Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Polymyxin B in The Treatment of Infections Caused by Multidrug-Resistant Gram-Negative Bacteria in Children: A Retrospective Case Series and A Literature Review

Aihua Yan[1,2,*], Xiangcheng Pan[1,3,*], Siyu Li[1], Yaxin Hu[4], Haiyang Zhang[5], Deyuan Li[5], Liang Huang[1,3,4,6]

[1]Department of Pharmacy and Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University, Chengdu, People's Republic of China; [2]Pharmaceutical Preparation Section, Children's Hospital of Kunming Medical University, Kunming, People's Republic of China; [3]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Chengdu, People's Republic of China; [4]West China School of Pharmacy, Sichuan University, Chengdu, People's Republic of China; [5]Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, People's Republic of China; [6]Laboratory of Molecular Translational Medicine, Center for Translational Medicine, Sichuan University, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Liang Huang, Email hliang_1022@163.com

Background: Multidrug-resistant Gram-negative bacteria (MRGN) pose a significant threat and require priority attention. Polymyxin B (PMB) retains substantial activity against MRGN and makes it potentially the last resort therapy for MRGN infections in children. To assess the effectiveness and safety of PMB in treating MRGN infections in Chinese children.

Methods: Paediatric patients aged 0–18 years who were treated with PMB for MRGN infections were enrolled in the study. These cases were then compared with those identified in a literature review. In logistic regression, three independent variables were used for analyzing clinical effectiveness, and two for nephrotoxicity.

Results: A cohort of 54 children was included in study and 24 eligible literature of 259 children were included in literature review. Out of the 54 patients, 53.7% showed favorable clinical responses, while 13.0% died during their hospitalization, of which 3.7% died within 30 days after receiving PMB. AKI was observed in 25.9% patients with 11.1% risk stage, 7.4% injury stage and 7.4% failure stage. The PMB co-administration with carbapenems was associated with significantly higher effectiveness (odds rate [OR] = 3.16, 95% confidence interval [CI]: 1.02–9.86, P = 0.05) and co-administration with potent diuretic (furosemide) may increase the risk of AKI (OR = 4.91, 95% CI: 0.96–24.98, P = 0.05).

Conclusion: PMB has advantages in treating MRGN infections in paediatric patients, showing favorable clinical responses and pathogen clearance. AKI is a notable safety concern. The small sample size might hinder reliable identification of factors affecting clinical effectiveness and adverse effects.

Keywords: polymyxin B, multidrug-resistant gram-negative bacteria, children, effectiveness, acute kidney injury

Introduction

Bacterial resistance poses a significant global public health challenge. According to the World Health Organization (WHO) classification of drug-resistant bacteria based on threat severity, Multidrug-resistant Gram-negative Bacteria (MRGN) are defined as being non-susceptible to at least 1 agent in 3 or more antimicrobial categories within the antibacterial spectrum (including drug resistance and intermediaries),[1] including Carbapenem-resistant *Enterobacteriaceae* (CRE), Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), represent the most critical threats deserving priority attention.[2] Therefore, it is

Received: 2 December 2024
Accepted: 25 January 2025
Published: 18 February 2025

imperative to actively explore treatment options for these bacteria, encompassing the continuous development of novel antibiotics, as well as research and application of existing antibiotics.

Polymyxins are important antibiotics used to combat multidrug-resistant MRGN. However, their were limited due to potential nephrotoxicity and the availability of alternative antibiotics in recent years.[3] In 1990s, polymyxins experienced a resurgence in clinical practice due to the emergence of MRGNs and the scarcity of effective new antibiotics.[4] For the past few years, new β-lactams such as ceftazidime-avibactam have emerged as the primary drugs recommended in guidelines for managing MRGN infections.[5,6] However, given the diverse distribution of carbapenemase across different regions and populations[7] and the challenges related to accessibility and affordability of β-lactam drugs, polymyxins continue to hold significance in the treatment of MRGN infections in Chinese children.

For invasive infections, the guideline recommended systemic use of polymyxin B (PMB) over colistin. The reason for the recommendation was that PMB had better pharmacokinetic properties and lower risk of nephrotoxicity.[8] Contradictorily, one study found that the incidence of acute kidney injury (AKI) associated with colistin was significantly lower than that associated with PMB, but the 30-day mortality rate was similar.[9] Another study concluded that nephrotoxicity was more common in patients receiving high-dose colistin than in those receiving PMB.[10] The nephrotoxicity of PMB deserves our attention. Despite having been available for over half a century, studies on the pharmacokinetics and optimal dosing of PMB remain limited, particularly in the context of paediatric use.[11] To assess the effectiveness and safety of PMB in treating MRGN infections in Chinese children, a retrospective study was conducted at a specialized tertiary hospital for women and children in Southwest China. Additionally, a comprehensive literature review was undertaken to provide valuable references for the judicious clinical utilization of PMB.

Methods

Retrospective Case Series

Inclusion criteria: ① The paediatric patients aged 0–18 years who received PMB were enrolled in the study who were hospitalized in West China Second University Hospital of Sichuan University, a tertiary teaching hospital special for women and children, Children's National Regional Medical Center in Southwest China, from October 1, 2019, to November 30, 2022. ② All enrolled patients obtained approval for the use of PMB as part of the pre-authorization management within paediatric antimicrobial stewardship programs (It was identified or strongly suspected to be caused by MRGN infection, particularly Gram-negative bacteria that are resistant to carbapenems but sensitive to PMB. Its use was approved following consultation and agreement between the physicians and pharmacists). Exclusion criteria: ① The patients who did not use PMB finally were excluded even though the approval form was submitted. ② The cases received PMB treatment for less than 3 days because of the difficulty in effectiveness evaluation. This study was approved and supervised by the Ethics Committee of West China Second University Hospital of Sichuan University (No.2022–337).

Data Collection

Demographic data, medication information and laboratory test results were collected through Hospital Information System. Demographic data include age, gender, body weight, underlying medical conditions, and site of infection. Medication information included the route of administration for PMB, dosage, duration of treatment, and any concomitant therapies administered. Laboratory tests include pathogen detection from culture and metagenomic next generation sequencing reports (mNGS) results, antibiotics sensitivity reports, renal function (serum creatinine, urine volume), white blood cell count, neutrophil percentage, C-reactive protein (CRP), and procalcitonin (PCT). Furthermore, the evaluation of organ dysfunction and mortality risk prior to the initiation of PMB therapy was conducted using the Paediatric Sequential Organ Failure Assessment score (pSOFA)[12] and the Paediatric Risk of Mortality III score (PRISM III).[13] These scores provided valuable insights into the patients' clinical status and prognosis before the administration of PMB.

Clinical Effectiveness

Refer to the US Food and Drug Administration (FDA) guidelines for the evaluation of clinical research on anti-infective drugs, and the American Society of infectious diseases (IDSA) guidelines for the evaluation of infectious diseases,[14] the therapeutic effect of PMB was divided into "effective" and "ineffective". The favourable clinical response was defined as:

① For febrile patients, the body temperature decreased within 72 hours.
② For patients exhibiting a high inflammatory index (including neutrophil count, CRP, and PCT), a significant reduction in the inflammatory index was observed during medication, resulting in either a cure or noticeable improvement within 3 days.
③ Improvement in the patient's symptoms, physical signs, as well as positive changes in imaging and laboratory test results were observed, leading to either recovery or discharge. Improvements in these aspects had been assessed by two intensivists and one antimicrobial pharmacist, all of whom possess extensive clinical experience. A unanimous conclusion must be reached ultimately.

