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ORIGINAL RESEARCH

The Efficacy and Influencing Factors of Polymyxin B in High-Level Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Xuedong Jia[1,2], Zhao Yin[1,2], Wan Zhang[1,2], Shuzhang Du[1,2]

[1]Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China; [2]The Precision Clinical Pharmacy Key Laboratory of Henan Province, Zhengzhou, People's Republic of China

Correspondence: Xuedong Jia; Shuzhang Du, Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe Dong Road, ErQi District, Zhengzhou, Henan, 450052, People's Republic of China, Email jiaxd.zzu@163.com; dushuzhang911@163.com

Background: Polymyxin B (PMB) is a remedial treatment for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection; however, there is a paucity of reports on the treatment of high-level CRKP infections with polymyxin B. Studies are needed to explore its treatment efficacy and associated influencing factors.

Methods: Patients with high-level CRKP infections treated with PMB during hospitalization from June 2019 to June 2021 in a hospital were retrospectively studied, and risk factors affecting the efficacy were explored by subgroup analysis.

Results: A total of 92 patients were enrolled, and the results showed that the PMB-based regimen had a bacterial clearance rate of 45.7%, an all-cause discharge mortality rate of 22.8%, and an incidence of acute kidney injury (AKI) of 27.2% for high-level CRKP treatment. The combination of β-lactams other than carbapenems facilitated bacterial clearance, and the combination of electrolyte disturbances and higher APACHE II scores was detrimental to microbial clearance. Risk factors for all-cause discharge mortality were advanced age, concomitant antifungal drugs, concomitant tigecycline and incidence of AKI.

Conclusion: PMB-based regimens are an effective option for the treatment of high-level CRKP infections. However, the optimal dose of treatment and the choice of combination regimens need to be explored in further studies.

Keywords: efficacy, influencing factors, polymyxin B, carbapenem-resistant *Klebsiella pneumoniae*

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) infections have broken out globally and have become epidemic in several countries.[1] A meta-analysis of 50 original studies showed that CRE-infected patients have a higher risk of death than those infected with the corresponding sensitive organisms,[2] so aggressive countermeasures against CRE infection are important to reduce mortality from infection in patients. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are the most common among CRE infections, and data from the China CRE Network showed that 73.9% of CRE isolates were CRKP.[3] From 2007–2018, the rate of CRKP increased from 0.9% to 19.9% in 19 tertiary hospitals in China.[4]

Infections caused by CRKP pose a major public health threat and are strongly associated with high mortality rates. Adherent villi, capsules, lipopolysaccharides (LPS) and glycosylated lipids or iron carriers constitute the main virulence factors leading to CRKP pathogenicity, and multiple mechanisms of drug resistance exist, of which carbapenemase (KPC) and metallo-β-lactamase (MBL) production are the most common.[5] Previous studies[6–8] showed that when the MIC of CRKP to carbapenems is less than 16 mg/L, infection treatment can be achieved through appropriate dose increases of carbapenems, longer infusion times, and shorter dosing intervals. However, for high-level CRKP strains (MIC ≥ 16 mg/L), carbapenems are no longer available for the treatment of this type of infection.[9] Although ceftazidime-avibactam, aztreonam-avibactam, cefiderocol, imipenem-relebactam, and meropenem-vaborbactam have been reported to

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be active against CRKP in recent years,[10,11] most of these drugs exert antimicrobial activity by inhibiting the action of KPC, and clinical isolates of CRKP strains often harbor multiple resistance mechanisms simultaneously, greatly limiting the choice of therapeutic agents.

Polymyxin B (PMB) has gained renewed interest in recent years because in vitro drug sensitivity tests have shown that it maintains high antimicrobial activity against CRE.[12] PMB exerts antibacterial effects by interacting with lipopolysaccharide (LPS) on the surface of bacterial cell walls, leading to changes in the permeability of bacterial cell membranes.[12] The unique mechanism of action results in minimal cross-resistance with commonly used clinical antibiotics.[13] It was relaunched for use in China in September 2017 and is currently recommended as a remedial treatment for CRKP infection.[13–15] The current use in China has still been relatively short, so the clinical outcomes of PMB-based regimens for high-level CRKP infections have been reported relatively infrequently, and the factors affecting their effectiveness have not been systematically explored. China's Henan province is generally consistent with the national situation, with CRKP accounting for 77% of CRE isolates.[16] With a large number of patients with CRKP infection, it is important to explore appropriate treatment options for the prevention and control of CRKP infection, and previous studies have shown the emergence of colistin-resistant KP strains,[17–19] so exploring the effectiveness of PMB in treating high-level CRKP and its influencing factors is of great reference value to promote the rational use of PMB and to delay the emergence of drug-resistant strains. In this study, we retrospectively analyzed cases of high-level CRKP infections treated with PMB and explored the factors influencing the treatment effect of PMB to provide some reference for the clinical response to high-level CRKP infection.

