Clinical Effects of Polymyxin B in Patients infected with Carbapenem-resistant organisms

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Abstract

Purpose: Carbapenem-resistant organisms (CROs) pose great challenges for clinical treatment. Polymyxin B (PMB) is one of the “last resort” choices of CRO infections. We explored the possible factors affecting PMB efficacy.

Methods: This retrospective study involved CRO infected patients treated with PMB for ≥ 72 h. The endpoint indicator was clinical efficacy. We compared the characteristics (demographics, pathogenic bacteria, PMB treatment) between patients who had “clinical success” (CS) and “clinical failure” (CF).

Results: A total of 192 patients were enrolled: 110 in the CS group and 82 in the CF group. The total cumulative dose for the CS group was higher than the CF group [1100 (700–1443.75) vs. 800 (500–1112.5) mg; $P = 0.001$]. Treatment duration in the CS group was longer than the CF group [11 (8–14) vs. 8 (6–11) days; $P < 0.000$]. Multivariate logistic regression analysis showed mechanical ventilation, vasoactive agents, multiple-site infection, and total cumulative dose to be independently associated with clinical efficacy. Cox survival analysis for 30-day mortality also showed that the use of vasoactive agents and the total cumulative dose of PMB could influence survival time and mortality rate independently.

Conclusion: PMB had good efficacy and a low prevalence of adverse reactions. The total cumulative dose, duration of PMB treatment, mechanical ventilation, vasoactive agents, and multiple-site infection were factors associated with the clinical efficacy of PMB.

1. Introduction

Carbapenem-resistant organisms (CROs) are Gram-negative bacteria that are resistant to carbapenem antibiotics. The main species of CROs are Enterobacteriaceae-resistant organisms (CREs), *Acinetobacter baumannii*-resistant organisms, and *Pseudomonas aeruginosa*-resistant organisms.[1] Due to limited treatment options and frequently a poor prognosis, CROs pose considerable challenges for clinical treatment. Therefore, research on treatment of CRO infections has attracted widespread attention. Drugs reported to be efficacious in treating CROs include colistin, aminoglycosides, tigecycline, fosfomycin, ceftazidime/avibactam, and ceftolozane/tazobactam, and combination therapy can be superior to monotherapy.[2]

Polymyxin B (PMB) is a type of polypeptide antibiotic discovered in 1947.[3] Polymyxins have strong antibacterial activity against most Gram-negative bacteria, but their clinical use has been restricted due to side effects, such as neurotoxicity and nephrotoxicity. Along with the emergence of multidrug-resistant Gram-negative bacteria, PMB and colistin have attained renewed attention because of their specific effects. Studies have shown that PMB has lower nephrotoxicity compared with colistin at recommended doses.[4–6] Therefore, PMB has been used as a first-line agent for CRO infections since it was listed in mainland China.

Studies on the pharmacokinetics, pharmacodynamics, and medications of PMB have been deepening gradually.[7] Related studies have demonstrated the efficacy, toxicity, and efficacy prediction of PMB in the treatment of CRO infections. Early treatment with PMB [8] and sound renal function [9] usually lead to better outcomes. However, PMB may have an inferior microbiologic clearance rate of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) compared with aminoglycoside.[10]

Although PMB is used widely clinically, several factors affecting efficacy and side effects must be explored in real-world scenarios. Therefore, we conducted a retrospective study on the administration, factors affecting efficacy, and adverse effects of PMB to provide a reference for the rational use of PMB.

2. Patients And Methods

2.1 Ethical approval of the study protocol

The study protocol was approved by the Ethics Committees of the Second Xiangya Hospital of Central South University (LYF-2020021) in Changsha, China. It was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients gave their written informed consent to have their data included in this study.