The unfavourable clinical response was defined as:

① There was a lack of lack of improvement or a significant worsening of symptoms, physical signs, laboratory examination results, and imaging findings.
② It was impossible to assess treatment effectiveness if the patient either passed away, was discharged automatically, or underwent surgical intervention within 3 days of PMB administration.
③ The treatment schedule was modified (discontinue PMB and switch to alternative agent) due to the patient's deteriorating condition after initiating PMB therapy.

Adverse Events

In the assessment of adverse drug events associated with PMB, a thorough data cleaning was conducted for relevant symptoms, physical signs, and laboratory examination results documented in the patient's medical records. Special attention was given to the potential nephrotoxic effects of PMB, in line with guidelines outlined by the FDA. The definition and staging of AKI were based on the RIFLE standards:[15]

① Higher Risk: A 1.5-fold increase in serum creatinine (SCr) or a decrease >25% in glomerular filtration rate (GFR), or urine output (UO) <0.5mL/(kg·h) × 6 h.
② Kidney Injury: A 2-fold increase in SCr or a decrease >50% in GFR, or UO <0.5mL/(kg·h) × 12 h.
③ Kidney Failure: A 3-fold increase in SCr or a decrease >75% in GFR. And even if the increase in SCr is less than 3-fold so long as the new SCr value is ≥4.0 mg/dL (350 μmol/L) in the setting of an acute increase of at least 0.5 mg/dL (44 μmol/L), or UO <0.3mL/(kg·h) × 24 h or anuria × 12 h.

The incidence of AKI was calculated as the sum of these three stages and was determined based on the maximum SCr value during PMB administration. This comprehensive approach allowed for a rigorous assessment of nephrotoxicity associated with PMB use.

Statistical Analysis

Normally distributed data were represented using mean and standard deviation (SD), and comparisons were conducted using the *t*-test. Non-normally distributed count data were presented as median and interquartile range (IQR) and analysed using the Mann–Whitney *U*-test. Count data were presented as numbers and percentages, and the Chi-square test (χ^2) or Fisher's exact test was utilized for analysis. Due to the limited sample size, the number of independent variables in the logistic regression analysis was based on the "10 events per variable".[16,17] The selection of these variables referred to the guidelines[8,18] and clinical research.[19] Ultimately, there were three independent variables (whether a loading dose was used, whether it was co-administered with carbapenems, and whether it was co-administered with tigecycline) were included in the logistic regression analysis of clinical effectiveness, and two independent variables (whether a loading dose was used,

whether it was co-administered with nephrotoxic drugs) were included in the logistic regression analysis of nephrotoxicity. A significance level of $P \leq 0.05$ was used as the criteria for statistical significance. All statistical analyses were conducted in R 4.3.1. with following packages: openxlsx, exactRankTests, stats, plyr.

Literature Review

A literature review was conducted to collect clinical studies focusing on the use of PMB in the treatment of infections caused by MRGN in paediatric patients. Three English databases and three Chinese database, including PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific Journals Database (VIP) were searched. The following terms were utilized to search: "PMB", "children", "paediatric", "infant", "newborn" and "children". The retrieval time was from the inception of the database to November 2022. The collected data were analysed as follows:

① Patient Demographics: The distributions of country, sample size, age, gender.
② Infection site and pathogen: The frequency and proportion of different infection sites, as well as the types of pathogens responsible for these infections, were tabulated and analysed. Additionally, any descriptions of drug resistance patterns among these pathogens were noted.
③ PMB usage and dose: Descriptive analysis was performed on the utilization of PMB, including the loading dose, maintenance dose, intrathecal dose, duration days.
④ Combination Therapy: Information regarding the choice of antibiotics used in combination therapy alongside PMB was collected and analysed.
⑤ Effectiveness outcomes: Mortality, effectiveness rates, and pathogen clearance rates were related to PMB therapy were recorded and analysed descriptively.
⑥ Safety outcomes: The incidence of adverse reactions, including nephrotoxicity, neurotoxicity, pigmentation, or others, were associated with PMB treatment in paediatric patients.

Results

Characteristics of Patients

There were 57 children who received PMB between October 1, 2019, to November 30, 2022, were initially identified. After screening, 3 cases were excluded from the study due to a treatment course of less than 3 days. Consequently, a final cohort of 54 children aged 0.23–192 months (1 neonate, 17 infants under 1 year old, 19 children aged 1 to 6 years old, 9 children aged 7 to 12 years old, 8 children aged 12 years and above) was included in this analysis. The demographic and clinical characteristics of these children are summarized in Table 1.

Polymyxin B and Combination Therapy

The loading dose of PMB was administered to 35 patients (64.8%). As shown in Table 2, the dose of PMB was divided into three levels: 12 patients (22.2%) received a daily dose of less than 2.5 mg/(kg·d), 27 patients (50.0%) were given a daily dose ranging from 2.5 to 3.5 mg/(kg·d), and 15 patients (27.8%) received a daily dose between 3.5 and 4.0 mg/(kg·d). The median duration of treatment was 16 days (IQR, 14 days to 21 days), and the median cumulative dose was 489.10 mg (IQR, 331.50 mg to 715.00 mg). The execution time (the time from receiving the antibiotics sensitivity test report to the administration of PMB) of 38 patients was recorded, with an equal number of patients, 19 in each category, exceeding 48 hours and ≤48 hours. It is worth noting that there were no significant differences in the usage and dosage of PMB between favourable clinical response group and unfavourable clinical response group.

Pathogens and Antibiotics Sensitivity Test

The antibiotics sensitivity tests were interpreted clinically with reference to the current clinical breakpoints of United States Committee on Antimicrobial Susceptibility Testing ($S \leq 2$ mg/L, $R \geq 4$ mg/L).[20] A total of 54 samples, bacterial cultures (n = 44) and mNGS (n = 10), were confirmed the presence of MRGN infections in 51 patients (48 patients with a single sample and 3 patients with 2 samples). Additionally, three patients with bone marrow immunosuppression and

