Clinical Outcomes and Safety of Polymyxin B in the Treatment of Carbapenem-resistant Gram-negative Bacterial Infections: a Real-world Multicenter Study

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Abstract

Background: High morbidity and mortality due to carbapenem-resistant Gram-negative bacilli (CR-GNB) has led to the resurgence of polymyxin B (PMB) use in the last decade. The aim of our multicenter, real-world study was to evaluate the effectiveness and safety of PMB in the treatment of CR-GNB infections.

Methods: The real-world study included patients treated with intravenous PMB for at least 7 days during the period of October 2018 through June 2019. Associations between these variables and 28-day mortality or all-cause hospital mortality were explored through univariate analyses and multivariable logistic regression.

Results: The study included 100 patients. Many patients presented with combined chronic conditions, septic shock, mechanical ventilation, and the presence of *Klebsiella pneumoniae*. The mean duration of PMB therapy was 11 days (range 7–38 days). Temperature (38°C vs 37.1°C), white blood cells (14.13×10^9/L vs 9.28×10^9/L), C-reactive protein (103.55 ug/l vs 47.60 ug/l), procalcitonin (3.89 ng/ml vs 1.70 ng/ml) and APACHE levels (17.75 ± 7.69 vs 15.98 ± 7.95) were significantly decreased after PMB treatment. The bacteria eradication rate was 77.65%. The overall mortality at discharge was 15%, and 28-day mortality was 40%. Major adverse reactions occurred in 16 patients. Nephrotoxicity was observed in 7 patients (7%).

Conclusions: Our results provide positive clinical and safety outcomes for PMB in the treatment of CR-GNB. Timely and appropriate use of PMB may be particularly useful in treating patients with sepsis in CR-GNB infections.

Introduction

In recent years, infections due to carbapenem-resistant Gram-negative bacilli (CR-GNB) have become an increasingly important cause of mortality and morbidity around the world[1]. The organisms most commonly identified in CR-GNB infections are *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*[2–4]. These bacteria can lead to bloodstream, respiratory tract, skin and soft tissue, urinary tract, intra-abdominal, and surgical infections [3, 5–7]. They are responsible for nosocomial infections, particularly among critically ill patients hospitalized in intensive care units (ICUs) [8].

Mortality rates of greater than 47% have been reported for CR-GNB infections[5, 9–13]. The decline in the development of newer antibiotics has created a challenge for clinicians treating CR-GNB infections[2, 14]. As a result, physicians have sought solutions in the arsenal of older therapeutics. This has led to the re-introduction the polymyxins in the treatment of infections caused by CR-GNB, as polymyxins are one of the few antibiotics that remain effective against these organisms[3]. Two polymyxins in clinical use, polymyxin B (PMB) and colistin, had fallen out of favor due to nephrotoxicity and neurotoxicity reported during their use in the 1960s. However, due to multiple drug resistance among Gram-negative bacilli, physicians have been increasingly forced to rely on polymyxins for the treatment of infections caused by

these pathogens. It has not been determined which of these agents is superior in terms of the cure rate or microbiological resolution[15, 16]. A systematic review and meta-analysis summarized findings that included no significant difference in mortality between patients treated with these two polymyxins; this study also found a lower nephrotoxicity profile for PMB[15]. Additionally, recently published research demonstrated that PMB, unlike colistin, is not cleared renally and therefore, dosing of PMB should not be adjusted based on renal function[17].

The international consensus guidelines for the optimal use of polymyxins recommend that patients intravenous PMB should receive a dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) PMB every 12 hours infused over 1 hour[16]. In one study, clinicians found that combination therapy with at least two in vitro active agents was associated with higher efficacy in treating bloodstream infections caused by CR-GNB[6, 18].

Currently, there is a lack of data available on the efficacy, 28-day mortality, and adverse events for PMB in the treatment of CR-GNB infections. Here, we report on a multicenter, real-world study of patients receiving intravenous PMB to investigate the clinical outcomes of antimicrobial therapy in patients infected with CR-GNB.

Methods

Study Design and Patients

This multicenter, real-world study was conducted at 14 hospitals in Henan province during the period of October 2018 through June 2019. The institutional research ethics committee of the First Affiliated Hospital of Zhengzhou University approved the study (SS-2019-015).

