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ORIGINAL RESEARCH

# Polymyxin B-Based Regimens for Patients Infected with Carbapenem-Resistant Gram-Negative Bacteria: Clinical and Microbiological Efficacy, Mortality, and Safety

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**Background:** The increasing prevalence of carbapenem-resistant Gram-negative bacteria (CR-GNB) represents a global healthcare crisis. This study explored the efficacy and safety of Polymyxin B (PMB)-based regimens and factors influencing their effectiveness.

**Methods:** Patients with CR-GNB infections treated with PMB for more than three days were enrolled in this retrospective study from 1st June 2018 to 30th April 2020. Data were collected on patient characteristics, bacterial culture, and drug-sensitivity test results; anti-infection treatment regimens, particularly details of PMB use; and adverse drug reactions. Clinical and microbiological efficacy, mortality, and safety of PMB-based regimens in CR-GNB infected patients were evaluated. Univariate analysis and multivariate logistic regression analyses were used to assess factors influencing efficacy and mortality.

**Results:** A total of 373 CR-GNB strains were cultured from 268 patients. About 41.04% of patients used PMB loading dose of 1.01 (0.84–1.69) mg/kg. Maintenance dose was 0.85 (0.82–1.00) mg/kg q12h. The clinical efficacy rate was 36.57% (98/268), the total bacterial clearance rate of PMB was 39.42%, and the all-cause mortality rate was 33.96%. The adverse drug reaction rate was 19.58%, among which the incidence of renal toxicity was highest (8.21%). Multivariate logistic regression analysis showed that clinical efficacy, bacterial clearance rate, and all-cause mortality were associated with patient-related facts, including mechanical ventilation use, underlying diseases (such as respiratory disease), the type and site of CR-GNB infection, and PMB administration timing and loading dose.

**Conclusion:** PMB is a relatively safe and effective antibiotic drug for treatment of critically ill patients with CR-GNB infection; however, PMB use should be subject to guidelines recommendations for early administration, loading administration, and adequate administration, which could help to improve the clinical efficacy, microbiological efficacy, and mortality.

**Keywords:** polymyxin B, carbapenem-resistant Gram-negative bacteria, clinical efficacy, bacterial elimination, mortality, adverse effect

## Introduction

The increasing prevalence of carbapenem-resistant Gram-negative bacteria (CR-GNB) represents a global healthcare crisis.[1] In particular, carbapenem-resistant *Enterobacteriaceae* (CRE) has been listed as an urgent threat by the World Health Organization.[2] Furthermore, according to a report from the China Antimicrobial Resistance Surveillance System in 2019, the detection rates of carbapenem-resistant *Klebsiella pneumonia* (CRKP), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) were 10.90%, 19.10%, and 56%, respectively.[3,4]

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Therapeutic options against CR-GNB infections include novel beta-lactam/beta-lactamase inhibitors such as ceftazidime/avibactam, cefiderocol, plazomicin, eravacycline, and polymyxins, such as colistin and polymyxin B (PMB).[5,6] PMB (but not colistin) and ceftazidime/avibactam are currently available on the market in mainland China, which are used to treat infections with clinically resistant bacteria.[7] Others were not available in mainland China. To date, research into the pharmacokinetic/pharmacodynamic (PK/PD) features of PMB is limited, and there remains a lack of consensus on the most appropriate dosing regimen for PMB.[8] The international consensus guidelines for the optimal use of the polymyxins suggested that an average steady-state plasma concentration of PMB of 2–4 mg/L may be acceptable in terms of toxicity;[9] however, there are no reports of large-scale detection of PMB concentrations in clinical practice. The current recommended loading dose of PMB is 2.0–2.5mg/kg (equivalent to 20,000–25,000 IU/kg), with a maintenance dose of 1.25–1.5 mg/kg every 12 h, for patients with severe infections;[9] however, many patients did not get the guideline recommended dose of PMB in clinical treatment.

There is limited research on the clinical and microbiological efficacy, mortality, and safety of PMB. A retrospective study of 40 patients found that early use of PMB reduces mortality resulting from CRKP bloodstream infection.[10] Another investigation reported that a sizable proportion of patients with CR-GNB infection treated with high-dose PMB developed acute kidney injury (AKI), suggesting that the potential benefits of treatment must be weighed against an increased risk of AKI.[11] A retrospective analysis of 39 patients with sepsis also showed that PMB could be an effective treatment option for patients with severe infection with extensively drug-resistant Gram-negative bacteria;[12] however, the roles of patient characteristics, different CR-GNB infections, and infection sites, as well as details of PMB use, such as presence or absence of loading dose, and the efficacy of PMB in combination regimens, are poorly-investigated. In this study, we reviewed clinical data from 268 patients with CR-GNB infections treated with PMB-based regimens to explore the efficacy and safety of PMB-based regimens and the factors influencing these.

# Patients and Methods

## Ethics

The Ethics Committees of the Second Xiangya Hospital of Central South University approved the study protocol (LYF-2020021). The study was conducted according to the ethical standards of the Helsinki Declaration (1964). Patients gave their written informed consent to have their data included in this study.

## Patients

This retrospective study involved patients admitted to the Second Xiangya Hospital of Central South University (a 3500-bed general hospital) from 1st June 2018 to 30th April 2020. The inclusion criteria were as follows: (1) CR-GNB infection confirmed by bacterial culture and drug sensitivity test; (2) a history of medication with PMB (Shanghai Number 1 Biochemical & Pharmaceuticals, Shanghai, China) for treatment ≥ 3 days; and (3) underwent infection index (such as white blood cell count, c-reactive protein, Procalcitonin, erythrocyte sedimentation rate) assessment at the end of the treatment course. The exclusion criteria were as follows: (1) < 18 years old or pregnant; (2) no CR-GNB was detected during the treatment; (3) the treatment efficacy could not be evaluated.

## Clinical Data Collection

Patients enrolled according to the inclusion and exclusion criteria were followed up until discharge or death. Data extracted from patient inpatient charts and electronic records included demographics, such as age, sex, baseline comorbidities, type of infections, type of CR-GNB, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, details of PMB use (loading dose, daily dose based on total body weight, duration of treatment, and cumulative PMB dose), concomitant infections and antibiotic use, and probable adverse effects of PMB.

## Outcomes and Definitions

Indicators used to evaluate the efficacy of PMB in this study included clinical treatment efficacy, microbiological efficacy (bacterial clearance after 7-days and at the end of PMB treatment), and in-hospital all-cause mortality.

