A Real-World Study for Polymyxin B in the Treatment of Carbapenems Resistant Gram-Negative Bacilli

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Research

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Abstract

Background: High morbidity and mortality due to carbapenem-resistant Gram-negative bacilli (CRGNB) was a challenge for clinicians has led to the resurgence of polymyxin B (PMB) use in the last decade. The goal of our multicenter, real-world study was to evaluate the efficacy and safety of PMB in the treatment of CRGNB.

Methods: The real-world study included the patients with intravenous PMB at least 7 days during the period of October 2018 to June 2019. Data was collected from electronic patients register and follow-up. The primary outcome was 28-day mortality, the secondary outcomes included hospital mortality, occurrence of adverse events during PMB therapy. Associations between these variables and 28-day mortality or all-cause hospital mortality were explored through univariate analyses and multivariable logistic regression. At the same time, therapeutic effects were observed.

Results: The study included 100 patients. There were 39% presence of septic shock, 49% need mechanical ventilation at the beginning of therapy. The infection and condition improved after 7 days of PMB treatment. The major adverse reactions occurred in 16 cases (16%). The overall 28-day mortality was 40%. In terms of clinical characteristics, mean Sequential Organ Failure Assessment (6.77 versus 9.25, $P = 0.004$) mean Acute Physiology and Chronic Health Evaluation II (APACHEII) scores (16.17 versus 19.78, $P = 0.016$) and the number of patient with mechanical ventilation (21 versus 30, $P = 0.000$) or septic shock (17 versus 32, $P = 0.000$) were lower in survivors group than nonsurvivors group. The mortality of 85 patients with identify pathogens was 38.82%, while the mortality of patients with negative pathogen culture results was 46.67% ($P = 0.580$). Multivariate analysis showed that mechanical ventilation ($P = 0.023$, OR = 3.5; CI: 1.194–10.739), septic shock ($P = 0.002$, OR = 5.960; CI: 1.923–18.473) were associated with 28-day mortality.

Conclusion: Our research found that PMB may be as effective and safe as standard antibiotics for the treatment of CRGNB. Timely and appropriate use of PMB will have a positive impact on the clinical outcomes of patients with sepsis in CRGNB.

Introduction

In recent years, infections due to carbapenem-resistant Gram-negative bacilli (CRGNB) are the leading cause of mortality and morbidity in the world[1]. The most common identified CRGNB are *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*[2–4]. These bacteria can lead to bloodstream infection, respiratory tract infections, skin and soft tissue infections, surgical infections, urinary tract, intra-abdominal[3, 5–7]. Meanwhile, they cause nosocomial infections and outbreaks, particularly among critically ill patients hospitalized in intensive care unit (ICU)[8].

The mortality rates more than 47% have been reported for CRGNB infections[5, 9–13]. At the same time the marked decline in the development of newer antibiotics creates a real daunting challenge for the

clinicians to against CRGNB[2, 14]. As a result, physicians have forced to seek a solution in the old therapeutic arsenal and re-introduce the polymyxins in the treatment of infections caused by CRGNB, when polymyxins were one of the last antibiotics remaining effective against these organisms[3]. There are two polymyxins used in clinical, polymyxin B(PMB) and colistin, which had fallen out of stock due to nephrotoxicity and neurotoxicity reported during their use in the 1960s. And, 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 is unclear whether one agent is better than another in terms of the cure rate or microbiological resolution[15, 16]. The meta-analysis summarized potentially useful findings regarding the safety and a nonsignificant difference in mortality between the two polymyxins, whereas, a milder nephrotoxicity profile for PMB[15]. Also, recently published research portrayed that PMB, unlike colistin, was not cleared nephrotoxicity and therefore dosing should not be adjusted for the renal dysfunction[17]. The experience with PMB for CRGNRs is still limited to studies, in which the association of PMB therapy with improved survival is controversial. The international consensus guidelines for the optimal use of the polymyxins recommend that patients intravenous PMB should receive dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) PMB every 12 hours is infused over 1 hour[18].

Currently, there is a lack of data with few research available on the association of the efficacy, 28-day mortality and the adverse drug events of PMB in the treatment of CRGNB. Thus we performed a multicenter, real-world study of patients receiving intravenous PMB to investigate the efficacy and safety of antimicrobial therapy in patients infected with CRGNB.

Methods

Patients

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

Patients aged more than 14 years who received PMB therapy for CRGNB infection for at least 7 days were randomly included in the study. Patients were excluded if they receive less than 7 days intravenous PMB.