Methods

Study Design

The study was conducted at the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China), a more than 8500-bed large tertiary teaching and four-district hospital, between June 2019 and June 2021. The inclusion criteria were as follows: patients treated with intravenous PMB monotherapy or in combination and bacterial culture results confirming CRKP infection. The exclusion criteria were as follows: younger than 18 years old or received PMB treatment for less than 7 days. This study was approved by the Research Ethics Commission of Zhengzhou Hospital (2021-KY-0063-002). Because this study was retrospective and information about the patients was withheld, the ethics committee approved our application for exemption from informed consent.

All demographic (age, sex, underlying disease), infection-related indicators (axillary temperature, white blood cell (WBC), procalcitonin (PCT), C-reactive protein (CRP)), microbiological data (before and after drug administration), PMB treatment information (dose, frequency, duration, combination drugs) and survival status at discharge were retrospectively extracted.

Definition of Related Indicators

The Vitek® 2 automated system (France Biomerieux) was used for bacterial identification and drug sensitivity testing. The Clinical and Laboratory Standards Institute (CLSI) 2017 standards were used for the interpretation of the drug sensitivity test results. Imipenem and meropenem were used to screen CRKP, and a minimum inhibitory concentration (MIC) $\geq$ 16 mg/L was considered a high level of resistance to carbapenems. Isolates with MIC $\leq$ 2 mg/L were considered sensitive to PMB (colistin breakthrough point of Enterobacteriaceae).[20]

Microbial clearance and patient hospital all-cause mortality were the primary outcomes, and the occurrence of acute kidney injury (AKI) was the secondary outcome. Bacterial clearance was considered if CRKP was not detected in all of the infected sites after treatment, and antimicrobial treatment failure was considered if CRKP was still detected in any infected site after treatment. All-cause discharge mortality was defined as all-cause death during hospitalization. A creatinine increase of 1.5 times the baseline level was defined as AKI.[21]

Statistical Methods

All data were statistically analyzed using IBM SPSS 24.0 software (IBM, United States). Count data were described by the number of patient cases and the percentages, and differences were compared using Pearson's chi-square test (χ^2) or Fisher's exact test. Normally distributed data were expressed as the mean ± standard deviation for measurement data and compared using the *t*-test; nonnormally distributed measures were expressed as median (interquartile range [IQR]) and compared using the Mann–Whitney *U*-test. Factors influencing the microbial clearance rate and all-cause discharge mortality of PBM were analyzed by logistic regression in the subgroup analysis. All variables with a $p \leq 0.1$ were further used in a multivariate logistic regression model in a backward stepwise manner. Differences were considered statistically significant at $p < 0.05$.

Results

Characteristics

A total of 92 patients treated with PMB for ≥7 days for high-level CRKP infection were included in this study (Figure 1). The general information of the patients is listed in Table 1. The overall median age was 63.5 years, and 81.5% for male patients (Table 1). The median number of hospital days was 35 (Table 1), and the number of ICU admission days was 25. Two or more sites of infection were present in 40 (43.5%) patients, of which 85 (92.4%) were pulmonary and 28 (30.4%) were predominantly bloodstream infections. There were 38 (41.3%) patients with coinfection with other pathogens, including 20 (21.7%) with *Pseudomonas aeruginosa* and 17 (18.5%) with *Acinetobacter baumannii* (Table 1). The drug sensitivity results showed that the isolates were resistant to most of the tested drugs, and most of the isolates were sensitive to polymyxin (90/92, 91.8%) and tigecycline (85/92, 92.4%), of which 40 (43.5%) isolates had MICs ≤0.5 mg/L for polymyxin, as detailed in Table 2.