2.2 Patients

This retrospective study involved patients admitted to the Second Xiangya Hospital of Central South University from 2018 to 2019. The inclusion criteria were patients: (i) with a medication history of PMB (Shanghai Number 1 Biochemical & Pharmaceuticals, Shanghai, China); (ii) infected with a CRO according to bacterial-culture results; (iii) with complete medical data and basic information. The exclusion criteria were: (i) PMB administration < 72 h; (ii) patients with severe liver/kidney dysfunction or a malignant tumor before PMB treatment.

After selecting patients based on inclusion and exclusion criteria, patients were divided into two groups according to treatment results.

2.3 Collection of clinical data

Collection of clinical data was based on medical records. We collected data on: basic demographic characteristics; diagnoses; infection sites; pathogenic bacteria (and their sensitivity); Acute Physiology and Chronic Health Evaluation (APACHE) II score; medication regimens (PMB and drugs it was combined with); treatment duration; parameters of efficacy evaluation; treatment results; adverse effects.

2.4 Definitions

Patients were divided into “clinical success (CS)” and “clinical failure (CF)” groups according to efficacy. “CS” was defined as improvements and disappearances of microbiologic and clinical symptoms and parameters including body temperature, biochemistry indicators of infection, culture results and clinician documented improvements. “CF” was defined as failure to meet all the criteria for CS and

deterioration/persistence of symptoms or death.[9, 11, 12].“Adverse effects” were defined as harmful reactions to PMB unrelated to the purpose of treatment which emerged after using the drug and disappeared when its use was stopped, including nerve–muscle blockade, nephrotoxicity, or skin pigmentation. Nephrotoxicity was based on the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria.[13]

2.5 Microbiology

Testing for drug sensitivity was done by laboratory physicians using analytical instruments by the broth-microdilution method. The minimum inhibitory concentration (MIC) was determined by a VITEK®2 system (bioMérieux, Marcy-l'Étoile, France) based on recommendations of the Clinical and Laboratory Standards Institute (Beijing, China). “Carbapenem resistance” was defined as the MIC of imipenem and meropenem ≥ 4 mg/L. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, v8.0, 2018), bacteria were resistant to tigecycline and colistin if their MIC was > 2 mg/L, respectively.[14]

2.6 Statistical analyses

Statistical analyses were undertaken using SPSS v21.0 (IBM, Armonk, NY, USA). Count data were analyzed by the chi-square test. Data with a normal distribution are expressed as the mean $\pm$ standard deviation, and were analyzed by the independent *t*-test. Data with a non-normal distribution are expressed by the median value and interquartile range, and were analyzed by the nonparametric test. Multivariate logistic regression was used to assess for the independent predictors of the clinical efficacy of PMB. Factors entered into the multivariate logistic model included any baseline differences between CS and CF groups that had $P < 0.1$ on bivariate analysis. $P < 0.05$ was considered significant. Moreover, those variables were included in the Cox model for 30-day mortality, $P < 0.05$ was considered significant.

3. Results

3.1. Characteristics

A total of 273 patients administered PMB were found in the database of the Second Xiangya Hospital of Central South University between 2018 and 2019. According to the inclusion and exclusion criteria, 192 patients were included in statistical analyses and most patients came from the “Intensive Care Unit” (59.4%).

The overall information for patients, including basic information, diagnostic information, and microbial infections, is listed in Table 1. Among all patients, 61.4% had a single-site infection and, in 56% of cases, the infection site was the respiratory tract. Also, 210 CRO strains were isolated from 192 patients. The highest proportion of pathogenic bacteria was *Acinetobacter baumannii* (63.0%), followed by *Klebsiella pneumoniae* (25.5%), *Pseudomonas aeruginosa* (17.2%), *Escherichia coli* and *Enterobacter cloacae* (3.6%). Testing for antimicrobial susceptibility showed that 15.0% of strains had a tigecycline MIC > 2 mg/L, and no strains had colistin MIC > 2 mg/L.