Patients aged more than 14 years with CR-GNB infection who received PMB therapy for at least 7 days were included in the study. Patients with positive culture of CR-GNB, or the patients were infected with suspected CR-GNB from two experienced professors. The organisms identified in CR-GNB infections are *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa, Escherichia coli,* and *Stenotrophomonas maltophilia.* Patients were excluded if they received intravenous PMB for fewer than 7 days.

Data Collection

Data was collected from electronic patient registration and follow-up. The database was generated by the clinician through a query of the electronic medical records. The following variables were recorded: age, gender, underlying disease, hospitalization date, dates of admission to and discharge from ICU, vital signs, Acute Physiology and Chronic Health Evaluation II (APACHEII) score, Sequential Organ Failure Assessment (SOFA) score, any major surgeries performed, ventilator care, site of isolation of organisms, exposure to antimicrobial therapies, clinical features, biochemical indices, and microbiological data on admission and on the day of introduction of PMB.

The dose and duration of PMB therapy, renal function, clinical and microbiological outcomes, and adverse reactions to PMB were noted. Patients were followed up until the end of treatment at 28 days.

Patient Diagnoses

Diagnoses of infections were based on clinical features and the isolation of bacteria from areas that are normally sterile. The microbiologically documented infection was defined as positive cultures in sterile of localized, and absence of any bacterial pollution or colonization. Severe sepsis was defined as sepsis associated with organ dysfunction or hypoperfusion. Septic shock was defined as sepsis 3.0[19]. Pulmonary infection included hospital-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP). HAP was defined as a pneumonia occurring 48h or more after admission. VAP was defined as a pneumonia developing 48h or more after tracheal intubation. Chronic diseases included heart disease, hypertension, stroke, cancer, diabetes mellitus, and chronic obstructive pulmonary disease.

Microbiology

The CR-GNB include *Enterobacteriaceae,Acinetobacter spp.,Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Burkholderia cepacia.* All CR-GNB infections were identified in the microbiology laboratory. The biological samples included blood, vein catheter samples, urine, sputum, tracheal secretions, bronchial-alveolar lavage fluid, intraperitoneal fluid, and pleural drainage fluid. Bacterial identification and drug sensitivity tests were performed using a Vitek® 2 automated system（France Biomerieux）. Susceptibility was interpreted according to Clinical and Laboratory Standards Institute criteria[20]. *Enterobacteriaceae* with a minimal inhibitory concentration(MIC) ≥ 4 μg/ml were considered resistance to carbapenem[20]. *Pseudomonas aeruginosa* and *Acinetobacter spp.* with a minimal inhibitory concentration (MIC) ≥ 8 μg/ml were considered resistance to carbapenem[20]. *Burkholderia cepacia* with a MIC ≥ 16 μg/ml were considered resistance to meropenem[20]. Isolates with a MIC ≤ 2 μg/ml were considered susceptible to PMB (colistin breakpoint for Enterobacteriaceae)[21]. The treating clinicians evaluated whether pathogens were the pathogenic bacteria according to the characteristics of pathogen distribution in the institution and their own experience.

Treatment Regimen

All patients were treated with intravenous PMB, to which all strains remained sensitive. The international consensus guidelines for the optimal use of polymyxins recommend that patients who require intravenous PMB receive a dose of 1.25~1.5 mg/kg (equivalent to 12,500~15,000 IU/kg) PMB every 12 hours infused over 1 hour[16]. Upon isolation of strains of CR-GNB that were resistant to carbapenem, an intravenous antibiotic regimen was initiated at the discretion of the attending physician.

Outcomes

The primary outcome of this analysis was 28-day mortality; the secondary outcomes included all-cause hospital mortality, ICU mortality, and the occurrence of adverse events during PMB therapy. The clinical

outcomes of this study were based on the recovery of patients following PMB therapy. The measure of 28-day mortality refers to patient deaths occurring within 28 days from the start of treatment, even if the death was related to other comorbidities that were not the infection.

Clinical cure was defined as a combined outcome of survival and the complete disappearance or improvement of signs and symptoms of infection after day 7 of PMB therapy. Failure of treatment was defined as maintenance or worsening of signs and symptoms of disease or radiologic deterioration.

Common adverse events included nephrotoxicity, neurotoxicity, skin hyperpigmentation, and eosinophil increase. Nephrotoxicity was defined as increase in serum creatinine (SCr) by ≥26.5 umol/L within 48 hours, or increase in SCr to ≥1.5 times baseline within 7 days, or urine volume 0.5 ml/Kg/hour for 6 hours[22]. Skin hyperpigmentation was evaluated based on changes of the skin of the face and neck during PMB therapy or four weeks after treatment completion. Neurotoxicity included any of the following: apnea, encephalopathy, paresthesia, or seizures.