Table 1 The Demographic and Clinical Characteristics of 54 Paediatric Patients

Patient Information	Total Patients (N = 54)	Favourable Clinical Response (N = 29)	Unfavourable Clinical Response (N = 25)	*P* value
Male, n (%)	23 (42.59)	11 (37.93)	12 (48.00)	0.64
Age (month), mean ± sd	56.95 ±57.08	41.48 ± 49.44	74.89 ± 62.09	0.04
Age (month), range	0.23–192.00	2.00–161.00	0.23–192.00	/
Weight (kg), mean ± sd	18.49 ± 17.13	15.03 ± 16.12	22.52 ± 17.70	0.11
Length of hospital stay, median (IQR)	35.00 (23.25, 67.00)	30.00 (23.00, 56.00)	41.00 (25.00, 68.00)	0.23
Length of ICU stay, median (IQR)	27.00 (8.00, 42.00)	23.00 (5.00, 32.00)	35.00 (10.00, 47.00)	0.07
WBC before medication, × 10^9/L, mean ± sd	9.83 ± 12.69	11.87 ± 16.17	7.47 ± 6.31	0.18
CRP before medication, mg/L, mean ± sd	65.03 ± 70.77	73.81 ± 84.45	53.18 ± 45.92	0.29
Cr before medication, μmol/L, mean ± sd	28.52 ± 22.21	20.10 ± 11.60	38.28 ± 27.34	< 0.01
pSOFA, median (IQR)	5.00 (3.00, 6.75)	3.00 (3.00, 6.00)	6.00 (4.00, 7.25)	0.05
PRISM 3, median (IQR)	15.00 (10.00, 18.25)	13.00 (10.00, 17.25)	15.50 (11.00, 19.25)	0.16
Infection site				
Pneumonia infection, n (%)	39 (52.70)	19 (51.35)	20 (54.05)	1.00
Bloodstream infection, n (%)	22 (29.73)	15 (40.54)	7 (18.92)	0.08
Intraabdominal infection, n (%)	5 (6.76)	2 (5.41)	3 (8.11)	1.00
Intracranial infection, n (%)	3 (4.05)	0 (0.00)	3 (8.11)	0.24
Skin infection, n (%)	4 (5.41)	1 (2.70)	3 (8.11)	0.61
Urinary tract infection, n (%)	1 (1.35)	0 (0.00)	1 (2.70)	1.00
Hospital mortality, n (%)	7 (12.96)	0 (0.00)	7 (28.00)	< 0.01
Microorganism clearance, n (%)				
Clear	34 (85.00)	23 (95.83)	11 (68.75)	0.03
Not clear	6 (15.00)	1 (4.17)	5 (31.25)	/
AKI, n (%)	14 (25.93)	6 (20.69)	8 (32.00)	0.53
Normal stage, n (%)	40 (74.07)	23 (79.31)	17 (68.00)	0.53
Risk stage, n (%)	6 (11.11)	4 (13.79)	2 (8.00)	1.00
Failure stage, n (%)	4 (7.41)	1 (3.45)	3 (12.00)	1.00
Injury stage, n (%)	4 (7.41)	1 (3.45)	3 (12.00)	1.00
Underlying medical conditions				
Pulmonary diseases, n (%)	50 (14.49)	25 (16.03)	25 (13.23)	0.56
Homeostatic imbalance, n (%)	43 (12.46)	20 (12.82)	23 (12.17)	0.99
Heart diseases, n (%)	25 (7.25)	14 (8.97)	11 (5.82)	0.36
Coagulation disorder, n (%)	28 (8.12)	13 (8.33)	15 (7.94)	1.00
Liver disease, n (%)	23 (6.67)	12 (7.69)	11 (5.82)	0.63
Gastrointestinal system diseases, n (%)	30 (8.70)	11 (7.05)	19 (10.05)	0.43
Central nervous system diseases, n (%)	25 (7.25)	11 (7.05)	14 (7.41)	1.00
Surgery and trauma, n (%)	16 (4.64)	10 (6.41)	6 (3.17)	0.24
Hematologic oncology, n (%)	19 (5.51)	9 (5.77)	10 (5.29)	1.00
Agranulocytosis, n (%)	13 (3.77)	7 (4.49)	6 (3.17)	0.72
Malnutrition, n (%)	17 (4.93)	7 (4.49)	10 (5.29)	0.93
Urological diseases, n (%)	12 (3.48)	5 (3.21)	7 (3.70)	1.00
Hypoalbuminemia, n (%)	18 (5.22)	4 (2.56)	14 (7.41)	0.08
Sepsis shock, n (%)	11 (3.19)	4 (2.56)	7 (3.70)	0.77
Transplantation status, n (%)	8 (2.32)	4 (2.56)	4 (2.12)	1.00

a strong suspicion of Carbapenem-Resistant Gram-Negative Bacteria (CR-GNB) infections were treated with PMB after prior antibiotic treatments with carbapenem, β-lactam, and tigecycline had proven ineffective. Based on the results of the bacterial cultures, the following MRGN isolates were identified: 15 *Klebsiella pneumoniae* (13 carbapenem-resistant and 2 extended spectrum β-lactamases), 13 CRAB, 11 *P. aeruginosa* (7 CRPA and 4 multidrug-resistant) and others (2 carbapenem-resistant *Enterobacter cloacae subsp*., 1 *Enterobacter cloacae subsp*., 1 carbapenem-resistant *Aeromonas*

https://doi.org/10.2147/IDR.S509782

Table 2 Polymyxin B and Combination Therapy in Patients With Favourable and Unfavourable Clinical Response

	Total Patients (N = 54)	Favourable Clinical Response (N = 29)	Unfavourable Clinical Response (N = 25)	*P* value
Polymyxin B				
Loading dose, n (%)	35 (64.81)	17 (58.62)	18 (72.00)	0.46
Daily dose < 2.5mg/(kg·d), n (%)	12 (22.22)	5 (17.24)	7 (28.00)	0.54
Daily dose 2.5–3.5mg/(kg·d), n (%)	27 (50.00)	14 (48.28)	13 (52.00)	1.00
Daily dose 3.5–4.0mg/(kg·d), n (%)	15 (27.78)	10 (34.48)	5 (20.00)	0.38
Duration days (d), median (IQR)	16 (14, 21)	17 (15, 18)	16 (7, 22)	0.45
Cumulative dose (mg), median (IQR)	489.10 (331.50, 715.00)	459.56 (333.00, 595.00)	537.00 (331.00, 1086.25)	0.45
Execution time > 48h, n (%)	19 (50.00)	10 (45.45)	9 (56.25)	0.74
Execution time ≤ 48h, n (%)	19 (50.00)	12 (54.55)	7 (43.75)	0.74
Concomitant drugs				
Carbapenems, n (%)	23 (7.23)	16 (10.60)	7 (4.19)	0.05
Fluoroquinolones, n (%)	18 (5.66)	6 (3.97)	12 (7.19)	0.32
Tigecycline, n (%)	10 (3.14)	5 (3.31)	5 (2.99)	1.00
Linezolid, n (%)	14 (4.40)	7 (4.64)	7 (4.19)	1.00
Vancomycin, n (%)	16 (5.03)	8 (5.30)	8 (4.79)	1.00
Cotrimoxazole, n (%)	23 (7.23)	7 (4.64)	16 (9.58)	0.14
Amikacin, n (%)	24 (7.55)	12 (7.95)	12 (7.19)	0.96
Ceftazidime, n (%)	8 (2.52)	3 (1.99)	5 (2.99)	1.00
Ceftazidime/Avibactam, n (%)	2 (0.63)	2 (1.32)	0 (0.00)	0.43
Other β-lactams, n (%)	17 (5.35)	10 (6.62)	7 (4.19)	0.48
Azithromycin, n (%)	1 (0.31)	1 (0.66)	0 (0.00)	0.96
Rifampicin, n (%)	3 (0.94)	1 (0.66)	2 (1.20)	1.00
Gentamicin, n (%)	1 (0.31)	1 (0.66)	0 (0.00)	0.96
Aztreonam, n (%)	2 (0.63)	0 (0.00)	2 (1.20)	0.52
Nitrofurantoin, n (%)	1 (0.31)	0 (0.00)	1 (0.60)	1.00
Amphotericin B, n (%)	12 (3.77)	3 (1.99)	9 (5.39)	0.29
Echinocandins, n (%)	23 (7.23)	11 (7.28)	12 (7.19)	1.00
Triazoles, n (%)	29 (9.12)	13 (8.61)	16 (9.58)	0.92
Glucocorticoids, n (%)	34 (10.69)	15 (9.93)	19 (11.38)	0.81
NSAIDs*, n (%)	15 (4.72)	10 (6.62)	5 (2.99)	0.21
Immunosuppressants, n (%)	8 (2.52)	3 (1.99)	5 (2.99)	0.83
Potent diuretic, n (%)	34 (10.69)	17 (11.26)	17 (10.18)	0.90
Concomitant blood products				
Gamma globulin, n (%)	36 (66.67)	22 (75.86)	14 (56.00)	0.21
Platelets, n (%)	28 (51.85)	11 (37.93)	17 (68.00)	0.05

Abbreviation: *NSAIDs, Non-steroidal anti-inflammatory drugs.

and 1 carbapenem-resistant *Escherichia coli*), as summarized in Table 3. Notably, 36 of these isolates had polymyxin susceptibility results, and all 36 isolates were susceptible to PMB.