Clinical efficacy was defined as meeting all of the following conditions: being hemodynamically stable without the need for vasopressors; body temperature <37.5°C within 72 hours; improvements of microbiologic and parameters including APACHE II score, biochemistry indicators of infection (White blood cell count in adults ≤ $10^9$, C-reactive protein ≤ 10mg/L, Procalcitonin < 0.05ng/mL, erythrocyte sedimentation rate < 15mm/h), twice negative culture results at least, control of infection symptoms and clinician documented improvements at the end of treatment.[13,14] Clinical treatment failure was defined as patients who failed to meet any clinical efficacy criteria, stopped treatment with low blood pressure, or died in hospital.[14]

Microbiological efficacy was defined as the clearance of CR-GNB within 7 days, or within the total course of PMB, demonstrated by negative microbial culture results of samples from the same site after PMB treatment.

In-hospital all-cause mortality was defined as all-cause death or stopped treatments with blood pressure less than 90/60 mmHg under pressure medication maintenance, who were transitioned to hospice.

Adverse reactions (ADRs) to PMB were defined as harmful reactions unrelated to the purpose of treatment that emerged after PMB use, including nerve-muscle blockade, nephrotoxicity, and skin pigmentation. Nephrotoxicity was evaluated based on the risk, injury, failure, or loss of kidney function and end-stage kidney disease criteria (RIFLE).[15]

## Microbiology

Laboratory physicians tested drug sensitivity by the broth microdilution method using analytical instruments. Bacteria isolates were identified using VITEK®2 system (bioMérieux, Marcy-l'Étoile, France). Based on the Clinical and Laboratory Standards Institute recommendations, the minimum inhibitory concentration (MIC) values were also determined using a VITEK®2 system (bioMérieux, Marcy-l'Étoile, France). Carbapenem resistance was defined as MIC value for imipenem and meropenem ≥ 4 mg/L. Meanwhile, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, v10.0, 2020), "MIC >2 mg/L" represented bacterial resistance to PMB.[16] "MIC ≤2 mg/L" represented the sensitivity of *Enterobacteriaceae* and *Acinetobacter* to tigecycline, and "MIC ≥8 mg/L" represented tigecycline resistance according to US Food and Drug Administration (FDA) standards (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021821s026s031lbl.pdf). Since no TGC MIC breakpoint was available for *Acinetobacter* spp. We used the same breakpoints defined by the FDA for *Enterobacteriaceae* for the interpretation of susceptibility testing results obtained for *A. baumannii*.

## Statistical Processing

Statistical analyses were undertaken using SPSS v21.0 (IBM, Armonk, NY, USA). Quantitative data are represented by median and interquartile range or mean ± standard deviation. For comparisons between two groups, *t*-tests were used for normally distributed data, and Mann-Whitney non-parametric tests were used for non-normally distributed data. Categorical data are expressed as numbers of cases and percentages and were analyzed by chi-square test. Multivariate logistic regression was used to assess potential independent predictors of PMB efficacy. Factors with p-values < 0.1 by univariate analysis were entered into the multivariate logistic analysis. $P < 0.05$ was considered significant. Patients with lean or normal body weight are calculated according to their actual body weight, and overweight patients are calculated according to their adjusted body weight. Adjusted body weight was calculated as ideal body weight + 0.4 (actual body weight - ideal body weight).[17]

# Results

## Clinical Characteristics

A total of 268 patients with CR-GNB infection were enrolled; general patient information is listed in Table 1. The median age of patients was 57.5 years (range, 46–71 years). One hundred eighty-two patients (67.91%) were admitted to the ICU, and 144 cases (53.73%) were maintained with vasoactive drugs. Patient comorbidities were as follows: respiratory diseases, 226 cases (84.33%); cardiovascular and cerebrovascular diseases, 169 cases (63.06%); kidney-related diseases, 120 cases (44.78%); hepatobiliary system diseases, 67 cases (25.00%); gastrointestinal and pancreatic disease, 52 cases (19.40%); malnutrition, 34 cases (12.69%); and diabetes, 44 cases (16.42%). In addition, there were 254 cases (94.78%) had respiratory tract infection, 84

**Table 1** Demographic and Clinical Characteristics of the Study Cohort

| Clinical Features | All Patients (N=268) |
|---|---|
| Sex (male) | 192 (71.64%) |
| Age (years) | 57.5 (46–71) |
| Mechanical ventilation | 189 (70.52%) |
| Vasoactive agents | 144 (53.73%) |
| Admission to ICU | 182 (67.91%) |
| APACHE II | 19.94 (13.17–25.91) |
| Comorbidities | |
| Cardiovascular and cerebrovascular diseases | 169 (63.06%) |
| Respiratory disease | 226 (84.33%) |
| Kidney disease | 120 (44.78%) |
| Liver disease | 67 (25.00%) |
| Diseases of digestive system | 52 (19.40%) |
| Nutritional disease | 34 (12.69%) |
| Diabetes mellitus | 44 (16.42%) |
| Infection site | |
| Respiratory tract | 254 (94.78%) |
| Blood | 84 (31.34%) |
| Urinary system | 29 (10.82%) |
| Intracranial | 17 (6.34%) |
| Digestive tract | 30 (11.19%) |
| Skin and soft tissue | 21 (7.84%) |
| Pathogenic bacteria (CR-GNB) | |
| *Acinetobacter baumannii* | 185 (69.03%) |
| *Klebsiella pneumoniae* | 116 (43.28%) |
| *Pseudomonas aeruginosa* | 64 (23.88%) |
| *E. coli or E. cloacae* | 8 (2.99%) |
| Multiple site infection | 119 (44.40%) |
| Number of patients with CR-GNB >1 | 65 (24.30%) |
| Antimicrobial susceptibility | |
| Tigecycline MIC >2 (mg/L) | 229/278 (82.37%) |
| Polymyxin MIC >2 (mg/L) | 9/370 (2.43%) |
| Previous carbapenem treatment time (days) | 5.00 (0.45–11.36) |
| Previous tigecycline treatment time (days) | 0.67 (0.00–7.27) |
| Previous use of carbapenem | 177 (66.04%) |
| Previous use of tigecycline FG | 109 (40.70%) |

**Notes**: Vasoactive drugs include norepinephrine, dopamine, epinephrine, isoproterenol, phentolamine, and nitroglycerin; the time of previous carbapenems and tigecycline use was defined as the time before PMB was used in this hospitalization.