Data Collection

Data was collected from electronic patients register and follow-up. The database was generated by the clinician through the electronics medical records query. The following variables were recorded: age, gender, underlying disease, hospitalization date, dates of admission and discharge from ICU, vital signs, Acute Physiology and Chronic Health Evaluation II (APACHEII) and the Sequential Organ Failure Assessment (SOFA) score, any major surgeries performed, ventilator care, site of isolation of organisms,

and exposure to antimicrobial therapies, clinical features, biochemical indices, microbiological data on admission and on the day of introduction of PMB.

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

Microbiology

All bacterial were identified in the microbiology laboratory. The biological samples include blood, vein catheter, urine, sputum, tracheal secretions, bronchial-alveolar lavage fluid, intraperitoneal and pleural drainage fluids. Bacterial identification and drug sensitivity tests were performed using Vitek2 automatized system. Susceptibility was interpreted according to Clinical and Laboratory Standards Institute criteria[19]. Isolates with a MIC $\leq$ 2 mg/L was considered susceptible to PMB (colistin breakpoint for Enterobacteriaceae)[20].

However, the pathogen culture of the site patients were negative. The clinician judges the pathogen according to the characteristics of pathogen distribution in the department and his experience.

Treatment Regimen

All patients were treated with intravenous PMB, to which all strains remained sensitive. All patients who require intravenous PMB should receive dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) PMB every 12 hours is infused over 1 hour[18]. In this study clinicians decide that combination therapy with at least two in vitro active agents as the definitive treatment was associated with higher effective[6]. On isolation of strains of CRGNB that were resistant to carbapenem, intravenous antibiotic regimen were initiated at the discretion of the attending physician.

Definitions

Diagnosis of infection was based on clinical features and isolation of bacteria from areas that normally sterile. Severe sepsis was defined as sepsis associated with organ dysfunction, or hypoperfusion. Septic shock was defined as sepsis 3.0. Pulmonary infection include hospital-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP). HAP was defined as a pneumonia occurring 48 h or more after admission. VAP was defined as a pneumonia develops 48 h or more after tracheal intubation. Chronic diseases include heart disease, hypertension, stroke, cancer, diabetes mellitus and chronic obstructive pulmonary disease.

Outcomes

The primary outcome of this analysis was the 28-day mortality, and the secondary outcomes included all-cause hospital mortality, ICU mortality, occurrence of adverse events during PMB therapy. The clinical outcomes of this study were based on the recovery of patients following PMB therapy. 28-day mortality refers to patient deaths occurring within 28 days from the start of treatment, even if the death related to other important comorbidities, not the infectious condition.

Treatment success was defined as the complete disappearance or improvement of signs and symptoms of infection whereas. We also monitored the empirical treatment, in which PMB was prescribed empirically because biological sample cultures results were reported before or negative. Finally, cases in which they were impossible to evaluate the response to the PMB treatment because no culture test was performed at the end of PMB therapy to assess the outcome of the treatment were evaluated by physicians based on clinical symptoms.

Statistical analysis

Statistical analyses were carried out using the statistical software package IBM SPSS Statistics 21.0 (SPSS, Chicago, IL). The binary variables are described as counts and percentages and were evaluated by the Chi-squared test or Fisher's exact test. Continuous variables of each group are presented as the mean $\pm$ SEM. Student's t-test was used to compare the normally distributed continuous variables; otherwise, the Mann-Whitney U test was used. Associations between these significantly statically variables and 28-day mortality or all-cause hospital mortality were explored through multivariable logistic regression. A p -value < 0.05 was considered statistically significant.

Results

Characteristics of patients receiving intravenous PMB

A total of 100 patients who received intravenous PMB between October 1, 2018 to June 30, 2019 were gathered. 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 days. As a general hospital, mechanical ventilation, as common primary diseases leading to ICU admission, accounted for 49%, the same as infectious diseases in our study. 23 patients had no chronic disease, 37 patients had one chronic illness, and the rest of patients had a combination of multiple chronic diseases. There were 39 cases presence of septic shock at the beginning of therapy, but then 10 patients later progress to shock. The more detail demographic and clinical features of patients receiving intravenous PMB are summarized in Table 1. Pathogen culture was positive for 85 patients, and some of them were infected with two types of disease-causing bacteria. 35 cases suffered from multi-site infection. All patients received combination therapy with tigecycline, carbapenems, fosfomycin, or cefoperazone-sulbactam.