Clinical Effectiveness

Out of the total participants, 53.7% (29/54) exhibited favourable clinical responses, while 46.3% (25/54) had unfavourable clinical responses. The results revealed that age ($P = 0.04$), Cr before medication ($P < 0.01$), and pSOFA ($P = 0.05$) showed significant differences between the two groups, while the remaining baseline characteristics were balanced between the two groups (Table 1). Specifically, 95.83% (23/24) in the favourable response group and 68.75% (11/16) in the unfavourable response group achieved microorganism clearance ($P = 0.03$). By individually including each of the three independent variables, the results of logistic regression analysis showed that co-administration with carbapenems was associated with significantly higher effectiveness (odds rate [OR] = 3.16, 95% confidence interval [CI]: 1.02–9.86, $P = 0.05$). But the loading dose (OR = 0.55, 95% CI: 0.18–1.72, $P = 0.31$) and co-administration with tigecycline (OR =

Table 3 Sensitivity, Intermediate and Resistance of Bacterial Strains to Antimicrobial Agents

Antibiotics	Klebsiella Pneumoniae (n = 15)			Acinetobacter Baumannii (n = 13)			Pseudomonas Aeruginosa (n = 11)			Other Pathogens (n = 5)		
	S	I	R	S	I	R	S	I	R	S	I	R
Tigecycline	11/13(84.6%)	0/13(0.0%)	2/13(15.4%)	6/12(50.0%)	6/12(50.0%)	0/12(0.0%)	0/9(0.0%)	0/9(0.0%)	9/9(100.0%)	3/3(100.0%)	0/3(0.0%)	0/3(0.0%)
Ceftazidime/Avibactam	3/12(25.0%)	0/12(0.0%)	9/12(75.0%)	–	–	–	–	–	–	–	–	–
Cefoperazone/Sulbactam	0/14(0.0%)	1/14(7.1%)	13/14(92.9%)	4/11(36.4%)	3/11(27.3%)	4/11(36.4%)	5/9(55.6%)	1/9(11.1%)	3/9(33.3%)	0/2(0.0%)	0/2(0.0%)	2/2(100.0%)
Meropenem	2/15(13.3%)	0/15(0.0%)	13/15(86.7%)	0/12(0.0%)	0/12(0.0%)	12/12(100.0%)	3/9(33.3%)	2/9(22.2%)	4/9(44.4%)	1/4(25.0%)	0/4(0.0%)	3/4(75.0%)
Piperacillin/Tazobactam	3/15(20.0%)	1/15(6.7%)	11/15(73.3%)	0/11(0.0%)	0/11(0.0%)	11/11(100.0%)	3/9(33.3%)	4/9(44.4%)	2/9(22.2%)	0/4(0.0%)	0/4(0.0%)	4/4(100.0%)
Ceftazidime	1/15(6.7%)	0/15(0.0%)	14/15(93.3%)	0/11(0.0%)	1/11(9.1%)	10/11(90.9%)	5/9(55.6%)	3/9(33.3%)	1/9(11.1%)	0/4(0.0%)	0/4(0.0%)	4/4(100.0%)
Cefepime	1/14(7.1%)	0/14(0.0%)	13/14(92.9%)	0/10(0.0%)	1/10(10.0%)	9/10(90.0%)	7/9(77.8%)	2/9(22.2%)	0/9(0.0%)	0/3(0.0%)	0/3(0.0%)	3/3(100.0%)
Aztreonam	0/14(0.0%)	0/14(0.0%)	14/14(100.0%)	0/10(0.0%)	0/10(0.0%)	10/10(100.0%)	2/9(22.2%)	2/9(22.2%)	4/9(44.4%)	1/3(33.3%)	0/3(0.0%)	2/3(66.7%)
Imipenem	2/15(13.3%)	1/15(6.7%)	12/15(80.0%)	0/11(0.0%)	0/11(0.0%)	11/11(100.0%)	2/9(22.2%)	0/9(0.0%)	7/9(77.8%)	1/4(25.0%)	0/4(0.0%)	3/4(75.0%)
Tobramycin	4/14(28.6%)	4/14(28.6%)	6/14(42.9%)	3/10(30.0%)	0/10(0.0%)	7/10(70.0%)	6/9(66.7%)	2/9(22.2%)	1/9(11.1%)	0/3(0.0%)	1/3(33.3%)	2/3(66.7%)
Amikacin	11/15(73.3%)	0/15(0.0%)	4/15(26.7%)	1/11(9.1%)	0/11(0.0%)	10/11(90.9%)	8/9(88.9%)	0/9(0.0%)	1/9(11.1%)	3/3(100.0%)	0/3(0.0%)	0/3(0.0%)
Ciprofloxacin	4/15(26.7%)	0/15(0.0%)	11/15(73.3%)	1/11(9.1%)	0/11(0.0%)	10/11(90.9%)	7/9(77.8%)	1/9(11.1%)	1/9(11.1%)	0/3(0.0%)	1/3(33.3%)	2/3(66.7%)
Levofloxacin	4/15(26.7%)	1/15(6.7%)	10/15(66.7%)	1/11(9.1%)	3/11(27.3%)	7/11(63.6%)	5/9(55.6%)	2/9(22.2%)	2/9(22.2%)	2/4(50.0%)	0/4(0.0%)	2/4(50.0%)
Cotrimoxazole	5/14(35.7%)	0/14(0.0%)	9/14(64.3%)	4/10(40.0%)	0/10(0.0%)	6/10(60.0%)	0/9(0.0%)	0/9(0.0%)	9/9(100.0%)	0/3(0.0%)	0/3(0.0%)	3/3(100.0%)
Polymyxin B	13/13(100.0%)	0/13(0.0%)	0/13(0.0%)	12/12(100.0%)	0/12(0.0%)	0/12(0.0%)	9/9(100.0%)	0/9(0.0%)	0/9(0.0%)	2/2(100.0%)	0/2(0.0%)	0/2(0.0%)

0.83, 95% CI: 0.21–3.29, $P = 0.79$) did not have significantly impact on effectiveness. After simultaneously including all three independent variables in multivariate analysis, none of them, including loading dose (OR = 0.60, 95% CI: 0.18–2.02, $P = 0.41$), co-administration with tigecycline (OR = 0.67, 95% CI: 0.15–2.91, $P = 0.59$), and co-administration with carbapenems (OR = 3.07, 95% CI: 0.97–9.75, $P = 0.06$), showed significant differences.

Among the 54 individuals, 13.0% (7/54) died during hospital stay, of which 3.7% (2/54) died within 30 days after receiving PMB. The age range of all patients who died was 4 months to 158 months. All patients had mixed infections, involving any two combinations of MRGN, viruses, and fungi. One infant aged 4 months was even infected with all three. The diseases and medications of the seven patients who died in the hospital were as follows. Four patients were diagnosed with acute leukaemia (three of them were complicated by graft-versus-host disease). The doses of PMB were 2.5–3.5 mg/(kg·d) and durations were 3–15 days. One patient had severe aplastic anaemia and had been treated with <2.5 mg/(kg·d) of PMB for four days. One patient had T-cell lymphoblastic lymphoma and had been treated with <2.5 mg/(kg·d) of PMB for 22 days. One infant aged 4 months was diagnosed with tricho-hepato-enteric syndrome and had been treated with 3.5–4.0 mg/(kg·d) of PMB for 14 days.