**Abbreviations**: ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; CR-GNB, Carbapenem-resistant Gram-negative Bacteria; MIC, minimum inhibitory concentration.

cases (31.34%) bloodstream infection, 29 (10.82%) cases of urinary system infection, 17 (6.34%) cases of central nervous system infection, 30 cases (11.19%) of abdominal infection, and 21 cases (7.84%) of skin and soft tissue infection.

## Pathogenic Examination

Bacterial culture and drug sensitivity tests confirmed that 268 patients were infected by CR-GNB, and a total of 373 CR-GNB samples were isolated. Among isolated strains were 185 of CRAB (49.60%), 116 of CRKP (31.10%), 64 of CRPA (17.16%), and 8 of carbapenem-resistant *E. coli* and *E. cloacae* (2.14%). Drug sensitivity analysis results showed that the tigecycline MICs of 229 strains (82.37%) were > 2 mg/L, while the PMB MICs of 9 strains (2.43%) were > 2 mg/L. The

numbers of patients with multi-site infection and multi-CR-GNB infection were 119 (44.40%) and 65 (24.30%), respectively (Table 1).

## Medications and Outcomes

Among the 268 patients, 177 cases (66.04%) had previously used carbapenems, for a median duration of 5 days and 109 cases (40.70%) had previously used tigecycline, for a median duration of 0.67 days. Further, of the 268 patients treated with PMB, PMB treatment was combined with tigecycline, carbapenems, β-lactams, glycopeptides, or other drugs (such as aminoglycosides and quinolones) in 84 (31.34%), 75 (27.99%), 90 (33.58%), 44 (16.24%), and 41 (15.30%) cases, respectively. A PMB loading dose was used in 110/268 patients (41.04%); median loading dose was 1.01 mg/kg, while 59 patients (22.01%) received a loading dose ≥ 2.0 mg/kg. Maintenance dose was calculated based on body weight; median maintenance dose was 0.85 mg/kg, and 39 cases (14.55%) had a maintenance dose > 1.25 mg/kg. The median cumulative dose was 925.57 mg, and the median duration of treatment was 9.67 days. After the course of PMB treatment, 136 strains (39.42%) were cleared. Ninety-six strains (29.36%) were cleared within seven days. In 98 cases (36.57%), clearance was clinically effective, and the median time for bacterial clearance was 6.67 days. All-cause mortality (including in-hospital deaths and critically ill patients who stopped treatment and were discharged) was 36.19% (97 cases). The median duration of hospitalization was 36 days (Table 2).

## Evaluation Results of Factors Associated with PMB Efficacy

### Clinical Efficacy

According to our definition of PMB clinical efficacy, there were 98 patients in which treatment was clinically effective and 170 in which it was clinically ineffective; hence, the effective clinical rate was 36.57%. Risk factors for poor clinical efficacy after PMB treatment, determined by analysis of 268 patients, are listed in Table 3. The results of the univariate analysis showed that older age, treatment with vasoactive agents, mechanical ventilation use, admission to ICU, comorbid respiratory disease, comorbid liver disease, bloodstream infection, different CR-GNB infection, multiple site infections, more than one CR-GNB infection, treatment duration, cumulative dose of PMB, and regimen combining carbapenems and PMB were risk factors for clinical efficacy of PMB treatment ($P < 0.05$). The portion of CRAB in the clinical success group is higher in the failure group, while the portion of CRKP in the clinical success group is lower in the failure group (p=0.013, p=0.04). Moreover, binary logistic regression showed that vasoactive agent and mechanical ventilation use, admission to ICU, and respiratory disease were independent risk factors for poor clinical efficacy of PMB treatment (all $P < 0.05$); Loading dose ≥ 2.0 mg/kg of PMB was an independent protective factor for poor clinical efficacy ($P < 0.05$).

### Microbiological Efficacy

To identify factors influencing the total bacterial clearance rate of PMB, we compared the characteristics and regimens of patients with CR-GNB that was cleared with those of patients whose infection was not cleared after PMB treatment (Table 4). After the treatment with PMB, 136 CR-GNB strains were cleared and residual CR-GNB was detected in 209 patients.

Univariate analysis results showed that urinary tract infection, different CR-GNB infection, preemptive therapy, PMB use delay days, treatment duration, and cumulative dose of PMB were related to CR-GNB clearance after PMB treatment ($P < 0.05$). The portion of CRAB in the microbiological cleaned group is lower in the microbiological failure groups, while the portion of CRPA in the microbiological cleaned group is lower in the microbiological failure clean group (p=0.008, p=0.012, respectively). In addition, binary logistic regression results also confirmed that urinary tract infection and CRAB infection were independent risk factors that could influence bacterial clearance by PMB treatment.

We also performed the univariate analysis and binary logistic regression analyses to identify factors influencing the PMB 7-day bacterial clearance rate (Table S1). Binary logistic regression results showed that nutritional diseases, urinary tract infection, CRAB infection, and preemptive therapy were related to the 7-day bacterial clearance rate of PMB ($P<0.05$).

**Table 2** Regimens, Adverse Reactions and Outcomes

| Treatment | Value |
|---|---|
| Preemptive therapy[a] | 207 (77.20%) |
| Loading dose% | 110 (41.04%) |
| Loading dose≥2.0mg/kg | 59 (22.01%) |
| Maintenance dose ≥1.25mg/kg q12h | 39 (14.55%) |
| Loading dose (mg/kg) | 1.01 (0.84–1.69) |
| Maintenance dose (mg/kg q12h) | 0.85 (0.82–1.00) |
| Cumulative dose (mg) | 928.57 (552.50–1361.11) |
| Treatment duration time (days) | 9.67 (6.12–13.81) |
| Combination of drugs* | |
| Tigecycline | 84 (31.34%) |
| Carbapenems | 75 (27.99%) |
| β-lactams | 90 (33.58%) |
| Glycopeptides | 44 (16.42%) |
| Others | 41 (15.30%) |
| Efficacy | |
| Clinical effectiveness | 98/268 (36.57%) |
| 7-day clearance | 96/326 (29.45%) |
| Course of treatment clearance | 136/345 (39.42%) |
| Bacteria removal time (days) | 6.67 (4.17–10.92) |
| All-cause mortality[b] | 91 (33.96%) |
| Survival time (days)[c] | 10 (6.0–20.5) |
| Length of hospital stay (days) | 36.00 (21.80–67.00) |
| Adverse reactions | 56 (19.58%) |
| Nephrotoxicity (AKI)[c] | 22 (8.21%) |
| Skin pigmentation | 20 (6.99%) |
| Drowsiness | 4 (1.49%) |
| Neuromuscular block | 3 (1.12%) |
| Drug-induced | 2 (0.75%) |
| Drug eruption | 1 (0.37%) |
| Itching | 1 (0.37%) |
| Feel nausea | 1 (0.37%) |
| Hepatotoxicity | 1 (0.37%) |
| Insomnia | 1 (0.37%) |

**Notes**: [a]Preemptive therapy defined as the use of PMB before or within two days of bacterial culture and drug sensitivity results; [b]All-cause mortality include in-hospital deaths and patients discharged from hospital in critical condition with low blood pressure after abandonment of treatment; [c]Survival time defined as the time from the beginning of PMB to the end of in-hospital death or abandonment of treatment; [c]Nephrotoxicity (AKI): Creatinine was increased by 2 times after treatment compared with baseline (before treatment). *There were two or more drugs combined with PMB.