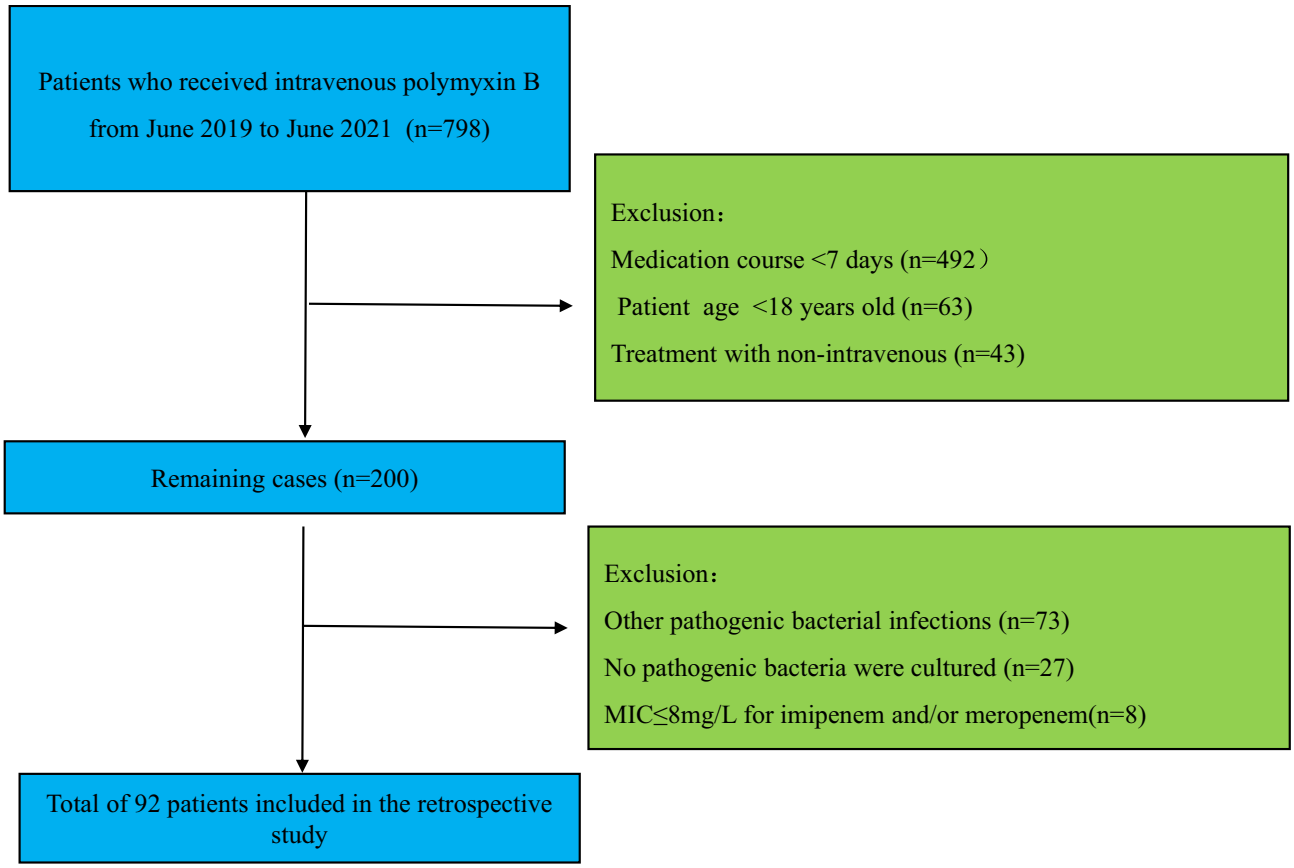

Figure 1 Schematic diagram of the patient screening process.