Statistical Analysis

Statistical analyses were carried out using the statistical software package IBM SPSS Statistics 21.0 (SPSS, Chicago, IL). Descriptive analysis was performed to describe the distribution of the variables of interest. Categorical variables were presented as counts and percentages and were compared between survivors and non-survivors using Chi-squared test or Fisher's exact test. Continuous variables of each group were presented as the mean ± SD or median with interquartile range (IQR) and were compared between survivors and non-survivors using Student's t-test or Mann–Whitney U test, as appropriate. Paired t-test or Wilcoxon signed rank test was used to compare the continuous variables before and after therapy and categorical variables were compared using the McNemar test. Associations between these covariates and 28-day mortality or all-cause hospital mortality were
explored through multivariable logistic regression. Kaplan-Meier curves were conducted to demonstrate the survival probability within 28 days and were compared using log-rank test between groups. A *P*-value < 0.05 was considered statistically significant.

Results

Data from 100 patients who received intravenous PMB between October 1, 2018 and June 30, 2019, were analyzed. The mean age of patients was 55.9 ± 17.1 years (range 17–91 years) and 79% were male. The mean length of hospitalization was 41.6 ± 26.42 days (range 7–130 days), and the mean residence time in the ICU was 26 days. Mechanical ventilation was given to 49% of patients in the study. There were 23 patients without chronic disease and 37 patients with one chronic illness; the remainder of patients had a combination of multiple chronic diseases. There were 39 patients who had septic shock at the beginning of therapy; an additional 10 patients later progressed to shock. The demographic and clinical features of patients who received intravenous PMB are summarized in Table 1. For 85 patients, the pathogen culture was positive; 21 patients of these were infected with two bacteria species. In 35 cases, the patient had multi-site infection. The most patients received combination therapy with carbapenems, tigecycline,

fosfomycin, or cefoperazone-sulbactam. There were 33 patients combined with meropenem, 27 patients combined with imipenem, 11 patients combined with biapenem. Only 3 patients were combined with doxycycline or amikacin.

Table 1
Clinical Features and details of Patients Receiving Intravenous PMB

Characteristic	Mean ± SD, or n (%)
Age (year)	55.91 ± 17.14
Male (%)	79 (79)
ICU admission, n (%)	98 (98)
Mechanical ventilation, n (%)	49 (49)
Chronic medical conditions, n (%)	
Heart disease	14 (14)
Hypertension	44 (44)
Stroke	19 (19)
Cancer	6 (6)
Diabetes mellitus	15 (15)
Chronic obstructive pulmonary disease	1 (1)
Renal insufficiency, n (%)	27 (27)
Septic shock, n (%)	39 (39)
SOFA score, mean ± SD	7.76 ± 4.30
APACHE II, mean ± SD	17.61 ± 7.59
ICU stay before intravenous PMB, days, median (IQR)	8(3,14)
MODS, n (%)	60 (60)
PCT, ng/ml, median(IQR),	3.89(1.08,11.43)
Bacterial, n (%)	
AB	33 (33)
KP	48 (48)
PA	16 (16)
Other	9 (9)
Unknown	15 (15)

PMB: polymyxin B; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; MODS: multiple organ dysfunction syndrome; PCT: procalcitonin; KP: *Klebsiella pneumoniae*, AB: *Acinetobacter baumannii*; PA: *Pseudomonas aeruginosa*; BSI: bloodstream infection

Characteristic	Mean ± SD, or n (%)
Infection sites, n (%)	
BSI	40 (40)
Pulmonary infection	64 (64)
Intraperitoneal infection	9 (9)
Incision infection	6 (6)
Others	18 (18)
Concomitant antibiotic therapy	
Carbapenem	71
Tigecycline	47
Cefoperazone and sulbactam	16
Cefepime	8
Others	8

PMB: polymyxin B; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; MODS: multiple organ dysfunction syndrome; PCT: procalcitonin; KP: *Klebsiella pneumoniae*, AB: *Acinetobacter baumannii*; PA: *Pseudomonas aeruginosa*; BSI: bloodstream infection

Overall, the condition of patients improved after the PMB treatment. Temperature, white blood cells, C-reactive protein (CRP), procalcitonin, and APACHE levels were significantly decreased among patients. Platelets were significantly increased ($P < 0.001$). The number of patients with mechanical ventilation or shock significantly decreased after PMB treatment (Table 2).