**Abbreviations**: PMB, Polymyxin B; ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; CR-GNB, Carbapenem-resistant Gram-negative Bacteria; MIC, minimum inhibitory concentration.

## Mortality

After evaluating the outcomes of patients treated with PMB, we analyzed the risk factors related to all-cause mortality. According to our definition, there were 177 surviving and 91 dead patients, with an all-cause mortality rate of 33.96%. Patients who died were older and more likely to have undergone mechanical ventilation, been treated with vasoactive agents, and been admitted to the ICU ($P < 0.05$) (Table 5). Further, patients who died had more underlying diseases, such as liver disease ($P = 0.006$). The dead group had 41.8% CR-GNB BSI compared with 26.0% in survivors (P=0.008), and *Escherichia coli* or *Enterobacter cloacae* infections were more common in patients who died (7.7% vs.1.7%, $P = 0.003$). Furthermore, multiple site infections were more frequent among patients that died (56.0% vs 38.4%).

**Table 3** Analysis of the Risk Factors of Poor Clinical Efficacy After PMB Treatment

| Risk Factors | Effective | Invalid | P value | Binary Logistic Regression | | | |
|---|---|---|---|---|---|---|---|
| | (N = 98) | (N = 170) | | B | OR | 95% CI | P value |
| Sex (male) | 71 (72.45%) | 121 (71.18%) | 0.824 | | | | |
| Age (years) | 54 (40.75–62.50) | 61 (47.75–75.00) | **0.004** | 0.004 | 1.004 | 0.986–1.023 | 0.666 |
| Mechanical ventilation | 45 (45.92%) | 144 (84.71%) | **0.000** | **1.867** | **6.472** | **2.505–16.719** | **0.000** |
| Vasoactive agents | 28 (28.57%) | 116 (68.24%) | **0.000** | **1.054** | **2.868** | **1.386–5.936** | **0.005** |
| Admission to ICU | 57 (58.16%) | 125 (73.53%) | **0.009** | **1.206** | **3.339** | **1.249–8.927** | **0.016** |
| APACHE II score | 20.0 (12.5–24.0) | 20.0 (13.0–28.0) | 0.215 | | | | |
| Comorbidities | | | | | | | |
| Cardiovascular and cerebrovascular diseases | 60 (61.22%) | 109 (64.12%) | 0.636 | | | | |
| Respiratory disease | 76 (77.55%) | 150 (88.24%) | **0.020** | **1.024** | **2.783** | **1.165–6.646** | **0.021** |
| Kidney disease | 46 (46.94%) | 74 (43.53%) | 0.589 | | | | |
| Liver disease | 16 (16.33%) | 51 (30.00%) | **0.013** | 0.681 | 1.976 | 0.892–4.376 | 0.093 |
| Diseases of digestive system | 24 (24.49%) | 28 (16.47%) | 0.110 | | | | |
| Nutritional disease | 15 (15.31%) | 19 (11.18%) | 0.328 | | | | |
| Diabetes mellitus | 12 (12.24%) | 32 (18.82%) | 0.161 | | | | |
| Infection site | | | | | | | |
| Respiratory tract | 91 (92.86%) | 163 (95.88%) | 0.284 | | | | |
| Blood | 21 (21.43%) | 63 (37.06%) | **0.008** | 0.393 | 1.482 | 0.649–3.381 | 0.350 |
| Urinary system | 12 (12.24%) | 17 (10.00%) | 0.569 | | | | |
| Intracranial | 11 (11.22%) | 6 (3.53%) | **0.013** | −0.028 | 0.972 | 0.2289–4.131 | 0.970 |
| Digestive tract | 10 (10.20%) | 20 (11.76%) | 0.696 | | | | |
| Skin and soft tissue | 6 (6.12%) | 15 (8.82%) | 0.428 | | | | |
| Pathogenic bacteria (CR-GNB) | | | | | | | |
| *Acinetobacter baumannii* | 57 (58.16%) | 121 (71.18%) | **0.030** | 0.130 | 1.139 | 0.368–3.528 | 0.822 |
| *Klebsiella pneumoniae* | 41 (41.83%) | 51 (30.00%) | **0.049** | −0.613 | 0.541 | 0.174–1.684 | 0.289 |
| *Pseudomonas aeruginosa* | 19 (19.38%) | 50 (29.41%) | 0.071 | 0.287 | 1.332 | 0.464–3.826 | 0.594 |
| *E. coli or E. cloacae* | 1 (1.02%) | 9 (5.29%) | 0.149 | | | | |
| Multiple site infection | 31 (31.63%) | 88 (51.76%) | **0.001** | 0.446 | 1.562 | 0.742–3.292 | 0.240 |
| Number of CR-GNBs | 1 (1.00–1.00) | 1 (1.00–2.00) | **0.013** | 0.653 | 1.922 | 0.612–6.033 | 0.263 |
| Number of patients with CR-GNB>1 | 16 (16.30%) | 49 (28.80%) | **0.022** | 1.100 | 3.005 | 0.826–10.932 | 0.095 |
| Antimicrobial Susceptibility | | | | | | | |
| Tigecycline MIC >2 (mg/L) | 65 (66.33%) | 99 (58.24%) | 0.497 | | | | |
| Polymyxin MIC >2 (mg/L) | 5 (5.10%) | 3 (1.80%) | 0.252 | | | | |
| Previous use of carbapenem | 67 (68.40%) | 110 (64.70%) | 0.542 | | | | |
| Previous use of tigecycline | 36 (39.90%) | 73 (42.90%) | 0.319 | | | | |
| Preemptive therapy | 74 (75.50%) | 133 (78.20%) | 0.608 | | | | |
| Delay days of PMB use (days) | 0 (0–2.25) | 0 (−0.25–2) | 0.397 | | | | |
| Loading dose≥2.0mg/kg | 27 (27.55%) | 32 (18.82%) | 0.097 | **−0.907** | **0.404** | **0.182–0.8895** | **0.026** |
| Maintenance dose≥1.25mg/kg q12h | 14 (14.29%) | 25 (14.71%) | 0.925 | | | | |
| Use loading dose | 41 (41.84%) | 69 (40.58%) | 0.841 | | | | |
| Maintenance dose (mg/kg q12h) | 0.83 (0.77–1.00) | 0.88 (0.83–1.00) | 0.147 | | | | |
| Loading dose (mg/kg) | 1 (0.83–1.80) | 1.01 (0.83–1.67) | 0.802 | | | | |
| Treatment duration time (days) | 11 (7.00–16.00) | 9 (5.50–13.00) | **0.002** | −0.075 | 0.927 | 0.832–1.033 | 0.171 |