Table 1
The demographic and clinical features of patients receiving intravenous PMB

Characteristic	mean $\pm$ SD, or n (%)
Age (y)	55.91 $\pm$ 17.14
Male/female, n/n	79/21
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 $\pm$ SD	7.76 $\pm$ 4.30
APACHE II, mean $\pm$ SD	17.61 $\pm$ 7.59
ICU stay before intravenous PMB, mean $\pm$ SD	10.54 $\pm$ 11.23
MODS, n (%)	60 (60)
PCT, mean $\pm$ SD	9.0 $\pm$ 18.54
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; APACHEII: 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 $\pm$ SD, or n (%)
Infection sites, n (%)	
BSI	40 (40)
Pulmonary infection	64 (64)
Intraperitoneal infection	9 (9)
Incision infection	6 (6)
Others	18 (18)
PMB: polymyxin B; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; APACHEII: 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	

Clinical Effects And Safety Of Pmb

The infection and condition improved after 7 days of PMB treatment. Temperature, white blood cells, procalcitonin and APACHE II levels were significantly decrease. Platelets was significantly increased ($P < 0.001$). The number of patients with mechanical ventilation or shock decreased after PMB treatment (Table 2).

Table 2
Comparison of infection and condition between before and treatment 7 days

Parameter	Day 0	Day 7	<i>P</i>
Heart rate, mean $\pm$ SD	92.020 $\pm$ 21.548	97.36 $\pm$ 20.353	0.895
Temperature, mean $\pm$ SD	38.069 $\pm$ 1.131	37.223 $\pm$ 0.727	< 0.001
WBC, mean $\pm$ SD	16.012 $\pm$ 7.814	10.612 $\pm$ 6.726	< 0.001
PLT, mean $\pm$ SD	111.709 $\pm$ 97.676	190.953 $\pm$ 162.986	< 0.001
CRP, mean $\pm$ SD	111.114 $\pm$ 77.248	64.330 $\pm$ 70.688	< 0.001
PCT, mean $\pm$ SD	15.709 $\pm$ 25.192	5.661 $\pm$ 11.556	< 0.001
SOFA, mean $\pm$ SD	7.740 $\pm$ 4.134	7.320 $\pm$ 4.410	0.282
APACHE II, mean $\pm$ SD	17.750 $\pm$ 7.685	15.98 $\pm$ 7.948	0.007
Mechanical ventilation, n (%)	51	26	< 0.001
Septic shock, n (%)	49	26	< 0.001
WBC: white blood cell; PLT: platelet count; PCT: procalcitonin; SOFA: Sequential Organ Failure Assessment; APACHEII: Acute Physiology and Chronic Health Evaluation II.			

The major adverse reactions occurred in 16 cases (16%), 7 cases had at least two adverse reactions, but none was discontinued for adverse reaction. The nephrotoxicity is manifested by transient creatinine and urea nitrogen elevations, and no patient required hemodialysis. Among the neurotoxicity, 4 cases showed persistent drowsiness, transient irritability, paresthesia, fatigue, dizziness, or drowsiness, and the other two cases underwent invasive mechanical ventilation due to adverse reactions of respiratory depression. Eosinophil increase were transient adverse reactions. The mean hospitalization time was 41 days, and the residence time of ICU was 26 days. The outcomes of patients receiving intravenous PMB are showed in Table 3. 25% deaths occurred 7–14 days after enrollment,as shown in the Kaplan-Meier survival curve (Fig. 1).

Table 3
The outcomes of patients receiving intravenous PMB

outcomes	n (%)
Adverse events, n (%)	16 (16)
Nephrotoxicity, n (%)	7 (7)
Neurotoxicity, n (%)	6 (6)
Skin hyperpigmentation, n (%)	3 (3)
Eosinophil increase, n (%)	7 (7)
ICU mortality	12 (12)
Hospital mortality	15 (15)
28-day mortality	40 (40)

Differences In Characteristics Between The Survivors And Nonsurvivors

The survivors and nonsurvivors had similar characteristics and great homogeneity (Table 4). Age, sex and chronic medical conditions were similar in the two groups, and types of adverse reactions were not significantly different. Laboratory parameters, including white blood cell count, procalcitonin, and C-reactive protein, were also similar in the two groups. But the platelet count in nonsurvivors group was less than survivors ($P=0.001$). In terms of clinical characteristics, SOFA (6.77 versus 9.25, $P=0.004$) APACHE II scores (16.17 versus 19.78, $P=0.016$) and the number of patients with mechanical ventilation (21 versus 30, $P<0.001$) or septic shock (17 versus 32, $P<0.001$) were lower in survivors group than nonsurvivors group. The mortality of 85 patients with identify pathogens was 38.82%, while the mortality of patients with negative pathogen culture results was 46.67% ($P=0.580$). During the treatment, there were similar adverse reactions related to PMB in the two groups.