Table 1 Clinical Characteristics of Patients and Univariate Analysis of Factors Associated with Microbiological Clearance and All-Cause Discharge Mortality

Related Indicators	Overall (N=92)	Clearance (N=42)	Failure (N=50)	*P* value	Non-Survivors (N=21)	Survivors (N=71)	*P* value
Demographics							
Age (years)	63.5 [52.0, 71.5]	69 [67.0, 78.0]	74 [67.0, 78.0]	0.520	76 [69.0, 91.0]	72 [67.0, 74.5]	0.020
Admission to ICU	25 [16.25, 36.75]	35 [20.0, 43.5]	21 [12.0, 31.0]	0.375	32 [21.0, 43.0]	21 [15.0, 36.5]	0.416
Hospitalization days	35 [26.0, 46.0]	37 [28.0, 66.0]	28 [20, 38]	0.540	38 [32.0, 88.0]	29 [22.0, 44.0]	0.907
APACHE II score	17 [12.75, 24.0]	13 [7.5, 19.0]	16 [14, 24]	0.039	17 [15.0, 24.0]	14 [8.0, 21.5]	0.229
Gender (male)	75 (81.5)	33 (78.6)	42 (84.0)	0.504	17 (81.0)	58 (81.7)	1.000
Comorbidities							
Septic shock	25 (27.2)	12 (28.6)	13 (26.0)	0.782	7 (33.3)	18 (25.4)	0.577
Sepsis	27 (29.3)	11 (26.2)	16 (32.0)	0.542	9 (42.9)	18 (25.4)	0.172
Hypoproteinemia	35 (38.0)	18 (42.9)	17 (34.0)	0.383	10 (47.6)	25 (35.2)	0.318
Mechanical Ventilation	26 (28.3)	13 (31.0)	13 (26.0)	0.599	6 (28.6)	20 (28.2)	1.000
Pulmonary disease	4 (4.3)	0 (0)	4 (8.0)	0.122	0 (0)	4 (5.6)	0.570
Cardiovascular diseases	27 (29.3)	13 (31.0)	14 (28.0)	0.757	8 (38.1)	19 (26.8)	0.414
Hypertension	36 (39.1)	18 (42.9)	28 (36.0)	0.502	8 (38.1)	28 (29.4)	1.000
Cerebrovascular diseases	44 (47.8)	19 (45.2)	25 (50.0)	0.649	9 (42.9)	35 (49.3)	0.629
Solid tumor	14 (15.2)	5 (11.9)	9 (18.0)	0.563	5 (23.8)	9 (12.7)	0.297
Hematological malignant disease	5 (5.4)	2 (4.8)	3 (6.0)	1.000	2 (9.5)	3 (4.2)	0.320
Diabetes	23 (25.0)	11 (26.2)	12 (24.0)	0.809	5 (23.8)	18 (25.4)	1.000
Kidney disease	4 (4.3)	0 (0)	4 (8.0)	0.122	0 (0)	4 (5.6)	0.570
Liver disease	6 (6.5)	2 (4.8)	4 (8.0)	0.684	2 (9.5)	4 (5.63)	0.617
Digestive system diseases	12 (13.0)	8 (19.0)	4 (8.0)	0.134	3 (14.3)	8 (12.7)	1.000
Transplantation history	2 (2.2)	1 (2.4)	1 (2.0)	1.000	0 (0)	2 (2.8)	1.000
Surgery	49 (53.3)	21 (50.0)	28 (56.0)	0.566	10 (47.6)	39 (54.9)	0.623
Electrolyte disturbance	29 (31.5)	9 (21.4)	20 (40.0)	0.056	6 (28.6)	23 (32.4)	0.769
Infection variables							
≥2 sites of infection	40 (43.5)	18 (42.9)	22 (44.0)	0.912	7 (33.3)	33 (46.5)	0.326
Pneumonia	85 (92.4)	38 (90.5)	47 (94.0)	0.525	21 (100)	64 (90.1)	0.345
Bloodstream	28 (30.4)	11 (26.2)	17 (34.0)	0.417	5 (23.8)	23 (32.4)	0.592
Abdominal	4 (4.3)	1 (2.4)	3 (6.0)	0.623	1 (54.8)	3 (4.2)	1.000
Urinary tract	8 (8.7)	5 (11.9)	3 (6.0)	0.463	1 (4.8)	7 (9.9)	0.677
Intracranial infection	2 (2.2)	4 (9.5)	3 (6.0)	0.698	0 (0)	7 (9.9)	0.345
Other site infections	7 (7.6)	2 (4.8)	5 (10.0)	0.448	2 (9.5)	5 (7.0)	0.675
Co-infection with other pathogens	38 (41.3)	18 (42.9)	20 (40.0)	0.782	9 (42.9)	29 (40.8)	1.000
Acinetobacter baumannii	17 (18.5)	6 (14.3)	11 (22.0)	0.424	2 (9.5)	15 (21.1)	0.341

(*Continued*)

Table 1 (Continued).