(*Continued*)

**Table 3** (Continued).

| Risk Factors | Effective | Invalid | P value | Binary Logistic Regression | | | |
|---|---|---|---|---|---|---|---|
| | (N = 98) | (N = 170) | | B | OR | 95% CI | P value |
| Cumulative dose (mg) | 1050 (600.00–1512.50) | 875 (500–1300) | **0.016** | 0.000 | 1.000 | 0.999–1.001 | 0.433 |
| Combination of drugs | | | | | | | |
| Tigecycline | 26 (26.53%) | 58 (34.12%) | 0.197 | | | | |
| Carbapenems | 36 (36.73%) | 39 (22.94%) | **0.015** | −0.040 | 0.960 | 0.475–1.943 | 0.911 |
| β-lactams | 36 (36.73%) | 54 (31.76%) | 0.407 | | | | |
| Glycopeptides | 13 (13.27%) | 31 (18.24%) | 0.290 | | | | |
| Others | 13 (13.27%) | 28 (16.47%) | 0.483 | | | | |

**Notes**: The measurement data are expressed by median and quartile, *t*-test is used to accord with normal distribution. Non-parametrictric test is used to disaccord with normal distribution, and counting data is expressed by cases and percentage, chi-square test is used. The parameters included in Binary logistic regression were those with P < 0.1 in univariate test. Bold font indicates data with significant differences. B indicates regression coefficient.

**Abbreviations**: PMB, Polymyxin B; ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; CR-GNB, Carbapenem-resistant Gram-negative Bacteria; MIC, minimum inhibitory concentration.

Regarding PMB treatment, maintenance dose (mg), treatment duration, cumulative dose (mg), and combination of drugs, such as tigecycline and carbapenems, differed significantly between the patients who survived and those who did not ($P < 0.05$). Binary logistic regression analysis demonstrated that mechanical ventilation, vasoactive agents, and having liver disease, as well as *E. coli or E. cloacae* infection, were independent factors associated with all-cause mortality ($P < 0.05$).

### Adverse Drug Reactions

Overall, 56 patients (19.58%) experienced ADRs to PMB treatment during hospitalization. The most prevalent ADR was nephrotoxicity (AKI) (28 cases; 8.21%), followed by skin hyperpigmentation (20 cases; 6.99%), drowsiness (4 cases; 1.49%), and neuromuscular block (3 cases; 1.12%). Moreover, some rare ADRs occurred, including drug-induced fever, drug-induced eruption, pruritus, nausea, general weakness, lethargy, and hepatotoxicity (Table 2).

## Discussion

CR-GNB, especially CRE infection, has been flagged as an urgent threat by the World Health Organization.[2] In China, CR-GNB infections have been treated with PMB since 2018. In this study, we aimed to explore the efficacy and safety of PMB-based regimens and factors influencing their efficacy. We enrolled 268 patients infected with 373 CR-GNB strains and treated them using PMB-based regimens. After treatment, the overall clinical effective rate was 36.57%, the bacterial clearance rate of PMB was 39.42%, the 7-day bacterial clearance rate was 29.36%, and the all-cause mortality rate was 33.96%. Binary logistic regression analysis showed that use of vasoactive agents and mechanical ventilation, admission to ICU, and having respiratory disease were independent risk factors for poor clinical efficacy after PMB treatment; PMB loading dose ≥ 2.0 mg/kg was an independent protective factor for poor clinical efficacy after PMB treatment. Further, urinary tract infection and CRAB infection were independent risk factors associated with bacterial clearance of PMB treatment. Moreover, mechanical ventilation, vasoactive agents, having liver disease, and *E. coli or E. cloacae* infection were independent factors associated with all-cause mortality.

The increasing prevalence of infections caused by CR-GNB has led to fewer effective antibiotics, and PMB has been used as a first-line agent to treat infections caused by these pathogens;[18] however, information about its pharmacokinetics, efficacy, and safety profile are scarce.[18] A previous study investigated the efficacy of PMB and found a treatment success rate of 25.1%,[19] which is lower than that reported here; however, the mortality rate described in the previous study (32.8%) is similar to our findings.[19] We also investigated potential risk factors for treatment failure and found that vasoactive agents and mechanical ventilation, admission to ICU, and respiratory disease were independent risk factors for clinical efficacy following PMB treatment. Further, patients benefited from a PMB loading dose > 2.0 mg/kg. Recent