Adverse Events

AKI was observed in 25.9% (14/54) patients with 11.1% (6/54) risk stage, 7.4% (4/54) injury stage and 7.4% (4/54) failure stage. The characteristics of patients with AKI group (n = 14) and without AKI group (n = 40) during treatment with PMB are shown in Supplementary Table 1. There were no significant differences in baseline characteristics between the two groups. No patients adjusted the dose of PMB due to AKI. Renal function recovery was observed in 71.42% (10/14) patients before PMB was discontinued, and one patient recovered renal function one day after PMB was discontinued. Three patients who had progressed to renal failure experienced further deterioration and were eventually discharged, with no additional records available. By individually including each of the two independent variables, the results of logistic regression analysis showed that co-administration with potent diuretic (furosemide) may be a contributing factor that increased the risk of AKI (OR = 4.91, 95% CI: 0.96–24.98, $P = 0.05$) and loading dose was not a contributing factor to AKI (OR = 0.97, 95% CI: 0.27–3.47, $P = 0.96$). When both factors were included in the model for analysis, the results showed that neither of them had a significant impact on AKI (loading dose: OR = 0.93, 95% CI: 0.25–3.47, $P = 0.92$; co-administration with potent diuretic: OR = 4.44, 95% CI: 0.87–22.61, $P = 0.07$). One patient developed erythema after using PMB, and no instances of neurological toxicity were observed.

Literature Review Results

There were 24 included literature had reported the information about PMB used in children with MRGN.[21–44] A total of 259 children's data were collected. Among the infection sites, the respiratory system infections were the most prevalent (123 cases), followed by the circulatory system infections (80 cases) and the central nervous system infections (21 cases). The most reported pathogen in these literature was *K. pneumoniae* (159 cases), followed by the *A. baumannii* (73 cases), *P. aeruginosa* (37 cases). The intravenous administration dosage range for PMB was 1.5–4.0 mg/kg, while the intrathecal injection range was 0.2–0.5 mg/kg. Excluding studies with only one case, the mortality rate in the remaining studies ranged from 6.3% to 42.9%, clinical effectiveness rate ranged from 47.8% to 93.7%, and pathogen clearance rate ranged from 30.8% to 100.0%. Correspondingly, the safety outcomes of nephrotoxicity ranged from 0.0% to 82.4%, neurotoxicity ranged from 0.0% to 17.6%, pigmentation ranged from 0.0% to 7.7%. Other adverse events reported in these literature include increased eosinophil count, erythema and papule, and skin desquamation. More details are shown in Supplementary Table 2.

Discussion

In summary, our findings indicated that more than half of patients exhibited favourable clinical responses, with 53.7% (29/54) achieving positive outcomes. 95.83% (23/24) in the favourable response group and 68.75% (11/16) in the unfavourable response group achieved microorganism clearance. 13.0% (7/54) died during their hospital stay. PMB co-administration with carbapenems may be a contributing factor in clinical effectiveness and PMB co-administration with potent diuretic (furosemide) may be a contributing factor in AKI.

In recent years, the emergence of MRGN infections presents a serious clinical challenge. Common antibiotics used to treat MRGN infections include carbapenems, tigecycline, ceftazidime-avibactam, polymyxins. Bacterial resistance to polymyxins is low and they have unique advantages. They can destroy the integrity of the outer membrane of Gram-negative bacteria and have rapid bactericidal activity. They can be used in combination with other antibacterial drugs to exert synergistic anti-infection effects. The bacterial resistance rate is low. Polymyxins has been a vital tool in addressing these infections.[45] Our study confirmed the presence of 54 bacterial strains in 94.4% (51/54) patients. Antimicrobial drug use management in our institution requires explicit microbiological results and should be reserved for severe infections caused by multidrug-resistant pathogens when other antimicrobial agents are ineffective or not tolerated. Wang et al[39] enrolled 19 children aged 3.2–17.8 years to build population pharmacokinetics (PK) and evaluate clinical outcomes of PMB. Clinical success, defined as patient survival, improved microbiological and clinical symptoms, body temperature ≤ 37.5°C, and enhanced infection-related biochemical indicators at the end of PMB treatment, occurred in 73.7% (14/19) of patients. The 28-day mortality was 10.5% (2/19). This study showed a better clinical effectiveness, a lower mortality rate compared to our study. This could be attributed to the smaller sample size, the consistent use of loading doses and looser clinical effectiveness criteria in their study. Jia et al[30] conducted a retrospective study to analyse effectiveness during treatment with PMB-based regimen. This study indicated effective rate of 52.7% (29/55). It was similar to our study, including the daily dose of PMB, duration of treatment, and concomitant antibiotics (carbapenems, tigecycline). Notably, our study also suggested that the co-administration of PMB with carbapenems may have influence on clinical effectiveness. One international guideline and two Chinese guidelines recommend PMB combination therapy (based on susceptible MIC) rather than monotherapy.[8,46,47] Two studies comparing colistin monotherapy versus colistin combined with meropenem produced conflicting conclusions, indicating that combination therapy did not improve 28-day mortality and clinical failure.[48,49] Most predominant bacteria were CRAB in these two studies (77% and 78%). The main isolates identified in our study were *Klebsiella pneumoniae* and *P. aeruginosa*. Although the two polymyxins have very similar antibacterial activity in vitro, they behave differently in patients, which may affect their clinical benefit against various types of infections.[50] PMB has advantages in the treatment of severe systemic infections in critically ill patients (administered as the active ingredient), allowing rapid and reliable achievement of effective antibiotic plasma concentrations.[51] The combination use of PMB with other antibiotics is a topic of ongoing debate. Due to the lack of high-quality clinical study, only PK analysis and vitro studies suggests that PMB combination therapy may be advantageous.[8,52–55] It should be noted that effectiveness estimates were affected by multiple confounding factors, including antibiotics combinations, site of infection, bacterial type, MIC differences, diseases severity, and surgical control of infection may significantly clinical effectiveness outcome.[56] Our study only included one neonate, 7 days old, who had pneumonia caused by Klebsiella pneumoniae. After PMB treatment, this neonate was unfavourable clinical responses and did not achieve microbial clearance, as well as no adverse events. Three studies were conducted to assess the effectiveness of colistin in neonates, and indicated colistin seems to be effective for treating MRGN infections.[57–59] However, no studies have yet established and reported a cohort of neonates using PMB. There were 7 deaths in our study, all of whom had mixed infections involving MRGN, viruses, or fungi. All patients developed sepsis. Additionally, their immune functions were impaired, including hematologic malignancies, severe aplastic anaemia, and genetic disorders. The increased risk of infection was significantly associated with allogeneic transplant and colonization by MRGN. Even worse, immunosuppression might be significantly associated with increased patient mortality.[60–62]