Related Indicators	Overall (N=92)	Clearance (N=42)	Failure (N=50)	*P* value	Non-Survivors (N=21)	Survivors (N=71)	*P* value
Pseudomonas aeruginosa	20 (21.7)	10 (23.8)	10 (20.0)	0.807	6 (28.6)	14 (19.7)	0.383
Other pathogens	2 (2.2)	2 (4.8)	0 (0)	0.206	1 (4.8)	1 (1.4)	0.406
Fever (°C)	38.1 [37.6, 38.9]	38 [37.3, 38.6]	38 [37.6, 39.7]	0.727	38 [36.9, 38.0]	38.3 [37.7, 38.7]	0.937
White blood cell count ($x10^9$/L)	10.75 [7.8, 13.4]	10.6 [7.35, 14.89]	9.99 [7.9, 12.35]	0.473	10.0 [7.1, 14.7]	10.8 [8.5, 10.8]	0.086
Procalcitonin (μg/L)	1.36 [0.51, 6.57]	0.74 [0.28, 1.57]	2.23 [0.70, 3.21]	0.946	0.568 [0.075, 0.700]	1.73 [0.79, 3.02]	0.713
C-reactive Protein (mg/L)	99.01 [43.12, 134.59]	82.39 [22.05, 137.12]	143.87 [69.09, 200.5]	0.098	56.3[18.06, 143.87]	127 [71.98, 195.7103]	0.371
Polymyxin B treatment							
Duration days	12 [8.0, 16.75]	16 [10.5, 21.0]	10 [7.0, 15.0]	0.229	14 [10.5, 20.0]	11[8.0, 16.0]	0.037
Daily dose (WIU)	150 [100, 150]	150 [100, 150]	150 [100, 150]	0.333	150 [100, 150]	150 [100, 150]	0.904
100 WIU/day	41 (44.6)	19 (45.2)	22 (44.0)	0.905	10 (47.6)	31 (43.7)	0.806
150 WIU/day	35 (45.2)	19 (45.2)	18 (32.0)	0.193	8 (38.1)	27 (38.0)	1.000
200 WIU/day	16 (17.4)	4 (9.5)	12 (24.0)	0.098	3 (14.3)	13 (18.3)	1.000
Concomitant drugs							
Anti-positive bacteria drugs[a]	26 (28.3)	13 (31.0)	13 (26.0)	0.599	11 (52.4)	15 (21.1)	0.011
Antifungal drugs[b]	37 (40.2)	15 (35.7)	22 (44.0)	0.419	14 (66.7)	23 (32.4)	0.010
Polymyxin B monotherapy	7 (7.6)	4 (9.5)	3 (6.0)	0.698	2 (9.5)	5 (7.0)	0.657
Tigecycline	43 (46.7)	17 (40.5)	26 (52.0)	0.270	14 (66.7)	29 (40.8)	0.048
Carbapenem	58 (63.0)	25 (59.5)	33 (66.0)	0.522	14 (66.7)	44 (62.0)	0.800
Concomitant β-lactams other than carbapenems[c]	20 (21.7)	16 (38.1)	4 (8.0)	0.001	4 (19.0)	16 (22.5)	1.000
Aminoglycoside	5 (5.4)	3 (7.1)	2 (4.0)	0.657	1 (4.8)	4 (5.6)	1.000
Fosfomycin	14 (15.2)	5 (11.9)	9 (18.0)	0.563	3 (14.3)	11 (15.5)	1.000
Immunosuppressant	4 (4.3)	2 (4.8)	2 (4.0)	1.000	1 (4.8)	3 (4.2)	1.000
Glucocorticoids	36 (39.1)	16 (38.1)	20 (40.0)	0.853	9 (42.9)	27 (38.0)	0.800
Outcome							
Mortality	37 (40.2)	16 (38.1)	21 (42.0)	0.704	10 (47.6)	15 (21.1)	0.025
Incidence of AKI	25 (27.2)	13 (31.0)	12 (24.0)	0.488	10 (47.6)	32 (45.1)	1.000

Notes: Data are presented as n (%) mean ± SD, or median [IQR]. [a]Including teicoplanin, vancomycin, desmethyl vancomycin, linezolid; [b]Including Voriconazole, posaconazole, caspofungin; [c]Including cefoperazone-sulbactam, piperacillin-tazobactam, ceftazidime and cefepime.