**Table 4** Analysis of Risk Factors of CR-GNB Clearance Failure After PMB Treatment

| Risk Factors | Success N=136 | Failure N=209 | P | Binary Logistic Regression | | | |
|---|---|---|---|---|---|---|---|
| | | | | B | OR | 95% CI | P |
| Sex (male) | 96 (70.59%) | 148 (70.80%) | 0.964 | | | | |
| Age (years) | 56 (46.25–70.00) | 58 (48–71) | 0.460 | | | | |
| Mechanical ventilation | 94 (69.12%) | 153 (73.20%) | 0.411 | | | | |
| Vasoactive agents | 63 (46.32%) | 115 (55.00%) | 0.114 | | | | |
| Admission to ICU | 94 (69.12%) | 152 (72.70%) | 0.469 | | | | |
| APACHE II score | 20 (14.00–23.50) | 20 (15–26) | 0.387 | | | | |
| Primary disease | | | | | | | |
| Cardiovascular and cerebrovascular diseases | 84 (61.76%) | 138 (66.00%) | 0.419 | | | | |
| Respiratory diseases | 110 (80.88%) | 175 (83.70%) | 0.495 | | | | |
| Kidney disease | 56 (41.17%) | 102 (48.80%) | 0.165 | | | | |
| Liver disease | 33 (24.26%) | 53 (25.40%) | 0.818 | | | | |
| Diseases of digestive system | 29 (21.32%) | 42 (20.10%) | 0.783 | | | | |
| Nutritional diseases | 27 (19.85%) | 26 (12.40%) | 0.062 | −0.576 | 0.562 | 0.299–1.057 | 0.074 |
| Diabetes mellitus | 22 (16.18%) | 41 (19.60%) | 0.419 | | | | |
| Infection site | | | | | | | |
| Respiratory tract | 120 (88.23%) | 188 (90.00%) | 0.615 | | | | |
| Blood | 33 (24.26%) | 52 (24.90%) | 0.897 | | | | |
| Urinary system | 21 (15.44%) | 16 (7.70%) | **0.022** | **−0.956** | **0.384** | **0.180–0.821** | **0.014** |
| Intracranial | 11 (8.09%) | 10 (4.80%) | 0.210 | | | | |
| Digestive tract | 15 (11.03%) | 23 (11.00%) | 0.994 | | | | |
| Wound | 6 (4.41%) | 9 (4.30%) | 0.963 | | | | |
| Pathogenic bacteria (CR-GNB) | | | | | | | |
| *Acinetobacter baumannii* | 79 (58.08%) | 91 (43.50%) | **0.008** | **−0.597** | **0.551** | **0.323–0.938** | **0.028** |
| *Klebsiella pneumoniae* | 39 (28.70%) | 70 (33.50%) | 0.347 | | | | |
| *Pseudomonas aeruginosa* | 15 (11.00%) | 45 (21.50%) | **0.012** | 0.600 | 1.822 | 0.866–3.836 | 0.114 |
| *E. coli or E. cloacae* | 3 (2.20%) | 3 (1.40%) | 0.684 | | | | |
| Multiple site infection | 72 (52.94%) | 110 (52.88%) | 0.955 | | | | |
| Antimicrobial susceptibility | | | | | | | |
| Tigecycline MIC >2 (mg/L) | 89 (65.44%) | 120 (57.69%) | 0.787 | | | | |
| Polymyxin MIC >2 (mg/L) | 2 (1.50%) | 7 (3.40%) | 0.456 | | | | |
| Previous carbapenem treatment time (days) | 3 (0–12) | 5 (0–12) | 0.232 | | | | |
| Previous tigecycline treatment time (days) | 0 (0–7) | 0 (0–7) | 0.145 | | | | |
| Previous use of carbapenem | 84 (61.80%) | 142 (67.90%) | 0.238 | | | | |
| Previous use of tigecycline | 50 (36.80%) | 99 (47.40%) | 0.052 | 0.313 | 1.368 | 0.844–2.218 | 0.204 |
| Preemptive therapy | 114 (83.80%) | 148 (70.80%) | **0.006** | −0.294 | 0.745 | 0.328–1.692 | 0.482 |
| Delay days of PMB use (days) | 0 (0–1) | 1 (0–4) | **0.015** | 0.058 | 1.060 | 0.983–1.143 | 0.127 |
| Loading dose≥2.0mg/kg | 31 (22.79%) | 48 (23.00%) | 0.970 | | | | |
| Maintenance dose≥1.25mg/kg q12h | 15 (11.00%) | 27 (12.90%) | 0.600 | | | | |
| Use loading dose | 66 (48.53%) | 88 (42.10%) | 0.241 | | | | |
| Maintenance dose (mg/kg q12h) | 0.83 (0.83–1.00) | 0.83 (0.83–1.00) | 0.833 | | | | |
| Loading dose (mg/kg) | 1.20 (0.83–1.67) | 1 (0.83–1.67) | 0.402 | | | | |
| Cumulative dose (mg) | 1150 (700–1550) | 950 (550–1350) | **0.015** | 0.000 | 1.000 | 1.000–1.001 | 0.296 |
| Treatment duration time (days) | 12 (7.50–15.50) | 10 (6–14) | **0.006** | −0.068 | 0.935 | 0.873–1.000 | 0.051 |
| Combination of drugs | | | | | | | |
| Tigecycline | 44 (32.35%) | 76 (36.40%) | 0.445 | | | | |
| Carbapenems | 38 (27.94%) | 58 (27.80%) | 0.969 | | | | |
| β-lactams | 49 (36.03%) | 67 (32.10%) | 0.445 | | | | |
| Glycopeptides | 21 (15.44%) | 32 (15.30%) | 0.974 | | | | |
| Others | 15 (11.03%) | 29 (13.90%) | 0.439 | | | | |

**Notes**: Bold font indicates data with significant differences. B indicates regression coefficient.

**Abbreviations**: PMB, Polymyxin B; ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; CR-GNB, Carbapenem-resistant Gram-negative Bacteria; MIC, minimum inhibitory concentration.