PMB has been used to treat infections caused by MRGN, but it fell out of favour due to significant nephrotoxicity and neurotoxicity in paediatric patients. Specifically, there was a paucity of pharmacokinetic and pharmacodynamic information regarding the administration of polymyxins in neonates and paediatric patients, raising safety-related apprehensions.[63] AKI was observed in 25.9% (14/54) paediatric patients. However, the incidence of nephrotoxicity reported in the literature varies widely. The highest reached 82.4%, which received therapy with PMB or colistin.[41] Most reported nephrotoxicity events were mild and recovered gradually after drug withdrawal. Measures that may reduce nephrotoxicity include avoiding exceeding recommended doses, performing therapeutic drug monitoring, and avoiding co-administration of other nephrotoxic drugs. Existing studies have reached the same conclusion as ours, that co-administration with potent diuretic (furosemide) may be a contributing factor to nephrotoxicity.[64] The mechanism by which PMB caused nephrotoxicity was related to the cumulative uptake of PMB mediated by megalin leading to cell apoptosis.[65] What's more, furosemide promoted the accumulation of nephrotoxic antibacterial drugs (such as gentamicin) in the tubules and aggravated the damage to renal tubular epithelial cells.[66] Some studies have found some risk factors for PMB-associated AKI in adult patients, including older age, too high loading and cumulative doses, combined use

of nephrotoxic drugs or vasoactive drug, septic shock, and abnormal baseline Cr.[19,67–69] However, due to the limited sample size and heterogeneous patient screening, it was a challenging to achieve consistency in identifying the risk factors associated with AKI related to PMB. Ferroptosis was one of the main mechanisms underlying PMB-induced renal injury, and decreased p53 acetylation level could inhibit ultimately attenuates AKI.[70] The results of PK model showed that an area under the curve across 24 h at steady state ($AUC_{ss,24h}$) of >100 mg·h/L was a good predictor for the probability of nephrotoxicity in adult.[71] But the pharmacokinetics of PMB in paediatric patients were extremely limited. Only one study including 19 children has built a two-compartment model with first-order elimination for PMB in paediatric patients, to evaluate the appropriateness of different PMB dosages, but did not explore independent predictors of efficacy and renal injury.[39] Our study found that loading dose did not increase clinical effectiveness and risk of AKI, which was also consistent with Jia's study.[30] Neurotoxicity was another important side-effect associated with PMB, usually manifesting as paraesthesia, dizziness, ataxia, respiratory depression, and meningeal irritation (intrathecal administration).[72] No relevant adverse event was collected in our study, possibly due to the inability to accurately describe such symptoms in paediatric patients. The intrathecal delivery of PMB bypassed the blood-brain barrier and were sometimes used for MRGN infections in central nervous system. Notwithstanding, polymyxins could induce mitochondrial dysfunction and activation of pro-inflammatory mediators in central and peripheral nervous tissue, thereby inducing neurotoxicity.[73]

Our study inevitably had some limitations. Firstly, due to the difficulty in collecting data on children using PMB, especially in neonate, our study was limited to a relatively small sample size of 54 patients, which made it less robust to conduct multivariate confirmatory logistic regression analysis to speculate on possible independent predictors of effectiveness and nephrotoxicity. We found that some influencing factors were significant in univariate analysis but not significant in multivariate analysis. Limited by the sample size, it was difficult to analyse the possible reasons (spurious correlation, indirect correlation or confounding) in detail. We elaborated in the discussion based on other published literature, guidelines, and clinical experience, and drew cautious conclusions. Secondly, the pharmacokinetics and pharmacodynamics of PMB in children are lacking in our study because our institution has not yet developed therapeutic drug monitoring technology in PMB. Thirdly, our study was a retrospective study. Due to the lack of a control group, the results might be affected by multiple confounding factors, and the causal relationship between multiple factors and clinical effectiveness and adverse events cannot be directly proved. Finally, the literature review only conducted a descriptive analysis of the included studies. Meta-analysis was not performed due to the heterogeneity in criteria for assessing clinical effectiveness and nephrotoxicity, as well as limited reported data in the literature.

Conclusion

Our study highlighted the importance of PMB in managing MRGN infections in paediatric patients by demonstrating favourable clinical responses and pathogen clearance rates. AKI was also a safety issue that cannot be ignored. The limited sample size might lead to the low confidence in determining factors that affect clinical effectiveness and adverse effects. More large sample studies are needed in the future to verify these conclusions.

Patient Data Confidentiality

All patient data used in this study has been treated with the utmost confidentiality. The relevant data were collected retrospectively through electronic medical records. Only the research team members who have a legitimate need to access the data for the purpose of this study have been granted access.

Data Sharing Statement

All the data are available in the manuscript and supplementary data and further inquiries can be made to the corresponding author.

Ethics Approval and Informed Consent

This study was carried out in full compliance with the principles of the Declaration of Helsinki. The study was conducted in compliance with the Declaration of Helsinki and was approved and supervised by the Ethics Committee of West China Second University Hospital of Sichuan University (No.2022-337). The informed consent was waived by the Ethics Committee of West China Second University Hospital of Sichuan University because the relevant data were collected

retrospectively through electronic medical records. The rights and well - being of the participants were always the top priority throughout the study, and any potential conflicts of interest were carefully managed and disclosed.

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.

Funding

This study did not receive any specific funding from public, commercial, or non-profit organizations.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268–281. doi:10.1111/j.1469-0691.2011.03570.x
2. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327. doi:10.1016/S1473-3099(17)30753-3
3. Huang Y, Liao M, Hu X, Hu H, Gong H. Advances in the clinical treatment of multidrug-resistant pathogens using polymyxins. *J Antimicrob Chemother*. 2024;79(12):3210–3229. doi:10.1093/jac/dkae344
4. Ezadi F, Ardebili A, Mirnejad R. Antimicrobial susceptibility testing for polymyxins: challenges, issues, and recommendations. *J Clin Microbiol*. 2019;57(4):e01390–18. doi:10.1128/JCM.01390-18
5. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America guidance on the treatment of extended-spectrum beta-lactamase producing enterobacterales (ESBL-E), carbapenem-resistant enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). *Clin Infectious Dis*. 2021;72(7):e169–e183. doi:10.1093/cid/ciaa1478
6. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America guidance on the treatment of ampc beta-lactamase-producing enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. *Clin Infect Dis*. 2022;74(12):2089–2114. doi:10.1093/cid/ciab1013
7. Hu F, Guo Y, Yang Y, et al. Resistance reported from China antimicrobial surveillance network (CHINET) in 2018. *Eur J Clin Microbiol Infect Dis*. 2019;38(12):2275–2281. doi:10.1007/s10096-019-03673-1
8. Tsuji BT, Pogue JM, Zavascki AP, et al. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American college of clinical pharmacy (ACCP), European society of clinical microbiology and infectious diseases (ESCMID), infectious diseases society of America (IDSA), international society for anti-infective pharmacology (ISAP), society of critical care medicine (SCCM), and SOCIETY OF INFECTIOUS DISEASES PHARMacists (SIDP). *Pharmacotherapy*. 2019;39(1):10–39. doi:10.1002/phar.2209
9. Zhang Y, Dong R, Huang Y, Ling X, Ye Z, Jiang S. Acute kidney injury associated with colistin sulfate vs. polymyxin B sulfate therapy: a real-world, retrospective cohort study. *Int J Antimicrob Agents*. 2024;63(1):107031. doi:10.1016/j.ijantimicag.2023.107031
10. Ballı FN, Ekinci PB, Kurtaran M, et al. Battle of polymyxin induced nephrotoxicity: polymyxin B versus colistin. *Int J Antimicrob Agents*. 2024;63(2). doi:10.1016/j.ijantimicag.2023.107035
11. Avedissian SN, Liu J, Rhodes NJ, et al. A review of the clinical pharmacokinetics of polymyxin B. *Antibiotics*. 2019;8(1):31. doi:10.3390/antibiotics8010031
12. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. *JAMA Pediatr*. 2017;171(10):e172352. doi:10.1001/jamapediatrics.2017.2352
13. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. *Crit Care Med*. 1996;24(5):743–752. doi:10.1097/00003246-199605000-00004
14. Smith C, Burley C, Ireson M, et al. Clinical trials of antibacterial agents: a practical guide to design and analysis. statisticians in the pharmaceutical industry working party. *J Antimicrob Chemother*. 1998;41(4):467–480. doi:10.1093/jac/41.4.467
15. Venkataraman R, Kellum JA. Defining acute renal failure: the RIFLE criteria. *J Intensive Care Med*. 2007;22(4):187–193. doi:10.1177/0885066607299510
16. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. 2020;368:m441. doi:10.1136/bmj.m441
17. Guoshuang F. Logistic regression analysis in observational study. *Chin J Epidemiol*. 2019;40(8):1006–1009. doi:10.3760/cma.j.issn.0254-6450.2019.08.025
18. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clin Infect Dis*. 2023. doi:10.1093/cid/ciad428
19. Chang K, Wang H, Zhao J, et al. Risk factors for polymyxin B-associated acute kidney injury. *Int J Infect Dis*. 2022;117:37–44. doi:10.1016/j.ijid.2022.01.055