Medications and Outcomes

All patients included in the statistical analysis were given PMB by intravenous drip. PMB was administered at doses of 100, 150, and 200 mg/day in 44.6%, 45.2%, and 17.4% of the patients, respectively (Table 1). A total of 85 (92.4%) patients were treated with other antimicrobial drugs in combination, mainly with carbapenem (58 patients, 63.0%) and tigecycline (43 patients, 46.7%) (Table 1). During treatment, 25 patients (27.2%) developed AKI, and the overall discharge mortality rate of the patients was 22.8% (21/92). The microbial clearance rate was 45.7% (42/92). Overall, the patients improved after treatment with PMB. The patients had significant decreases in temperature, leukocytes, CRP, PCT, and APACHE II levels (Table 3). Two patients with

Table 2 Susceptibility Profile and Minimal Inhibitory Concentration (MIC) of CRKP to Various Antibiotics

Antimicrobial Agents	No. of Susceptible Isolates (%)		
Amikacin	8 (8.7)		
Ceftazidime	1 (1.1)		
Piperacillin-tazobactam	0 (0)		
Cotrimoxazole	18 (19.6)		
Minocycline	25 (27.2)		
Doxycycline	9 (9.8)		
Ciprofloxacin	0 (0)		
Polymyxin B or Colistin	90 (91.8)		
Tigecycline	85 (92.4)		
Antimicrobial Agents	MIC range (mg/L)		
	≤ 0.5	0.5–2.0	>2.0
Polymyxin B or Colistin	40 (43.5)	51 (55.4)	1 (1.1)
Tigecycline	7 (7.6)	77 (83.7)	8 (8.7)

Table 3 Comparison of Patient Conditions Before and After Therapy

Parameter	Baseline	After Therapy	*P* value
Fever (°C)	38.0 (37.6, 38.8)	37.5 (36.8, 38.2)	< 0.001
White blood cell count	10.6 (7.85, 13.39)	9.5 (7.32, 12.5)	0.214
C-reactive Protein (mg/L)	99.01 (44.18, 133.55)	32.4 (16.55, 95.54)	< 0.001
Procalcitonin (μg/L)	1.4 (0.504, 5.465)	0.776 (0.193, 4.365)	0.041

PMB-resistant infections were unsuccessfully treated, with a discharge mortality rate of 100% (2/2), and 7 patients with infections with bacteria that were tigecycline-resistant or intermediate (including 1 with concurrent PMB resistance) had a discharge mortality rate of 28.6 (2/7), which was higher than the overall mortality.

Factors Related to Microbiological Clearance

The microbial clearance rate was 45.7% for PMB. The characteristics of the failure and clearance groups are shown in Table 1. The results in the table show that the APACHE II score, electrolyte disturbance, concomitant cephalosporins and PMB 200 WIU/day had statistically significant differences (Table 1). The results of the binary logistic regression analysis indicated that APACHE II score [OR=0.888 (0.799, 0.986), p=0.027], concomitant β-lactams other than carbapenems (including cefoperazone-sulbactam, piperacillin-tazobactam, ceftazidime and cefepime) [OR=15.757 (2.528, 98.215), p=0.003] and electrolyte disturbance (OR=0.127 (0.021, 0.754), p=0.023) were independently associated with a lower rate of microbiological clearance (Table 4).

Table 4 Multivariate Analysis of Factors Associated with Microbiological Clearance

Risk Factor	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
APACHE II score	0.932 (0.874, 0.995)	0.034	0.888 (0.799, 0.986)	0.027
Concomitant β-lactams other than carbapenems[a]	7.077 (2.139, 23.415)	0.001	15.757 (2.528, 98.215)	0.003
C-reactive Protein (mg/L)	0.994 (0.988, 1.001)	0.085	0.989 (0.976, 1.001)	0.084
Electrolyte disturbance	0.409 (0.162, 1.036)	0.059	0.127 (0.021, 0.754)	0.023
PMB 200 WIU/day	0.333 (0.099, 1.126)	0.077	0.195 (0.025, 1.531)	0.120

Note: [a]Including cefoperazone-sulbactam, piperacillin-tazobactam, ceftazidime and cefepime.