Table 1
Demographics and clinical characteristics of the study cohort

Characteristic	Patients
	(N = 192)
Age	55.0 ± 20.2
Sex	
Male	140 (72.9%)
Female	52 (27.1%)
Weight (kg)	60.0 (50.0–60.0)
APACHE II score	19.0 (12.0–24.2)
Mechanical ventilation	131 (68.2%)
Vasoactive agents	101 (52.6%)
Infection site	
Multiple	74 (38.5%)
Single	118 (61.4%)
Source of infection	
Respiratory tract	170 (88.5%)
Blood	27 (23.4%)
Intracranial	10 (5.2%)
Urinary tract	13 (6.8%)
Digestive tract	4 (2.1%)
Abdomen	23 (12.0%)
Skin/soft tissue	3 (1.6%)
Underlying disease	
Pulmonary disease	140 (72.9%)
Hypertension	54 (28.1%)
Diabetes mellitus	27 (14.1%)
Recent surgery	17 (8.8%)
Nervous system	58 (30.2%)
Data are reported as numbers (%) or median value (interquartile ranges [IQR]), as appropriate.	

Characteristic	Patients
	(N = 192)
Pathogenic bacteria (N = 210)	
<i>Acinetobacter baumannii</i>	121 (63.0%)
<i>Klebsiella pneumoniae</i>	49 (25.5%)
<i>Pseudomonas aeruginosa</i>	33 (17.2%)
<i>Escherichia coli</i> or <i>Enterobacter cloacae</i>	7 (3.6%)
Antimicrobial susceptibility	
Tigecycline MIC > 2 (mg/L)	24/160 (15.0%)
Colistin MIC > 2 (mg/L)	0/210 (0.0%)
Data are reported as numbers (%) or median value (interquartile ranges [IQR]), as appropriate.	

3.2. Medications and outcomes

All patients used PMB (Shanghai Number 1 Biochemical & Pharmaceuticals) according to manufacturer instructions and International Consensus Guidelines for the Optimal Use of the Polymyxins [15]. Almost all patients included in statistical analyses were administered PMB by intravenous drip (99.5%) (Table 2). We found that 35.9% of patients were given a loading dose of 50.0–100.0 mg. The dose per kilogram (mg/kg/q12h) was 0.86 (range, 0.82–1.00). Treatment duration was 10.0 (range, 7.0–13.5) days. PMB combined with another drug was given to 91.1% of cases. Meropenem was the agent combined most commonly with PMB (32.8%), followed by tigecycline (32.8%), and cefoperazone/sulbactam (27.6%).

Table 2
Regimens and outcomes

Treatment	Value
Total daily dose of PMB (mg)	100.0 (100.0–100.0)
Loading dose (N, %)	69 (35.9%)
Loading dose (mg)	50.0 (50.0–100.0)
Maintenance dose (mg)	50.0 (50.0–50.0)
Total cumulative dose (mg)	950.0 (650.0–1350.0)
Dose per kg (mg/kg/q12h)	0.86 (0.82–1.00)
Administration (N, %)	
Intravenous drip	191 (99.5%)
Intrathecal injection	5 (2.6%)
Injection	1 (0.5%)
Inhalation	8 (4.2%)
Start of PMB treatment after CRO confirmed (days)	1.0 (0.0–4.0)
Treatment duration (days)	10.0 (7.0–13.5)
Combination	
Alone	17 (8.9%)
Meropenem	64 (33.3%)
Tigecycline	63 (32.8%)
Cefoperazone/sulbactam	53 (27.6%)
Outcome	Value
30-day mortality rate	29 (15.1%)
Duration of hospitalization, median (IQR), days	34.0 (21.0–56.8)
Bacteria elimination	46 (24.0%)
Time needed to clear bacteremia (days)	8.0 (6.0–13.0)
Data are reported as numbers (%) or median values (interquartile ranges [IQR]), as appropriate.	

