin or with piperacillin-tazobactam led to a higher risk of AKI. Adjusting the PMB dose based on TDM is recommended to ensure adequate efficacy, though this needs further analysis of larger samples of cases.

Abbreviations

IQR, interquartile range; OR odds ratio; CI confidence interval; WBC, White Blood Cells; CRP, C-reactive protein; PCT, Procalcitonin; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MIC, Minimal Inhibitory Concentration; COVID-19, Coronavirus Disease 2019; CRKP, *Carbapenem-resistant Klebsiella Pneumoniae*; CRAB, *Carbapenem-resistant Acinetobacter baumannii*; CRPA, *Carbapenem-resistant Pseudomonas aeruginosa*; C_{min}, Trough concentration; C_{max}, Peak concentration; AUC, Area Under the concentration-time Curve; TDM, Therapeutic drug monitoring; eGFR, estimated glomerular filtration rate. CR-GNB, Carbapenem-resistant Gram-negative bacterial.

Ethical Approval and Informed Consent

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committees of Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University (No. XHEC-D-2024-014). Patient consent was waived by the Ethics Committees (as confirmed by the ethics approval document we provided) due to retrospective data used in this study were fully desensitized.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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