Table 2
Comparison of Patient Conditions Before and After Therapy

Parameter	Baseline	After therapy	*P*
Heart rate, bpm, mean ± SD	92.02 ± 21.55	97.36 ± 20.35	0.895
Temperature,℃,median (IQR)	38(37.1,38.7)	37.1(36.7,37.6)	< 0.001
WBC, $\times 10^9$, median (IQR)	14.13(10.08,20.02)	9.28(7.02,13.40)	< 0.001
PLT, $\times 10^9$, mean ± SD	111.71 ± 97.68	190.95 ± 162.99	< 0.001
CRP, ug/l, median (IQR)	103.55(56.96,180.83)	47.6(13.08,102.58)	< 0.001
PCT, ng/ml, median (IQR)	3.89(1.09,11.43)	1.695(0.46,5.41)	< 0.001
SOFA, mean ± SD	7.74 ± 4.13	7.32 ± 4.41	0.282
APACHE , mean ± SD	17.75 ± 7.69	15.98 ± 7.95	0.007
Mechanical ventilation, n (%)	51	26	< 0.001
Septic shock, n (%)	49	26	< 0.001

WBC: white blood cell; CRP; C-reactive protein; PLT: platelet count; PCT: procalcitonin; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Microbiological eradication occurred in 66 (77.65%) out of 85 patients with electropositive germiculture. Serious adverse reactions occurred in 16 patients (16%). Seven patients experienced at least two adverse reactions. No patients had treatment discontinued because of an adverse reaction. Nephrotoxicity was manifested by transient creatinine and urea nitrogen elevations, and no patient required hemodialysis. Among 6 patients demonstrating neurotoxicity, 4 patients showed persistent drowsiness, transient irritability, paresthesia, fatigue, dizziness, or drowsiness, and the other 2 patients underwent invasive mechanical ventilation due to adverse reactions of respiratory depression. Transient adverse reactions included eosinophil increase. The outcomes of patients receiving intravenous PMB are shown in Table 3. The 28-day mortality was 40%. More than 60% deaths occurred 7–14 days after enrollment, as shown in the Kaplan-Meier survival curve (Fig. 1).

Table 3
Outcomes of Patients Receiving Intravenous PMB

Outcomes	n (%)
Bacteria eradication rate, n (%)	66 (77.65)
Treatment Duration, median (IQR)	11(9,13)
Adverse events, n (%)	16 (16)
Nephrotoxicity	7 (7)
Neurotoxicity	6 (6)
Skin hyperpigmentation	3 (3)
Eosinophil increase	7 (7)
ICU mortality, n (%)	12 (12)
Hospital mortality, n (%)	15 (15)
28-day mortality, n (%)	40 (40)

The survivors and nonsurviviors had similar characteristics (Table 4). Age, sex, and chronic medical conditions were similar in the two groups, and the types of adverse reactions were not notably different. Markers of infection, including white blood cell count, procalcitonin, and CRP, were also similar in the two groups. However, the platelet count in the nonsurvivors group was lower than in the survivor group (P = 0.001). In terms of clinical characteristics, SOFA scores (6.77 ± 4.07 vs 9.25 ± 4.25,P = 0.004)APACHE II scores (16.17 ± 7.80 vs 19.7 8 ± 6.80, P = 0.016) and the number of patients on mechanical ventilation (21% vs 30%, P < 0.001) or having septic shock (17% vs 32%, P < 0.001) were lower in the survivor group than in the nonsurvivor group. There were no different therapeutic outcomes among the different combinations. The mortality among the 85 patients with identified pathogens was 38.82%, while the mortality among patients with negative pathogen culture results was 46.67% (P = 0.58). During treatment, similar adverse reactions related to PMB were observed in the two groups.