20. Pogue JM, Jones RN, Bradley JS, et al. Polymyxin susceptibility testing and interpretive breakpoints: recommendations from the United States committee on antimicrobial susceptibility testing (USCAST). *Antimicrob Agents Chemother*. 2020;64(2). doi:10.1128/AAC.01495-19
21. Xiao J, Zhang C, Ye S. Acinetobacter baumannii meningitis in children: a case series and literature review. *Infection*. 2019;47(4):643–649. doi:10.1007/s15010-018-1234-1
22. Saleem AF, Shah MS, Shaikh AS, Mir F, Zaidi AK. Acinetobacter species meningitis in children: a case series from Karachi, Pakistan. *J Infect Dev Ctries*. 2011;5(11):809–814. doi:10.3855/jidc.1697
23. Austin G, Mauer AM. An acute massive overdose of polymyxin B sulfate. *AMA J Dis Child*. 1956;91(6):628–629. doi:10.1001/archpedi.1956.02060020630020
24. Liu X, Lu H, Lu F, Zhang J, Xuan M, Li B. Analysis of Klebsiella pneumoniae infection and polymyxin B application in children after cardiopulmonary bypass surgery. *Shanxi Med J*. 2021;20(21):3041–3043.
25. Rai S, Niranjan DK, Mishra P, Singh NP. Antibiotic pressure mediated selection of non-biofilm forming strain of Elizabethkingia meningosepticum causing fatal nosocomial meningitis in a term infant. *Indian J Pathol Microbiol*. 2013;56(3):309–311. doi:10.4103/0377-4929.120408
26. Guanghua W, Yabing X, Miao Z, Shuli M. Clinical analysis of polymyxins B in treatment of hospital acquired pneumonia with carbapenem resistant gram negative bacteria in children. *Drugs Clinic*. 2022;37(4):876–881.
27. Zhen L, Yueniu Z, Lili X, Wei X, Xiaodong Z. Clinical observation of polymyxin in the treatment of severe carbapenem-resistant Gram-negative bacterial infection in children. *Chin Pediatr Emerg Med*. 2020;27(12):893–898.
28. Wang P, Hu L, Wang Y. Clinical pharmacists participated in the medication analysis of one child with carbapenem-resistant Klebsiella pneumoniae infection. *Xinjiang Med J*. 2019;49(8):840–842.
29. Hong Y, Li X, Chen X, et al. Combination of four drugs for bloodstream infection caused by carbapenem-resistant Enterobacteriaceae in severe agranulocytosis patients after hematopoietic stem cell transplantation. *Blood*. 2019;134(Supplement_1):5664. doi:10.1182/blood-2019-128257
30. Jia X, Yin Z, Zhang W, Guo C, Du S, Zhang X. Effectiveness and nephrotoxicity of intravenous polymyxin B in carbapenem-resistant gram-negative bacterial infections Among Chinese children. *Front Pharmacol*. 2022;13:902054. doi:10.3389/fphar.2022.902054
31. da Silva PS, Pereira GH. Elizabethkingia meningoseptica: emergent bacteria causing pneumonia in a critically ill child. *Pediatr Int*. 2013;55(2):231–234. doi:10.1111/j.1442-200X.2012.03650.x
32. Hasassri ME, Boyce TG, Norgan AP, et al. An immunocompromised child with bloodstream infection caused by two Escherichia coli strains, one harboring NDM-5 and the other harboring OXA-48-like carbapenemase. *Antimicrob Agents Chemother*. 2016;60(6):3270–3275. doi:10.1128/AAC.03118-15
33. Posener LJ, Pow CG, Jain KK, Bau S. Life threatening disease. An unusual case of severe burns, meningitis, obstructive hydrocephalus and neuroblastoma in a child under age two. *Clin Pediatr*. 1968;7(5):288–293. doi:10.1177/000992286800700511
34. Alamarat ZI, Babic J, Tran TT, et al. Long-term compassionate use of cefiderocol to treat chronic osteomyelitis caused by extensively drug-resistant Pseudomonas aeruginosa and extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae in a pediatric patient. *Antimicrob Agents Chemother*. 2020;64(4). doi:10.1128/AAC.01872-19
35. Angel C, Patrick CC, Lobe T, Rao B, Pui CH. Management of anorectal/perineal infections caused by Pseudomonas aeruginosa in children with malignant diseases. *J Pediatr Surg*. 1991;26(4):487–492. doi:10.1016/0022-3468(91)91001-f
36. Siddiqui NU, Qamar FN, Jurair H, Haque A. Multi-drug resistant gram negative infections and use of intravenous polymyxin B in critically ill children of developing country: retrospective cohort study. *BMC Infect Dis*. 2014;14:626. doi:10.1186/s12879-014-0626-9
37. Liu X, Li B, Hua Y, Wu K, Hu M, Fan T. Polymyxin B for postoperative carbapenem-resistant Gram-negative bacteria-infected pneumonia in children with congenital heart disease. *J Chin Pract Diagn Ther*. 2021;35(11):1178–1181.
38. Ye J, Tan LH, Shen ZP, et al. Polymyxin for the treatment of intracranial infections of extensively drug-resistant bacteria in children after neurosurgical operation. *World J Pediatr*. 2020;16(5):528–532. doi:10.1007/s12519-020-00350-8
39. Wang PL, Liu P, Zhang QW, et al. Population pharmacokinetics and clinical outcomes of polymyxin B in paediatric patients with multidrug-resistant Gram-negative bacterial infections. *J Antimicrob Chemother*. 2022;77(11):3000–3008. doi:10.1093/jac/dkac265
40. Ong J, Ngiam N, Aye WM, Maclaren G. Prolonged venovenous extracorporeal membrane oxygenation in a child with leukemia and persistent bacteremia. *Pediatr Crit Care Med*. 2011;12(6):e395–7. doi:10.1097/PCC.0b013e3181fe25ce
41. Barco-Cabrera C, Reina YA, Davalos DM, et al. Use of polymyxins for carbapenem-resistant infections in children and adolescents. *JAC Antimicrob Resist*. 2022;4(3):dlac073. doi:10.1093/jacamr/dlac073
42. Xing H, Cheng C, Zhang Y, et al. Successful treatment with intrathecal and intravenous polymyxin B-based combination against MDR Acinetobacter baumannii meningitis in pediatric patient: a case report. *Front Pediatr*. 2021;9:564991. doi:10.3389/fped.2021.564991
43. Fitzrol DN, Ang SY, Suhaimi A, Yeap TB. Rare occurrence of polymyxin B-induced hyperpigmentation in a child with ventriculitis. *BMJ Case Rep*. 2023;16(4):e253959. doi:10.1136/bcr-2022-253959
44. Huang X, Han M, Jin F, Zhu Z, Zhang H. Analysis of a refractory case of pediatric meningitis caused by Klebsiella pneumoniae Co-resistant to carbapenems and polymyxins. *Infect Drug Resist*. 2022;15:5309–5313. doi:10.2147/IDR.S376776
45. Landman D, Georgescu C, Martin DA, Quale J. Polymyxins revisited. *Clin Microbiol Rev*. 2008;21(3):449–465. doi:10.1128/CMR.00006-08
46. Infectious Diseases Society of China, Chinese Thoracic Society, Chinese Society of Critical Care Medicine, et al. Chinese multidisciplinary expert consensus on the rational clinical use of polymyxins. *Chin J Tubercul Respirat Dis*. 2021;44(4):292–310. doi:10.3760/cma.j.cn112147-20201109-01091
47. Critical Care Medicine Professional Committee of Chinese Research Hospital Association. Infectious diseases evidence-based and translation professional committee of Chinese research hospital association. Chinese expert consensus on clinical application of polymyxins. *Chin J Emergency Med*. 2019;28(10):1218–1222. doi:10.3760/cma.j.issn.1671-0282.2019.10.007.
48. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis*. 2018;18(4):391–400. doi:10.1016/S1473-3099(18)30099-9
49. Kaye KS, Marchaim D, Thamlikitkul V, et al. Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. *NEJM Evid*. 2023;2(1). doi:10.1056/evidoa2200131
50. Nation RL, Li J, Cars O, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. *Lancet Infect Dis*. 2015;15(2):225–234. doi:10.1016/S1473-3099(14)70850-3