There were 110 patients in the CS group and 82 patients in the CF group. PMB was clinically efficacious in 57.3% of cases. The prevalence of all-cause in-hospital mortality was 14.6%. Bacteria elimination was

successful in 24.0% of cases, and the time required to clear bacteremia was 8.0 (range, 6.0–13.0) days. Duration of hospitalization was 34.0 (range, 21.0–56.8) days.

3.3 Factors related to the clinical efficacy of PMB

To explore the factors that affected the clinical efficacy of PMB, we compared all the demographics, clinical characteristics, and details of PMB treatment (dose, loading dose, timing of medication, combined medication, treatment duration) between the two groups. There was no significant difference in the time for starting PMB treatment after CROs infection confirmation (1.0 vs. 1.5 days, $P = 0.761$). Meanwhile, statistical difference in the combination rate of commonly used drugs did not exist in CF and CS groups (Table 3). The median total cumulative dose of patients in the CS group tended to be higher (1100 vs. 800 mg, $P = 0.001$) and median treatment duration was longer (11 vs. 8 days, $P = 0.000$). More patients in the CF group had mechanical ventilation and vasoactive agents ($P \leq 0.001$). The clinical effect for patients with multiple-site infections was worse compared with that for patients with a single-site infection (29.1% vs. 70.9%, $P = 0.002$) (Table 3). The Mantel–Haenszel chi-square test revealed a linear association between treatment duration ($P = 0.003$) and total cumulative dose ($P = 0.005$), which correlated with CS (Fig. 1). The most common combination drugs include meropenem, tigecycline and Cefoperazone/sulbactam. However, no significant differences were found for the mode of administration and drug combination.

Table 3
Clinical characteristics of patients in the CS group and CF group after PMB treatment

Parameters	Success	Failure	P
	(N = 110)	(N = 82)	
Age	53.3 ± 18.4	57.3 ± 22.3	0.187
Sex (male)	84 (76.4%)	56 (68.3%)	0.213
APACHE II score	19.0 (13.2–24.0)	19.0 (11.0–26.5)	0.878
Mechanical ventilation	60 (54.5%)	71 (86.6%)	< 0.001
Vasoactive agents	41 (37.3%)	60 (73.2%)	< 0.001
Infection site			0.002
Multiple	32 (29.1%)	42 (51.2%)	
Single	78 (70.9%)	40 (48.8%)	
Source of infection			
Respiratory tract	100 (90.9%)	70 (85.4%)	0.233
Blood	12 (10.9%)	15 (18.3%)	0.145
Intracranial	6 (5.5%)	4 (4.9%)	1.000
Urinary tract	7 (6.4%)	6 (7.3%)	0.795
Digestive tract	2 (1.8%)	2 (2.4%)	1.000
Abdomen	13 (6.4%)	10 (6.1%)	0.940
Skin/soft tissue	2 (1.8%)	1 (1.2%)	1.000
Underlying diseases			
Pulmonary disease	79 (71.8%)	61 (74.4%)	0.692
Hypertension	35 (31.8%)	19 (23.2%)	0.187
Diabetes mellitus	15 (13.6%)	12 (14.6%)	0.844
Recent surgery	12 (10.9%)	5 (6.1%)	0.246
Nervous system	39(35.5%)	19(23.2%)	0.067
Pathogenic bacteria			
<i>Acinetobacter baumannii</i>	70 (63.6%)	51 (62.2%)	0.838
<i>Klebsiella pneumoniae</i>	30 (27.3%)	19 (23.2%)	0.519