Table 4
Characteristics Associated With 28-Day Mortality Among Patients Who Received Intravenous PMB

Parameter	Value for:		*P*
	Survivors (n = 60)	Nonsurvivors (n = 40)	
Age, y, mean ± SD	54.65 ± 16.23	57.8 ± 18.45	0.370
Female, n (%)	47 (78.3)	32 (80.0)	0.840
WBC,×10^9, median(IQR)	14.28(10.58,20.44)	13.84(9.55,19.65)	0.359
PLT, ×10^9, mean ± SD	131.37 ± 101.96	71.15 ± 66.27	0.001
PCT, ng/ml, median (IQR)	2.30(0.70,10.07)	5.00(1.97,15.93)	0.062
CRP, ug/l, median (IQR)	100.15(50.70,174.33)	119.96(79.58,186.0)	0.624
SOFA, mean ± SD	6.77 ± 4.07	9.25 ± 4.25	0.004
APACHE □, mean ± SD	16.17 ± 7.80	19.78 ± 6.80	0.016
Mechanical ventilation, n (%)	21 (35.0)	30 (75.0)	< 0.001
Septic shock, n (%)	17 (28.3)	32 (80.0)	< 0.001
Hospitalization before intravenous PMB, days, median (IQR)	12.00(5.25,20.75)	11.50(3.25,21.00)	0.882
ICU stay before intravenous PMB, days, median (IQR)	9.00(3.00,15.00)	5.00(1.00,14.00)	0.156
Treatment Duration, days, median (IQR)	11.00(9.00,13.00)	10.00(8.25,13.75)	0.697
Concomitant antibiotic therapy, n (%)			
Carbapenem	45(75)	26(65)	0.393
Tigecycline	28(46.67)	19(47.5)	0.935
Cefoperazone and sulbactam	9(15)	7(17.5)	0.956
Cefepime	3(5)	5(12.5)	0.328
Identify microorganisms, n (%)	52 (86.67)	33 (82.5)	0.580
KP, n (%)	32 (53.3)	16 (40.0)	0.191

WBC: white blood cell; PLT: platelet count; PCT: procalcitonin; CRP: C-reactive protein; SOFA: Sequential Organ Failure Assessment; APACHEII: Acute Physiology and Chronic Health Evaluation II; PMB: polymyxin B; ICU: intensive care unit; KP: *Klebsiella pneumoniae*; AB: *Acinetobacter baumannii*; BSI: Bloodstream Infection.

Parameter	Value for:		*P*
	Survivors (n = 60)	Nonsurvivors (n = 40)	
AB, n (%)	19 (31.7)	14 (35)	0.728
Multisite infection, n (%)	20 (33. 3)	15 (37.5)	0.669
Pulmonary infection, n (%)	35 (58.3)	29 (72.5)	0.217
BSI, n (%)	26 (43.3)	14 (35.0)	0.405
Chronic medical conditions, n (%)	45 (75.0)	32 (80.0)	0.734
Nephrotoxicity, n (%)	13 (21.7)	13 (32.5)	0.251
Adverse reactions, n (%)	8 (13.3)	8 (20.0)	0.373

WBC: white blood cell; PLT: platelet count; PCT: procalcitonin; CRP: C-reactive protein; SOFA: Sequential Organ Failure Assessment; APACHEII: Acute Physiology and Chronic Health Evaluation II; PMB: polymyxin B; ICU: intensive care unit; KP: *Klebsiella pneumoniae*; AB: *Acinetobacter baumannii*; BSI: Bloodstream Infection.

The factors demonstrating statistically significant differences in univariate analysis in Table 4 were analyzed by logistic regression (Table 5). Multivariate analysis showed that mechanical ventilation (P = 0.023, odds ratio (OR) = 3.58; confidence interval (CI): 1.194–10.739) and septic shock (P = 0.002, OR = 5.96; CI: 1.923–18.473) were independently associated with 28-day mortality in patients with sepsis due to CR-GNB. The 28-day mortality was 58.82% for patients on mechanical ventilation compared to 20.41% for patients who were not on mechanical ventilation. The 28-day mortality was 65.31% in patients with septic shock compared to 15.69% in patients who did not have septic shock. Survival of patients is shown in Fig. 2.

Table 5
Multivariate Analysis of Factors Associated With 28-Day Mortality

Variable	OR (95% CI)	*P*-value
PLT	1.578 (0.965–2.580)	0.069
Mechanical ventilation	3.580 (1.194–10.739)	0.023
Septic shock	5.960 (1.923–18.473)	0.002
APACHE II	1.013 (0.613–1.673)	0.960
SOFA	0.941 (0.553–1.601)	0.823

OR: odds ratio; CI: confidence interval; PLT: platelet count; APACHE II, Acute and Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