Table 4

Characteristics associated with 28-day mortality among patients who received intravenous PMB

Parameter	Value for:		<i>P</i>
	Survivors (n = 60)	Nonsurvivors (n = 40)	
Age, y, mean $\pm$ SD	54.65 $\pm$ 16.23	57.8 $\pm$ 18.45	0.370
Female, n (%)	47 (78.3%)	32 (80.0%)	0.840
WBC, mean $\pm$ SD	15.89 $\pm$ 7.18	15.97 $\pm$ 8.90	0.966
PLT, mean $\pm$ SD	131.37 $\pm$ 101.96	71.15 $\pm$ 66.27	0.001
PCT, mean $\pm$ SD	11.08 $\pm$ 18.58	18.12 $\pm$ 27.68	0.173
CRP, mean $\pm$ SD	131.36 $\pm$ 105.03	126.69 $\pm$ 67.46	0.824
SOFA, mean $\pm$ SD	6.77 $\pm$ 4.07	9.25 $\pm$ 4.25	0.004
APACHE II, mean $\pm$ SD	16.17 $\pm$ 7.80	19.78 $\pm$ 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, mean $\pm$ SD	15.98 $\pm$ 15.52	17.6 $\pm$ 20.24	0.670
ICU stay before intravenous PMB, mean $\pm$ SD	8.69 $\pm$ 8.62	11.76 $\pm$ 12.58	0.155
duration of PMB therapy, mean $\pm$ SD	12.07 $\pm$ 5.72	12.16 $\pm$ 6.38	0.067
Identify microorganisms, n (%)	52 (86.67%)	33 (82.5%)	0.580
KP, n (%)	32 (53.3%)	16 (40.0%)	0.191
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

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:		<i>P</i>
	Survivors (n = 60)	Nonsurvivors (n = 40)	
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.			

Univariate and Multivariate Analyses of Factors Associated with 28-day mortality

The factors with statistically significant difference in univariate analysis were analyzed by Logistic regression (Table 5). Patients were grouped according to quartiles of PLT, SOFA score, APACHE II score. Multivariate analysis showed that mechanical ventilation ($P = 0.023$, OR = 3.58; CI: 1.194–10.739), 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 CRGNB. The 28-day mortality was 58.824% in the mechanical ventilation patients compared to 20.408% in the non-mechanical ventilation patients. The 28-day mortality was 65.306% in the septic shock patients compared to 15.686% in the non-septic shock patients. Survival of patients are shown in Fig. 2.

Table 5
Multivariate analysis of factors associated with 28-day mortality

Variable	OR (95%CI)	<i>P</i> -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

Infections caused by CRGNB usually affect patients with multiple comorbidities and lead to higher mortality rates. And gram-negative bacilli are rapidly emerging in the world, these isolates are resistant to virtually all commonly used antibiotics, finding effective antibiotics is crucial[10]. In our research, PMB treatment of CRGNB infection patients with ICU-related mortality was 12%, hospital mortality was 15%, 28-day mortality was 40%. In infected carbapenem-resistant *Acinetobacter baumannii* patients without

appropriate empirical antimicrobial therapy, the overall mortality rate was 86.1%[21]. The ICU mortality rate was 45.2% in critically ill patients infected with CRGNB who received tigecycline therapy[22], and the in-hospital mortality rate was 62.5%[23]. The 30-day mortality in the treatment of infections due to carbapenem-resistant Enterobacteriaceae was 50% after ceftazidime-avibactam treatment[24]. Therefore, PMB may reduce the mortality of patients with CRGNB.

Our study found that after 7 days of PMB treatment, the temperature of patients with CRGNB 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 C-reactive protein were all reduced. The symptoms of thrombocytopenia in patients with CRGNB infection also improved. APACHE II scores were also lower than the initial scores. So, PMB treatment was clinically effective drug for the patients infected with CRGNB. The mortality of PMB target therapy was 38.82%, while the mortality of patients with empiric therapy was 46.67% ($P = 0.580$). The unnecessary or inadequate broad empiric antibiotics were associated with higher mortality[25]. We should underscore the need to better identify patients with CRGNB quickly and for more judicious use of PMB.