Parameters	Success	Failure	P
	(N = 110)	(N = 82)	
<i>Pseudomonas aeruginosa</i>	18 (16.4%)	15 (18.3%)	0.726
<i>Escherichia coli</i> or <i>Enterobacter cloacae</i>	2 (1.8%)	5 (6.1%)	0.139
Loading dose (N, %)	43 (39.1%)	26 (31.7%)	0.292
Loading dose (mg/d)	50.0 (50.0–100.0)	50.0 (50.0–100.0)	0.477
Maintenance dose (mg/d)	100.0 (100.0-100.0)	100.0 (100.0–100.0)	0.651
Total cumulative dose (mg)	1100.0 (700.0–1443.8)	800.0(500.0–1112.5)	0.001
Dose per kg (mg/kg/q12h)	0.87 (0.79–1.00)	0.86 (0.83–1.00)	0.541
Daily PMB dose (mg)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	0.794
Administration			
Intravenous drip	110 (100.0%)	81 (98.8%)	1.000
Intrathecal injection	3 (2.7%)	2 (2.4%)	1.000
Injection	0	1(1.2%)	0.427
Inhalation	6 (5.5%)	2 (2.4%)	0.470
Starting PMB treatment after CRO confirmed (days)	1.0 (0.0–4.0)	1.5 (0.0–3.8)	0.761
Treatment duration (days)	11.0 (8.0–14.0)	8.0(6.0–11.0)	< 0.001
Combination			
PMB alone	7 (6.4%)	10 (12.2%)	0.159
Meropenem	40 (36.4%)	24 (29.3%)	0.302
Tigecycline	32 (29.1%)	31 (37.8%)	0.203
Cefoperazone/sulbactam	31 (28.2%)	22 (26.8%)	0.836

Data are reported as numbers (%), mean $\pm$ standard deviation or median values (interquartile ranges [IQR]), as appropriate. Bold font indicates data with significant differences.

We also created a multivariate logistic regression model for the clinical efficacy of PMB that incorporated use of mechanical ventilation and vasoactive agents, multiple-site infection, duration of PMB treatment (days), and total cumulative dose of PMB. After adjustments, use of mechanical ventilation (odds ratio =

3.043; 95% confidence interval: 1.253–7.389; P = 0.014), vasoactive agents (2.560; 1.180–5.554; 0.017), multiple-site infection (1.280; 1.077–4.083; 0.001), and the total cumulative dose of PMB (1.001; 1.000–1.001; 0.037) were independently associated with the clinical efficacy of PMB (Table 4). Moreover, the results of Cox-regression survival analysis for 30-day mortality showed that the use of vasoactive agents (4.335; 1.006–18.685; 0.049) and the total cumulative dose of PMB (0.998; 0.996–0.999; 0.006) could influence survival time and mortality rate independently (Table 5). High cumulative dose was an independent protective factor, while the use of vasoactive drugs was an independent risk factor (Fig. 2).

Table 4
Multivariate logistic regression of clinical efficacy of PMB treatment

Variable	Adjusted OR	95% CI	P value
Mechanical ventilation	3.043	1.253–7.389	0.014
Vasoactive agents	2.560	1.180–5.554	0.017
Multiple-site infection	1.280	1.077–4.083	0.001
Total cumulative dose (mg)	1.001	1.000–1.001	0.037
Treatment duration (days)	0.960	0.906–1.018	0.174
Bold font indicates data with significant differences.			

Table 5
Cox-regression survival analysis for 30-day mortality

variable	Hazard ratio	95%CI	P
Mechanical ventilation	1.434×10^5	$0.000-7.251 \times 10^{133}$	0.937
Vasoactive agents	4.335	1.006–18.685	0.049
Multiple-site infection	1.907	0.873–4.165	0.105
Total cumulative dose (mg)	0.998	0.996–0.999	0.006
Treatment duration (days)	1.088	0.941–1.257	0.253
Bold font indicates data with significant differences.			

3.4. Adverse effects

Overall, 22 cases (11.4%) suffered the adverse effects of PMB treatment. The most prevalent adverse effect was nephrotoxicity (eight cases; 4.2%), followed by nerve–muscle blockade (three cases; 1.6%) and skin hyperpigmentation (three cases; 1.6%). Moreover, some rare adverse effects occurred, including two cases of drug-induced fever, and drug-induced eruption, pruritus, nausea, general weakness, lethargy, and hepatotoxicity in one patient (Table 6).