**Table 5** Analysis of Risk Factors of All-Cause Mortality After PMB Treatment

| Parameters | Survival | Death | P | Binary Logistic Regression | | | |
|---|---|---|---|---|---|---|---|
| | (N = 177) | (N = 91) | | B | OR | 95% CI | P |
| Sex (male) | 132 (74.6%) | 60 (65.9%) | 0.137 | | | | |
| Age (years) | 55 (42–65) | 65 (49–76) | **0.001** | 0.009 | 1.009 | 0.990–1.028 | 0.343 |
| Mechanical ventilation | 102 (57.6%) | 87 (95.6%) | **0.000** | **1.901** | **6.691** | **1.838–24.354** | **0.004** |
| Vasoactive agents | 70 (39.5%) | 74 (81.3%) | **0.000** | **1.174** | **3.235** | **1.519–6.891** | **0.002** |
| Admission to ICU | 109 (61.6%) | 73 (80.2%) | **0.002** | 0.293 | 1.341 | 0.535–3.360 | 0.531 |
| APACHE II score | 19 (13.0–25.5) | 20 (14.0–27.5) | 0.232 | | | | |
| Primary diseases | | | | | | | |
| Cardiovascular and cerebrovascular diseases | 109 (61.6%) | 60 (65.9%) | 0.485 | | | | |
| Respiratory diseases | 144 (81.4%) | 82 (90.1%) | 0.062 | 1.014 | 2.757 | 0.952–7.981 | 0.062 |
| Kidney disease | 80 (45.2%) | 40 (44.0%) | 0.847 | | | | |
| Liver disease | 35 (19.8%) | 32 (35.2%) | **0.006** | **0.946** | **2.575** | **1.190–5.571** | **0.016** |
| Diseases of digestive system | 35 (19.8%) | 17 (18.7%) | 0.830 | | | | |
| Nutritional diseases | 25 (14.1%) | 9 (9.9%) | 0.324 | | | | |
| DM | 24 (13.6%) | 20 (22.0%) | 0.078 | 0.196 | 1.216 | 0.509–2.908 | 0.660 |
| Infection site | | | | | | | |
| Respiratory tract | 167 (94.4%) | 87 (95.6%) | 0.662 | | | | |
| Blood | 46 (26.0%) | 38 (41.8%) | **0.008** | 0.042 | 1.043 | 0.458–2.374 | 0.921 |
| Urinary system | 21 (11.9%) | 8 (8.8%) | 0.443 | | | | |
| Intracranial | 16 (9.0%) | 1 (5.9%) | **0.024** | −1.344 | 0.261 | 0.024–2.807 | 0.268 |
| Digestive tract | 17 (9.6%) | 13 (14.3%) | 0.250 | | | | |
| Wound | 16 (9.0%) | 5 (5.5%) | 0.306 | | | | |
| Pathogenic bacteria | | | | | | | |
| *Acinetobacter baumannii* | 114 (64.4%) | 64 (70.3%) | 0.331 | | | | |
| *Klebsiella pneumoniae* | 67 (37.9%) | 25 (27.5%) | 0.090 | −0.182 | 0.834 | 0.411–1.692 | 0.614 |
| *Pseudomonas aeruginosa* | 51 (28.8%) | 18 (19.8%) | 0.109 | | | | |
| *E. coli or E. cloacae* | 3 (1.7%) | 7 (7.7%) | **0.014** | **2.388** | **10.889** | **1.446–82.015** | **0.020** |
| Multiple site infection | 68 (38.4%) | 51 (56.0%) | **0.006** | 0.412 | 1.509 | 0.700–3.253 | 0.294 |
| Number of patients with CR-GNB>1 | 44 (24.9%) | 21 (23.1%) | 0.747 | | | | |
| Antimicrobial susceptibility | | | | | | | |
| Tigecycline MIC >2 (mg/L) | 107 (84.9%) | 57 (80.3%) | 0.403 | | | | |
| Polymyxin MIC >2 (mg/L) | 6 (3.4%) | 2 (2.7%) | 0.602 | | | | |
| Previous carbapenem treatment time (days) | 5 (0–12) | 5 (0–11) | 0.664 | | | | |
| Previous tigecycline treatment time (days) | 0 (0–7.5) | 0 (0–7.0) | 0.433 | | | | |
| Previous use of carbapenem | 117 (66.1%) | 60 (65.9%) | 0.978 | | | | |
| Previous use of tigecycline | 75 (42.4%) | 34 (37.4%) | 0.429 | | | | |
| Preemptive therapy | 140 (79.1%) | 67 (73.6%) | 0.312 | | | | |
| Delay days of PMB use (days) | 0 (0–2) | 1 (0–3) | 0.608 | | | | |
| Loading dose≥2.0mg/kg | 35 (19.8%) | 24 (26.4%) | 0.217 | | | | |
| Maintenance dose≥1.25mg/kg q12h | 27 (15.3%) | 12 (13.2%) | 0.649 | | | | |
| Use loading dose | 69 (39.0%) | 41 (45.1%) | 0.339 | | | | |
| Loading dose (mg) | 50 (50–100) | 50 (50–100) | 0.113 | | | | |
| Maintenance dose q12h (mg) | 50 (50–50) | 50 (50–50) | **0.006** | 0.027 | 1.027 | 0.970–1.088 | 0.353 |
| Maintenance dose (mg/kg q12h) | 0.83 (0.80–1) | 0.89 (0.83–1.0) | 0.279 | | | | |
| Loading dose (mg/kg) | 1 (0.83–1.67) | 1 (0.83–1.72) | 0.312 | | | | |
| Treatment duration time (days) | 11 (7–15) | 8.5 (4–12) | **0.000** | 0.132 | 1.141 | 0.874–1.489 | 0.331 |
| Cumulative dose (mg) | 1015 (600–1500) | 800 (400–1150) | **0.002** | −0.002 | 0.998 | 0.995–1.001 | 0.139 |
| Combination of drugs | | | | | | | |
| Tigecycline | 48 (27.1%) | 38 (39.6%) | **0.038** | 0.463 | 1.590 | 0.804–3.143 | 0.183 |
| Carbapenems | 60 (33.9%) | 15 (16.5%) | **0.003** | −0.425 | 0.654 | 0.298–1.436 | 0.289 |

(*Continued*)

**Table 5** (Continued).

| Parameters | Survival (N = 177) | Death (N = 91) | P | Binary Logistic Regression | | | |
|---|---|---|---|---|---|---|---|
| | | | | B | OR | 95% CI | P |
| β-lactams | 63 (35.6%) | 27 (29.7%) | 0.331 | | | | |
| Glycopeptides | 29 (16.4%) | 15 (16.5%) | 0.983 | | | | |
| Others | 28 (15.8%) | 13 (14.3%) | 0.741 | | | | |

**Notes**: The patients in the death group were those who died in hospital or gave up treatment after aggravation of the disease. The parameters included in Binary logistic regression were those with P < 0.1 in univariate test. Bold font indicates data with significant differences. B indicates regression coefficient.
**Abbreviations**: PMB, Polymyxin B; ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; CR-GNB, Carbapenem-resistant Gram-negative Bacteria; MIC, minimum inhibitory concentration.

guidelines recommend a loading dose of 2–2.5 mg/kg of PMB for severely ill patients.[9] In this study, the PMB loading dosage was ≥ 2 mg/kg in 22.01% of the cases, while the maintenance dose was ≥ 1.25 mg/kg in 14.55% of cases, which represented a significant deviation from the dose recommended in the literature.[9,20] A population pharmacokinetic study of patients with severe infections showed that administration of 1.25 mg/kg (equivalent to 12,500 IU/kg) every 12 h resulted in plasma PMB concentration after the first administration of approximately 56–70% of the observed steady-state concentration.[21] Further, the results of a Monte Carlo simulation analysis showed that, at a loading dose of 2.0 mg/kg (equivalent to 20,000 IU/kg), the probability of exposure to steady-state drug levels on the first day is 76%–94%.[21]

For the combination use of PMB, the international guideline recommended that PMB should be combined with other drugs to treat CR-GNB, including CRAB, CRE, and CRPA.[9] A study investigated the colistin versus colistin plus meropenem for the treatment of CRAB in critically ill patients, and found that the meropenem plus colistin regimen caused a reduction in 30-day mortality, higher clinical and microbiological responses, and did not increase nephrotoxicity compared to colistin monotherapy.[22] Colistin combination with vancomycin was not necessary for the management of critically ill patients infected with CRAB.[23] In patients with septic shock, the mean arterial pressure and ventilator use are related to mortality,[24] which is consistent with the conclusions of the clinical efficacy analysis in our study; that is, mechanical ventilation, use of vasoactive drugs, respiratory diseases, hepatobiliary diseases, and the number of CR-GNB infections were related to clinical failure of patients.