Table 5 Multivariate Analysis of Factors Associated with All-Cause Discharge Mortality

Risk Factors	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age (years)	1.052 (1.009, 1.098)	0.018	1.078 (1.025, 1.135)	0.004
Duration days	1.062 (0.994, 1.135)	0.073	1.076 (0.992, 1.167)	0.077
Concomitant anti-positive bacteria drugs[a]	4.107 (1.468, 11.487)	0.007	3.442 (0.976, 12.147)	0.055
Concomitant antifungal drugs[b]	4.174 (1.483, 11.744)	0.007	4.226 (1.129, 15.821)	0.032
Concomitant tigecycline	2.897 (1.041, 8.059)	0.042	4.253 (1.157, 15.628)	0.029
Incidence of AKI	3.394 (1.213, 9.494)	0.020	3.197 (1.056, 14.523)	0.041

Notes: [a]Including teicoplanin, vancomycin, desmethyl vancomycin, linezolid; [b]Including voriconazole, posaconazole, caspofungin.

Factors Related to All-Cause Discharge Mortality

The all-cause discharge mortality was 22.8% for PMB. The characteristics of the survivor and nonsurvivor groups are shown in Table 3. The results in the table show that patient age, the course of PMB use, concomitant anti-positive bacterial drugs, concomitant antifungal drugs, concomitant tigecycline, and the incidence of AKI had statistically significant differences (Table 1). The results of the binary logistic regression analysis indicated that age [OR=1.708 (1.025, 1.135), p=0.004], concomitant antifungal drugs [OR=4.226 (1.129, 15.821), p =0.032], concomitant tigecycline [OR=4.253 (1.157, 15.628), p=0.029] and incidence of AKI [OR=3.197 (1.056, 14.523), p=0.041] were independently associated with all-cause discharge mortality (Table 5).

Factors Related to the Incidence of AKI

The results of the univariate analysis of this study showed that combined liver disease, concomitant anti-positive bacteria drugs and concomitant antifungal drugs had statistically significant differences (detailed results are available in the supplementary materials, Table S1). The binary logistic regression analysis indicated that combined liver disease [OR=17.149 (1.651, 178.158), p=0.017] and concomitant antifungal drugs [OR=3.916 (1.361, 11.269), p =0.011] were independently associated with all-cause discharge mortality (detailed results are available in the supplementary materials, Table S2).

Discussion

This study retrospectively analyzed the clinical data of 92 patients treated with PMB for high-level CRKP infections, and the results showed that 45.7% of the patients achieved bacterial clearance. Also, the results showed that the combination of β-lactams other than carbapenems facilitated bacterial clearance, and the combination of electrolyte disturbances and higher APACHE II scores in the patients was detrimental to microbial clearance. The all-cause mortality rate of patients discharged from the hospital was 22.8%, and risk factors contributing to all-cause discharge mortality were advanced

patient age, concomitant antifungal drugs, concomitant tigecycline and incidence of AKI, indicating that PMB may be an effective therapeutic agent for the treatment of high-level CRKP infections. While 27.2% of the patients experienced AKI during treatment, monitoring of patients' renal function needs to be enhanced during treatment with PMB.

The results of previous studies[22–31] showed that the overall bacterial clearance rate of PMB for CRO infections was 39%-42%, and only the results of a multicenter retrospective cohort study conducted by Zhang et al[25] showed a bacterial eradication rate of 77.65% using PMB for carbapenem-resistant bacterial infections. The results of the present study were generally consistent with those of a previous study (45.7%), suggesting that the bacterial clearance rate of PMB in the treatment of high-level CRKP infections may be independent of its degree of resistance to carbapenems and may be used as one of the basic drugs in the treatment of high-level CRKP infections.

Based on the PK/PD characteristics of PMB, it is hypothesized that an appropriate increase in the dose of PMB is beneficial in improving the clinical efficacy of the drug,[32] and the results of existing studies also show that an appropriate increase in the dose of PMB can reduce the all-cause mortality of patients.[29,33] The results of our study showed that the bacterial clearance group used high-dose PMB (200 WIU/day) more than the noncleared group, but the multifactorial analysis did not find any therapeutic advantage of high-dose PMB on microbial clearance and all-cause mortality of patients. This may be related to the small number of patients included in our study, and the small sample size may have affected the statistical efficacy of the study, so future studies with large samples are needed for further exploration.