Table 6
Adverse reactions following PMB therapy

Adverse effects	Number (%)
Nephrotoxicity	8 (4.2%)
Nerve–muscle blockade	3 (1.6%)
Skin hyperpigmentation	3 (1.6%)
Drug-induced fever	2 (1.0%)
Drug-induced eruption	1 (0.5%)
Pruritus	1 (0.5%)
Nausea	1 (0.5%)
General weakness	1 (0.5%)
Lethargy	1 (0.5%)
Hepatotoxicity	1 (0.5%)
Total	22 (11.4%)

4. Discussion

CRO infections (especially CRE) represent an urgent threat because few drugs are available to treat infections caused by these pathogens. PMB is one of the “last resort” choices for CRO infections. Therefore, the factors that affect PMB efficacy must be clarified for its rational and efficacious application.

We wished to explore the factors affecting PMB efficacy. We enrolled 192 CRO-infected patients; 110 of these patients had CS after PBM treatment and 82 had CF after PBM treatment. PMB was more efficacious in patients who had a longer duration of treatment and a higher total cumulative dose. There was a linear association between treatment duration and total cumulative dose that correlated with CS. More patients in the CF group had mechanical ventilation and vasoactive agents than those in the CS group.

The results of the current study are different from past investigations on the dose and efficacy of PMB. [16–18] Elias et al. showed (in a retrospective study) that increasing the daily dose of PMB (≥ 200 mg/day) reduced in-hospital mortality, and that its benefits outweighed the risk of renal insufficiency.[16] Mortality after PMB treatment was associated with an inappropriate daily dose ($< 15,000$ units/kg/day) in critically ill patients according to a retrospective study conducted by Ismail et al.[17] An investigation on the association between the colistin dose taking into account body weight and microbiologic outcomes showed that higher doses led to better outcomes. [18] However, the exact relationship between the daily dose and efficacy of PMB was not discovered in our study. In the International Consensus Guidelines for

the Optimal Use of the Polymyxins published in 2019.[15] the recommended daily dose of PMB is 1.25–1.50 mg/kg (q12h), and a loading dose of 2.0–2.5 mg/kg is suggested. However, the median daily dose of PMB in our study was 0.86 mg/kg (q12h). Furthermore, the recommended dose given by the PMB manufacturer was 500,000–1000,000 IU divided into two administrations per day, and the median daily dose in our study was 1000,000 IU. Hence, the daily dose in our study was lower than that recommended in guidelines but in accordance with manufacturer instructions. Obviously, the recommended dose in the manufacturer instructions was lower than that in the guidelines. This different association of daily dose and efficacy may be attributed to the cutoff of 200 mg/day set explicitly in Elias's study and the different evaluation method for efficacy and in-hospital mortality.[16] No scholars have reported on the relationship between the cumulative dose and efficacy of PMB. The total cumulative dose of PMB in patients in the CS group was higher than that in the CF group [1100.0 (700.0–1443.8) vs. 800.0 (500.0–1112.5) mg; $P = 0.001$]. High cumulative dose was an independent protective factor for 30-day mortality (0.998; 0.996–0.999; 0.006), however, which was inevitably related to the longer duration of treatment.

Few studies have demonstrated that the efficacy of PMB is related to treatment duration. One retrospective study suggested that prolonging the duration of direct hemoperfusion with PMB-immobilized fibers can improve the clinical efficacy of PMB in septic-shock patients.[19] No scholars have shown that mechanical ventilation and application of vasoactive agents influence the efficacy of PMB. At the same time, the use of mechanical ventilation and vasoactive agents also inevitably means that patients have more serious diseases. This may also be the cause of the different efficacy. However, PMB treatment has been shown to improve the prognosis of patients undergoing mechanical ventilation. [20, 21]

Studies on the timing of medication administration have yielded differing results. In a study on the timing of PMB administration in CRKP-infected patients, early administration of PMB was found to be beneficial for improving bacterial clearance and patient survival.[8] In our study, there was no statistical difference in the timing of PMB medication between different clinical effects. This may indicate that after the confirmation of CROs infection, the timing of PMB medication may not affect the clinical efficacy of PMB in the short term.