Few studies have investigated the microbiological efficacy of PMB for treatment of CR-GNB.[25] Here, we investigated the microbiological clearance rate of the total course of treatment and 7-day microbiological clearance, which were 39.42% and 29.45%, respectively. Our results showed that urinary tract infection and CRAB infection were independent risk factors associated with bacterial clearance following PMB treatment. Further, clearance rates varied among different bacteria, with the rates higher for patients with CRAB infection and lower for those with CRKP and CRPA infection. Although there was no difference between patients who survived and those who died in terms of response to preemptive PMB therapy, we found that PMB delay was shorter in patients with successful bacterial clearance than in the failure group (Table 4). Moreover, preemptive therapy was also more common in patients with successful bacteria clearance than that in those with clearance failure (Tables 4 and S1), implying that preemptive PMB therapy can improve microbiological efficacy in patients infected with CR-GNB.

The mortality rate from CR-GNB infection in critically ill patients was high. A previous study found that delayed administration of both the initial and first appropriate antimicrobial therapy were independent risk factors for mortality and prolonged organ dysfunction.[26] A small case-control study found that early use of PMB reduces mortality from CRKP bloodstream infection.[10] In our research, we also analyzed the effects of preemptive PMB therapy and found no difference between patients who survived and those who died. Further, we found that patient-related factors, such as mechanical ventilation, vasoactive agent use, admission to ICU, more underlying diseases (eg, liver disease), and *E. coli* or *E. cloacae* infection, were associated with death. In patients with septic shock, the mean arterial pressure and ventilator use are related to mortality.[24] A study also found that the number of patients on mechanical ventilation or having septic shock was lower in the survivor group than in the nonsurvivor group in patients infected with CR-GNB treated with PMB.[27]

Moreover, patients who died had a lower maintenance dose, cumulative dose of PMB, and treatment duration. A previous study also found that a PMB dose ≥ 200 mg/day was associated with lower in-hospital mortality.[28] Further, a combination of carbapenems with PMB was more frequently administered to patients who survived than those who died, while the combination of tigecycline with PMB was less frequently administered to surviving patients.

The main route of polymyxin-induced nephrotoxicity is both concentration-dependent and time-dependent;[29] however, there is evidence that reducing the daily dose of PMB to avoid nephrotoxicity is not feasible because it use of < 15,000–25,000 IU/kg of PMB per day can lead to sub-therapeutic antibiotic exposure.[21,30] Such sub-therapeutic exposure may have multiple harmful effects, including the impairment of clinical results, due to insufficient drug exposure, and the expansion of PMB-resistant subgroups.[31,32] However, our data indicate that the proportion of clinical success (27.55%) was only greater than that of clinical failure (18.82%) when the loading dose was ≥ 2 mg/kg; thus, clinical treatment efficacy was better in patients treated with a loading dose ≥ 2 mg/kg, relative to that in patients without a loading dose ≥ 2 mg/kg. Maintenance dose was not significantly related to clinical efficacy. In addition, total treatment course and 7-day bacterial clearance rates were not related to the recommended dosage requirements, which was not wholly consistent with previous population pharmacokinetic research, which suggests that PMB injection dosage should be calculated based on body weight.[29]

ADRs (particularly severe ADRs) to PMB are infrequent. Our study found that 56 patients (19.58%) suffered from ADRs to PMB during hospitalization. The most prevalent ADR was AKI (28 cases; 8.21%) in our study, which is lower than in previous publications.[11,19,33–35] The difference may be due to the variation in PMB doses administered to patients. For example, Mattos et al reported nephrotoxicity of PMB in 40.5% of cases administered doses of 15,000–25,000 UI/kg/d in patients with normal kidney function.[19] In comparison, our enrolled patients were administered with relatively low doses. Moreover, a study found that the nephrotoxicity rates were similar for colistin alone group and colistin plus vancomycin group.[23] While another study also found the use of two or more nephrotoxic drugs combination with PMB was the independent risk factor for the occurrence of nephrotoxicity.[36] Although the guidelines recommend that the dose of PMB in patients with renal insufficiency does not need to be adjusted,[9] many studies have found that the AKI caused by PMB is related to high dose and concentration, combined use of other nephrotoxic drugs.[11,37] Therefore, physicians and pharmacists could cooperate with each other to formulate the optimal scheme according to the monitoring results of therapeutic drug concentration and other individualized conditions of patients, so as to improve the curative effect and reduce the occurrence of AKI.

Our study has some limitations. First, it was a single-center retrospective study with a limited sample size. Second, because of the limited sample size, we did not conduct sub-group analysis according to types of CR-GNB and infection sites. Thus, the data may not be representative of PMB characterization in other carbapenem-resistant pathogens and sites of infection. Third, we did not consider other pathophysiological conditions, such as albumin levels, which may also influence PMB efficacy. Fourth, the combination of PMB with other antimicrobial drugs made it difficult to isolate ADR and the sole efficacy of PMB, which may have also caused certain limitations in the results. Moreover, as a retrospective study, the medication histories or the combinations of other medications used by patients were not strictly controlled, as this would have severely limited the sample size; however, this is a double-edged sword, since medications are inherently present in clinical situations; hence the results of our research are relevant to real-world situations. The results should be interpreted with caution due to possible confounders. Due to limited data and lack of dynamic monitoring of renal function, this study only defined renal toxicity without further investigating its severity. Further studies will assess this aspect, focusing on the severity of nephrotoxicity.

## Conclusions

PMB is a relatively safe and effective antibiotic drug for patients critically ill with CR-GNB infection; however, PMB use should be subject to guideline recommendations for early administration, loading administration, and adequate administration, which could help to improve clinical efficacy, microbiological efficacy, and mortality.

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## Author Contributions

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

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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