Discussion

In this study, patients with CR-GNB infection treated with PMB had a bacteria eradication rate of 77.65%, ICU-related mortality of 12%, hospital mortality of 15%, and 28-day mortality of 40%. These results are favorable compared with those reported for studies of patients receiving different treatments for CR-GNB infections[23]. For example, in patients infected with carbapenem-resistant *Acinetobacter baumannii* who did not receive appropriate empirical antimicrobial therapy, the overall mortality rate was 86.1%[24]. In one retrospective study, the overall ICU mortality rate was 45.2% for critically ill patients infected with CR-GNB who received tigecycline therapy[25]. In another retrospective study, the in-hospital mortality rate for patients receiving tigecycline for the treatment of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections was 62.5%[26]. In a retrospective cohort study of the treatment of infections due to carbapenem-resistant Enterobacteriaceae, the 30-day mortality was 50% after ceftazidime-avibactam treatment[27]. Our results suggest that treatment with PMB may reduce the mortality of patients with CR-GNB.

Our study found that after 7 days of PMB treatment, the temperature of patients with CR-GNB infection returned to normal, and the number of patients with septic shock or mechanical ventilation decreased. Moreover, the infection indicators of white blood cell, procalcitonin, and CRP were all significantly reduced. The symptoms of thrombocytopenia in patients with CR-GNB infection improved. APACHE scores were also lower than the initial sepsis. The mortality of PMB target therapy was 38.82%, while the mortality of patients with empiric therapy was 46.67% ($P = 0.580$). Our results suggest that PMB may be a clinically effective treatment for patients infected with CR-GNB.

Our results suggest that PMB therapy is safe for the treatment of infections caused by CR-GNB, as intravenous PMB was well tolerated in most patients. Serious adverse reactions occurred in 16 patients (16%), 7 patients had at least two adverse reactions, eight of whom had transient adverse reactions.

Prior PMB population pharmacokinetic studies have made a contributions to optimizing the clinical use of this important last-line antibiotic in patients[17]. In our study, adverse effects related to nephrotoxicity occurred in 7 patients (7%) and were mild and reversible; none required renal replacement therapy. While the prevalence of nephrotoxicity was not lower in our study than in other observational studies (6–40.5%) [11, 28–31], it was at the lower end of these reported ranges. Assessment of the contribution of PMB to renal impairment may be complicated by other factors such as infection, septic shock, multiple organ dysfunction syndrome (MODS), and concomitant use of other nephrotoxic drugs.

Neurotoxicity of PMB is less common than nephrotoxicity, and it is usually mild and resolves after prompt discontinuation of therapy[11, 28]. In a previous study on the use of PMB in patients, intravenous PMB was associated with neurotoxicity in 7% of cases, and no adverse reactions of respiratory depression were seen[11]. In another study, however, no cases of neurotoxicity complications occurred among 247 patients who were given PMB therapy [28]. In our study, among the 6 patients with neurotoxicity, 2 patients underwent invasive mechanical ventilation due to the adverse effects of respiratory depression.

Neither patient used sedative analgesics. PMB therapy was not stopped in the patients with respiratory depression and the endotracheal tube was removed before the end of PMB treatment.

In the present study, 3 cases (3%) developed skin hyperpigmentation in the face and neck. This incidence is lower than was reported in previous studies[28]. During treatment, there were no other adverse reactions such as rashes, itching, dermatitis, or fever. While our results support the use of PMB, the safety of polymyxin therapy requires further study.

Mechanical ventilation and septic shock were independent factors associated with higher 28-day mortality risk in the present study. A previous study of a large US cohort found that most patients with culture-positive community onset sepsis did not have resistant bacteria [32], while a study of the epidemiology of sepsis in Chinese ICUs found that only 12% of culture-positive were multi-drug resistant organisms[33]. In our study, the mortality of patients with empiric PMB therapy was higher. This underscores the need for rapid identification of CR-GNB infection and an increased of judicious use of PMB for the treatment of sepsis, to avoid progression to mechanical ventilation or septic shock. In this regard, the optimization and validation of PMB-based combinations may have considerable clinical benefits.

The present study has several limitations, including its retrospective, real-world design and lack of a control group or direct basis of comparison with other treatments. Another limitation was the relatively small number of patients included in the study. Serum PMB concentrations were not determined in the study. The decision to use additional antibiotics was made by individual clinicians, which may have introduced bias. Additionally, the concomitant use of other antibiotics with PMB makes it impossible to attribute treatment efficacy solely to PMB. Further, it was difficult to properly evaluate adverse effects attributable to PMB in view of the use of other drugs in seriously ill patients. Despite these limitations, our study represents a multicenter study evaluating a range of CR-GNB infections treated with PMB combination therapy.