Our results shown that PMB therapy was safe in the treatment of infections caused by CRGNB. The intravenous PMB was well tolerated in most of our patients, the major adverse reactions occurred in 16 cases (16%), 7 cases had at least two adverse reactions, eight of whom had transient adverse reactions. Nephrotoxicity occurred in 7 cases (7%) were mild and reversible, none required renal replacement therapy. The prevalence of nephrotoxicity was not lower in our study than in observational studies (6–40.5%)[11, 26–28]. Assessing of the contribution of PMB to renal impairment difficult. This was not attributed solely to PMB due to presence of other factors such as infection, septic shock, multiple organ dysfunction syndrome (MODS), and concomitant use of other nephrotoxic drugs. The PMB population pharmacokinetics study has made a significant contribution to optimizing the clinical use of this important last-line antibiotic in patients[17].

Neurotoxicity of PMB is less frequent than nephrotoxicity, and it's usually mild and resolve after prompt discontinuation of therapy. But, among the 6 patients with neurotoxicity, 2 cases underwent invasive mechanical ventilation due to adverse reactions of respiratory depression. Neither patient used sedative analgesics. Patients with respiratory depression did not stop PMB therapy and removed the endotracheal tube before the end of PMB treatment. In previous study on the use of PMB in patients, 7% course of intravenous PMB was associated with neurotoxicity[11], no adverse reactions of respiratory depression. Yet another study, however, none of the cases occurred neurotoxicity complications among 247 patients who were therapy with PMB in Brazil[26]. Besides, 3 cases (3%) developed skin hyperpigmentation in the face and neck, found no effect from skin hyperpigmentation on the efficacy of PMB. The incidence is lower than previous studies[26]. During treatment, there were no other adverse reactions such as rashes, itching, dermatitis, drug fever, etc. Anyway, the safety of polymyxins therapy requires further monitor, caution is of necessity.

Mechanical ventilation and septic shock were all independent factor associated with higher 28-day mortality risk. Clinicians faced with high mortality risk patients with sepsis and limited treatment options may resort to PMB-based combination therapy. But a previous study of a large US cohort found that most patients with culture-positive community onset sepsis did not have resistant bacteria [25], the epidemiology of sepsis in Chinese ICUs found that only 12% of culture-positive were multi-drug resistant organisms[29]. In our study, the mortality of patients with empiric PMB therapy was Higher. So, we underscore the need for quickly identify CRGNB and an increased on judicious use of PMB for the target treatment of sepsis, to avoid progression to mechanical ventilation or septic shock. Because the optimization and validation of PMB-based combinations will have considerable clinical benefits.

Limitation

In the present study has several major limitations, including the real-world design, lacking control group, patients with CRGNB infections who were treated with PMB less than 7 days were not included. Another limited was the small number of patients with CRGNB. The serum PMB concentrations were not determined in the study. The decision to use additional antibiotics was made by the primary clinicians, which may have introduced bias. Of course, the concomitant use of other antibiotics with PMB cannot allow attributing efficacy solely to PMB. The success of microbiology depends on subsequent culture clearance, but we judge by clinical symptoms, which can introduce bias. Side effects were difficult to evaluate properly due to other drugs in serious ill. Despite these limitations, our study is a large multicenter study evaluating a range of CRGNB infections treated with PMB combination therapy.

Conclusion

In summary, the findings from our study suggest that PMB may be as effective and safe as standard antibiotics for the treatment of CRGNB. we should quickly identify CRGNB and early use of PMB for sepsis are recommended because of the higher mortality risk in patients with septic shock or mechanical ventilation. Clinicians should apply strict protocols when using this antimicrobial agent to prevent the occurrence and spread of polymyxin resistance. Timely and appropriate use of PMB will have a positive impact on clinical outcomes.

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 acquisition of the data. Zhang XJ and Sun TW had all the data in the research and take responsibility for the full 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 reviewing this article and making necessary changes to improve it. All authors review and approved the final manuscript.

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 on 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 for reasons of the real-world design and anonymization of patient identifiers before analysis.

Consent for publication

All the authors have read the manuscript, approved this submission, and consented for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Survival analysis at 28 days: Kaplan-Meier curve

Figure 2

Survival curves of patients with mechanical ventilation(A) or septic shock (B), (Log-rank, $P < 0.01$)