51. Liu X, Huang C, Bergen PJ, et al. Chinese consensus guidelines for therapeutic drug monitoring of polymyxin B, endorsed by the infection and chemotherapy committee of the Shanghai Medical Association and the therapeutic drug monitoring committee of the Chinese pharmacological society. *J Zhejiang Univ Sci B*. 2023;24(2):130–142. doi:10.1631/jzus.B2200466
52. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. *Clin Infect Dis*. 2013;57(4):524–531. doi:10.1093/cid/cit334
53. Landersdorfer CB, Wang J, Wirth V, et al. Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against Klebsiella pneumoniae in mouse thigh and lung infection models. *J Antimicrob Chemother*. 2018;73(2):462–468. doi:10.1093/jac/dkx409
54. Lenhard JR, Thamlikitkul V, Silveira FP, et al. Polymyxin-resistant, carbapenem-resistant Acinetobacter baumannii is eradicated by a triple combination of agents that lack individual activity. *J Antimicrob Chemother*. 2017;72(5):1415–1420. doi:10.1093/jac/dkx002
55. Ardebili A, Izanloo A, Rastegar M. Polymyxin combination therapy for multidrug-resistant, extensively-drug resistant, and difficult-to-treat drug-resistant gram-negative infections: is it superior to polymyxin monotherapy? *Expert Rev Anti Infect Ther*. 2023;21(4):387–429. doi:10.1080/14787210.2023.2184346
56. Pogue JM, Ortwine JK, Kaye KS. Clinical considerations for optimal use of the polymyxins: a focus on agent selection and dosing. *Clin Microbiol Infect*. 2017;23(4):229–233. doi:10.1016/j.cmi.2017.02.023
57. Alan S, Yildiz D, Erdeve O, et al. Efficacy and safety of intravenous colistin in preterm infants with nosocomial sepsis caused by Acinetobacter baumannii. *Am J Perinatol*. 2014;31(12):1079–1086. doi:10.1055/s-0034-1371361
58. Serafettin Tekgunduz K, Kara M, Caner I, Demirelli Y. Safety and efficacy of intravenous colistin in neonates with culture proven sepsis. *Iran J Pediatr*. 2015;25(4):e453. doi:10.5812/ijp.453
59. Ipek MS, Aktar F, Okur N, Celik M, Ozbek E. Colistin use in critically ill neonates: a case-control study. *Pediatr Neonatol*. 2017;58(6):490–496. doi:10.1016/j.pedneo.2016.10.002
60. Patriarca F, Cigana C, Massimo D, et al. Risk factors and outcomes of infections by multidrug-resistant gram-negative bacteria in patients undergoing hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(2):333–339. doi:10.1016/j.bbmt.2016.11.005
61. Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT international cohort study. *Intensive Care Med*. 2012;38(12):1930–1945. doi:10.1007/s00134-012-2695-9
62. Kreitmann L, Helms J, Martin-Loeches I, et al. ICU-acquired infections in immunocompromised patients. *Intensive Care Med*. 2024;50:332–349. doi:10.1007/s00134-023-07295-2
63. Thomas R, Velaphi S, Ellis S, et al. The use of polymyxins to treat carbapenem resistant infections in neonates and children. *Expert Opin Pharmacother*. 2019;20(4):415–422. doi:10.1080/14656566.2018.1559817
64. Wu X-L, Long W-M, Lu Q, et al. Polymyxin B-associated nephrotoxicity and its predictors: a retrospective study in carbapenem-resistant gram-negative bacterial infections. *Front Pharmacol*. 2022;13. doi:10.3389/fphar.2022.672543
65. Manchandani P, Zhou J, Babic JT, Ledesma KR, Truong LD, Tam VH. Role of Renal Drug Exposure in Polymyxin B-Induced Nephrotoxicity. *Antimicrob Agents Chemother*. 2017;61(4). doi:10.1128/AAC.02391-16
66. Nakahama H, Fukuhara Y, Orita Y, Yamauchi A, Takama T, Kamada T. Furosemide accelerates gentamicin accumulation in cultured renal cells (LLC-PK1 Cells). *Nephron*. 1989;53(2):138–141. doi:10.1159/000185726
67. Jia X, Guo C, Yin Z, Zhang W, Du S, Zhang X. Risk factors for acute kidney injury induced by intravenous polymyxin B in Chinese patients with severe infection. *Infect Drug Resist*. 2022;15:1957–1965. doi:10.2147/IDR.S363944
68. Mendes CA, Cordeiro JA, Burdmann EA. Prevalence and risk factors for acute kidney injury associated with parenteral polymyxin B use. *Ann Pharmacother*. 2009;43(12):1948–1955. doi:10.1345/aph.1M277
69. Sisay M, Hagos B, Edessa D, Tadiwos Y, Mekuria AN. Polymyxin-induced nephrotoxicity and its predictors: a systematic review and meta-analysis of studies conducted using RIFLE criteria of acute kidney injury. *Pharmacol Res*. 2021;163:105328. doi:10.1016/j.phrs.2020.105328
70. Yu M, Li H, Wang B, et al. Baicalein ameliorates polymyxin B-induced acute renal injury by inhibiting ferroptosis via regulation of SIRT1/p53 acetylation. *Chem Biol Interact*. 2023;382. 110607. doi:10.1016/j.cbi.2023.110607
71. Wang P, Zhang Q, Zhu Z, et al. Comparing the population pharmacokinetics of and acute kidney injury due to polymyxin b in Chinese patients with or without renal insufficiency. *Antimicrob Agents Chemother*. 2021;65(2) doi:10.1128/AAC.01900-20
72. Dai C, Xiao X, Li J, et al. Molecular mechanisms of neurotoxicity induced by polymyxins and chemoprevention. *ACS Chem Neurosci*. 2019;10 (1):120–131. doi:10.1021/acschemneuro.8b00300
73. Velkov T, Dai C, Ciccotosto GD, Cappai R, Hoyer D, Li J. Polymyxins for CNS infections: pharmacology and neurotoxicity. *Pharmacol Ther*. 2018;181:85–90. doi:10.1016/j.pharmthera.2017.07.012