Conclusions

In summary, the findings from our study suggest that timely and appropriate use of PMB may have a positive impact on clinical outcomes in the treatment of CR-GNB infections. These results underscore the need to more quickly identify patients with CR-GNB who may benefit from judicious use of PMB, in particular, patients with septic shock or on mechanical ventilation who may be at higher risk of mortality. Clinicians should apply strict protocols when using this antimicrobial agent to prevent the occurrence and spread of polymyxin resistance.

Abbreviations

CRGNB: carbapenem-resistant Gram-negative bacilli; PMB: polymyxin B; ICU: intensive care unit; APACHEII: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure

Assessment; HAP: hospital-associated pneumonia; VAP: ventilator-associated pneumonia; PCT: procalcitonin; CRP: C-reactive protein; PLT: platelet count; MODS: Multiple organ dysfunction syndrome.

Declarations

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Authors' contributions

All authors were involved in the research concept and design. Zhang XJ, Qi SY, and Duan XG contributed to the data acquisition. Zhang XJ and Sun TW have reviewed and take responsibility for all of the data. Zhang XJ, Han B, Zhang SG, Liu SH, and Wang HX performed the analysis and interpretation of the data. Zhang XJ contributed to the writing of the first draft. Sun TW and Zhang HB reviewed this article and made necessary changes to improve it. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed in this study are not publicly available due to privacy issues but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional research ethics committee of The First Affiliated Hospital of Zhengzhou University, and waived informed consent based on the real-world design and anonymization

of patient identifiers before analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

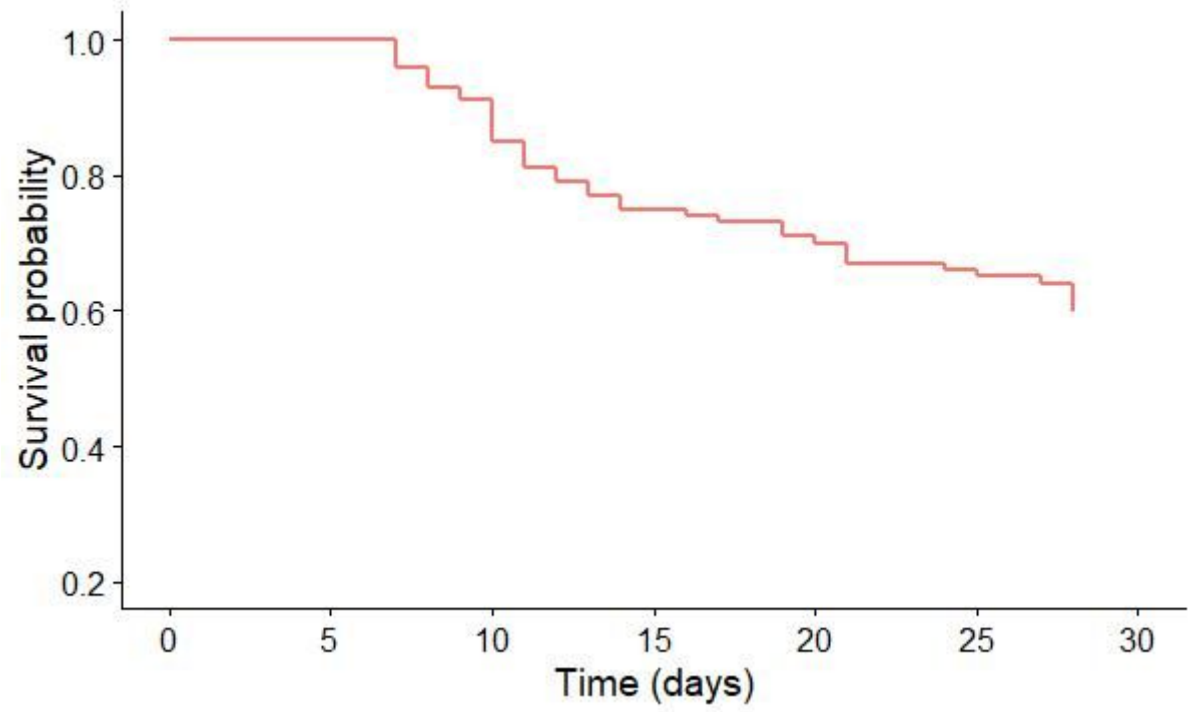

Figure 1

Survival analysis at 28 days: Kaplan-Meier curve. Shown are survival curves from the receiving intravenous PMB to 28 days. The 28-day mortality was 40%. 25 patients died during their 7–14 days after enrollment.