The results of Medeiros et al[31] showed that receiving a combination of two in vitro appropriate antimicrobials based on bacterial sensitivity (mainly PMB plus amikacin) had a higher patient survival rate than treatment with a single appropriate drug. However, our findings did not show an advantage of the combination in reducing patient mortality. This may be because the vast majority of the patients included in our study were infected with fully or panresistant CRKP and had very few appropriate antibiotics in their sensitivity tests. Although the vast majority of the patients were given combination therapy, most of the drugs combined were drugs that showed resistance patterns in vitro. Wistrand-Yuen et al evaluated the synergistic effect of PMB with 13 commonly used antibiotics (including minocycline, amikacin, cefepime, ciprofloxacin, fosfomycin, meropenem, minocycline, etc.) against CRKP (MIC>16 mg/L) and showed that only the combination with minocycline, rifampicin or fosfomycin showed a synergistic antibacterial effect.[34] Therefore, further studies are needed to explore the effectiveness of the PMB combination regimen on high-level CRKP infections.

A previous study showed that clinical isolates of CRKP have high rates of heteroresistance to PMB and tigecycline,[27] and in vitro studies have shown that the combination of PMB and tigecycline can kill resistant bacteria at lower drug doses.[22,27] Therefore, it is hypothesized that a combination regimen of PMB and tigecycline may be a potentially effective treatment strategy for patients infected with CRKP. Combination regimens of polymyxin and tigecycline are also recommended in the CRE treatment guidelines.[9,35] However, our results showed that the combination of tigecycline did not improve bacterial clearance and was a risk factor for increased all-cause mortality, similar to the results of a multicenter retrospective study by Chang et al.[26] Therefore, the effectiveness of PMB in combination with tigecycline in the treatment of high-level CRKP infections needs to be explored in further prospective studies.

The results of this study showed that the incidence of AKI during the use of PMB was 27.2%, which was similar to the results of a previous study.[12,36] Since the incidence of AKI is an independent risk factor for all-cause mortality in patients, monitoring of renal function needs to be improved during the use of PMB.

The results of this study showed that the combination of PMB with antifungal drugs was an independent risk factor for increased all-cause mortality in patients, so in the clinical use of PMB for CRKP treatment, the indications for the use of antifungal drugs should be strictly grasped in patients and should not blindly cover antifungal treatment without any basis. Since this study is a retrospective study and the sample size of the study is small, further attention needs to be paid to the effect of PMB combined with antifungal drugs on all-cause mortality in patients in the future.

The results of previous studies[37,38] showed that polymyxin exposure is an important risk factor for polymyxin resistance, so optimizing the use of PMB should be a key strategy to stop the spread of polymyxin resistance. The treatment of polymyxin-resistant strains is even more challenging, and the two patients with polymyxin-resistant infections included in this study were not clinically successful, so in the future, there is a need to improve the control of the clinical use of PMB and more strictly use PMB clinically to minimize the production of PMB-resistant bacteria. Shein and team showed that colistin-EDTA combination therapy reduced bacterial load and serum creatinine in the

visceral organs of colistin-resistant *Klebsiella pneumoniae*-infected mice as well as reduced mortality in mice,[17–19] so future studies could be conducted to explore whether similar effects exist for PMB and to explore new pathways for the treatment of PMB-resistant bacteria.

The limitations of this study are as follows: (i) This study was retrospective, and the exact timing of PMB use could not be clarified. The results of a previous study by Liang et al[30] showed that for patients with sepsis, early use of PMB resulted in significantly higher bacterial clearance compared with delayed administration (65. 22% versus 29.41%, P=0.025; OR=0.533) and may have an impact on research studies. (ii) The sample size included in this study was small, and the data were obtained from a single center, which has some limitations in the generalization of the findings.

Conclusion

PMB may be a potential therapeutic agent for high-level CRKP infections and can provide an important reference for the treatment of these infections. Since this study is a retrospective small-sample exploratory study, the risk factors and dosing strategy of PMB for high-level CRKP infections need to be further explored through multicenter, large-scale prospective studies.

Ethical Approval

This study was approved (Approval number: 2021-KY-0063-002) and supervised by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University and was conducted in strict accordance with the Declaration of Helsinki.

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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

We declare that we have no conflicts of interest.

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