There was no difference in the combination rate of these drugs between the CF and CS groups. It could be seen that the combination of drugs in this study may not be one of the factors that cause the difference in clinical efficacy. Several studies have also shown that PMB efficacy is related to its combination with other drugs [22, 23] such as tigecycline and enrofloxacin, but we did not find this to be the case. The differences in these conclusions were associated with the choice of endpoint indicators. PMB, tigecycline, and ceftazidime/avibactam are important drugs in the treatment of CRO infections. An *in vitro* study showed that CRE was much more sensitive to PMB than tigecycline,[24] and that the efficacy of PMB and tigecycline combined was greater than that of PMB alone or tigecycline alone.[10, 25] The combination of PMB and ceftazidime has been demonstrated to have a synergistic effect on CRKP *in vitro*.[26]

The prevalence of total adverse effects was 11.4% in our study. The prevalence of nephrotoxicity was 4.2%, which is lower than that in the study by Mattos and colleagues (40.5%),[27] Oliveira and co-workers (26.8%),[28] and Agarwal and collaborators (11.8%).[6] PMB neurotoxicity is caused mainly by inhibition of acetylcholine in neuromuscular junctions and PMB reabsorption by renal-cell receptors, but the overall mechanism is not known.[29, 30] The reason for the low prevalence of nephrotoxicity may have been the relatively low dose of PMB used in our study. The prevalence of skin hyperpigmentation was 1.6% in our study, which is lower than that reported by Mattos and colleagues (8.1%).[27] The reasons for pigmentation/darkening of skin vary, but the most common reason is melanin production in skin cells (especially in dermal macrophages). [31]

Our study had four main limitations. First, biases could not be controlled completely because this was a retrospective study. Second, the objectivity of PMB efficacy as an endpoint was insufficient. Third, the study cohort was small. Finally, patients had various underlying diseases that would have affected PMB efficacy.

In the future, the factors that affect the efficacy and adverse reactions of PMB must be explored in depth. In addition, pharmacokinetic parameters should be investigated more deeply by measuring the drug concentration in blood to achieve individualized administration of PMB.

5. Conclusions

PMB is an option for patients with CRO infection. It had good efficacy and a low prevalence of adverse reactions in the present study. The total cumulative dose and duration of PMB treatment, mechanical ventilation, vasoactive agents, and multiple-site infection were factors associated with the clinical efficacy of PMB.

Abbreviations

CROs: Carbapenem-resistant organisms; PMB: Polymyxin B; CS: clinical success; CF: clinical failure; CREs: Enterobacteriaceae-resistant organisms; MIC: minimum inhibitory concentration.

Declarations

Availability of data and materials

Available.

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Conflicts of interest:

All authors report no conflicts of interest relevant to this article.

Author Contributions:

JQ and QL conceptualized and designed the study. GHL, HHZ, ZBOY, WQW, JJW, TTQ, and HYY collected data. QQ, HL and HY analyzed the data. GHL, HY, JQ, and QL drafted the manuscript. All authors contributed to the revision and approved the final version of the manuscript.

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Figures

Figure 1

Prevalence of clinical success versus treatment duration and total cumulative dose (Mantel–Haenszel chi-square test).

Figure 2

a. Cox-regression survival analysis of cumulative dose for 30-day mortality. About half of the patients have a total cumulative dose of more than 1000 mg, defined as high cumulative dose. b. Cox-regression survival analysis of vasoactive agents for 30-day mortality.