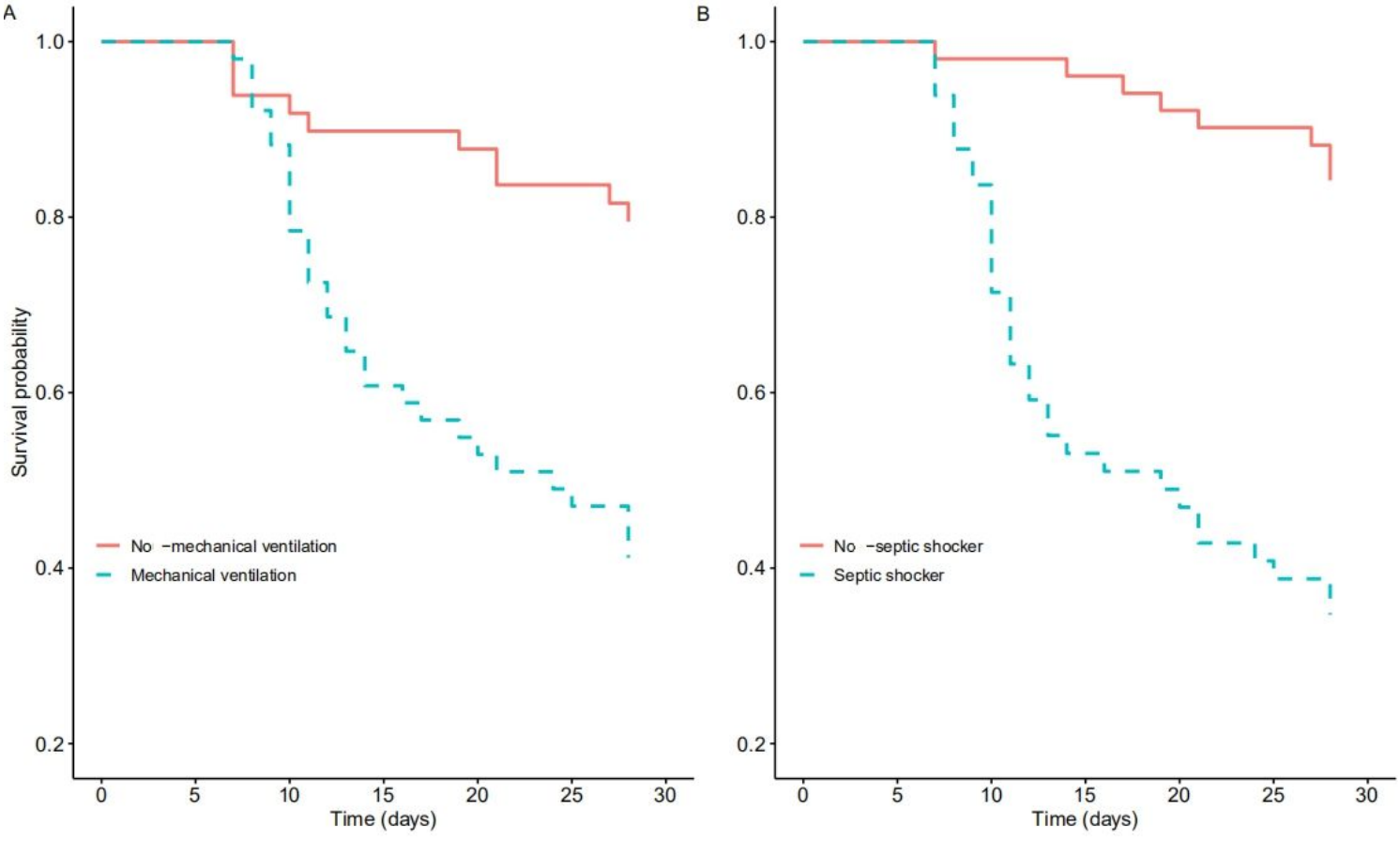

Figure 2

Kaplan-Meier 28-day survival curve comparing patients on mechanical ventilation or with septic shock. (A) 28-day mortality were 58.82% and 20.41% in patients on mechanical ventilation and not on mechanical ventilation, respectively (Log-rank, $P < 0.01$). (B) 28-day mortality were 65.31% and 15.69% in patients with septic shock and without septic shock, respectively (Log-rank, $P < 0.01$).