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A retrospective observational study of the treatment with polymyxin B for liver transplantation recipients infected by multidrug-resistant gram-negative bacteria

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Abstract

What Is Known and Objective: Only a few studies about polymyxin B (PMB) against multidrug-resistant gram-negative bacteria (MDR GNB) infection were conducted in liver transplantation recipients (LTRs). The purpose of this study was to investigate the efficacy and safety of PMB in the treatment of MDR-GNB in liver transplant recipients and to determine the risk factors affecting clinical cure and 30-day all-cause mortality.

Methods: Data of LTRs receiving PMB from January 2016 to February 2020 were collected. Clinical cure and 30-day all-cause mortality were the main efficacy outcomes, while the incidence of nephrotoxicity, neurotoxicity, and hyperpigmentation of PMB was the main safety outcome.

Results and Discussion: Data of 42 LTRs were included. Clinical cure with PMB was observed in 27 recipients (64.3%), and the 30-day all-cause mortality rate was 31.0% (13/42). The incidence of acute kidney injury (AKI), neurotoxicity, and hyperpigmentation was 57.1% (16/28), 4.8% (2/42), and 16.7% (7/42), respectively. Logistic regression analysis showed that Acute Physiology and Chronic Health Evaluation (APACHE) II score (OR, 1.203; 95% CI, 1.016–1.423, $p = 0.032$) was an independent risk factor for 30-day all-cause mortality, whereas renal replacement therapy (OR, 0.128; 95% CI, 0.019–0.860, $p = 0.034$) was an independent risk factor for clinical cure with PMB.

What Is New and Conclusions: This is the first study to evaluate the application of PMB in LTRs. If there were no better therapeutic options left for LTRs other than PMB, it can be used against MDR GNB infection in LTRs. We should closely observe adverse events or reactions, and adjust the dose based on the balance of efficacy and safety.

KEYWORDS

liver transplantation, multidrug-resistant gram-negative bacteria, polymyxin B

Ling-Ling Yu and Xiao-Ping Shi had equal contribution to the manuscript.

1 | WHAT IS KNOWN AND OBJECTIVE

Infectious complications are significant contributors to morbidity and mortality after liver transplantation.[1] About one-third of liver transplant recipients suffer at least one infection within 30 days after transplantation, predominantly bacterial infection during the first 2 months post-transplantation.[2] In the last decade, data from solid organ transplantation showed a steady upward trend of gram-negative bacteria (GNB) and an 8-fold increase of multidrug-resistant gram-negative bacteria (MDR GNB).[3] Due to the significantly high mortality rates of MDR GNB,[2] they have become an increasing challenge for clinicians to manage, especially in liver transplantation recipients (LTRs).

Several novel antibiotics were developed and approved in response to the need to fight the increasing rates of infections caused by MDR bacteria with lower mortality and better safety profiles. However, in China where novel antibiotics (e.g., ceftazidime/avibactam, imipenem/relebactam, and cefiderocol) are not available or not yet covered by health insurance, polymyxin B (PMB) becomes the last line of treatment for MDR GNB infections, including *Klebsiella* spp, *Acinetobacter* spp, and *Pseudomonas aeruginosa*.[4] PMB was developed in the 1940s but was gradually replaced by other antibiotics in the sixties in the world due to its nephrotoxicity and neurotoxicity. The potent in vitro activity of PMB against MDR GNB, the rapid increase of bacterial resistance strains, and the lack of new effective antibiotics have led to its reintroduction to clinical use in recent years. Only a few studies about PMB against MDR GNB were conducted in LTRs in the past because of its limited use.[4] Additionally, acute kidney injury (AKI) is a common complication after liver transplantation;[5] thus, PMB safety in LTRs remains unclear. The purpose of this study was to investigate the efficacy and safety of PMB in the treatment of MDR-GNB in liver transplant recipients and to determine the risk factors affecting clinical cure and 30-day all-cause mortality.

2 | METHODS

2.1 | Research design and methods

In the present retrospective, single-center study, medical records of LTRs who received intravenous PMB for MDR GNB in a tertiary teaching hospital in Shanghai from January 2016 to February 2020 were analysed. Medical Ethics Committee of Zhongshan Hospital approved this study (approval No. B2020-320R) and waived the requirement for informed consent because this retrospective analysis was limited to preexisting data from medical records and collected as a part of the routine treatment by clinicians.

Patients were recruited if they met the following inclusion criteria: (1) received liver transplantation; (2) age ≥18 years old; (3) had a culture-confirmed MDR GNB infection. The exclusion criteria were: (1) the length of treatment <72 h; (2) incomplete or missing patient information. MDR GNB were defined as those that acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[6] MDR GNB identification and antibiotic susceptibility testing were confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (bioMérieux, Marcy l'Etoile, France) and automated susceptibility testing system VITEK 2 Compact (bioMérieux, France) and Phoenix M50 instrument (BD Diagnostics, CA). Minimum inhibitory concentration (MIC) was interpreted according to Clinical and Laboratory Standards Institute (CLSI) breakpoints.

Data were collected from the hospital's electronic database, including demographic characteristics, clinical information, laboratory results, microbial culture, antimicrobial susceptibility testing, therapeutic regimen, and outcomes. The primary outcomes were clinical cure with PMB at the end of the treatment course and 30-day all-cause mortality. The secondary outcomes were adverse drug events and toxic reactions of PMB.

2.2 | Observed indicators

Bacteremia was a positive blood culture with clinical signs of systemic inflammatory response syndrome. Systemic inflammatory response syndrome was defined as the presence of two or more of the following parameters: body temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20 breaths/min, and white blood cell count $>12 \times 10^9$ or $<4 \times 10^9$ cells/L. Non-bacteremia infection was defined as positive non-blood sample cultures (sputum, urine, bronchial-alveolar lavage fluid, pleural drainage fluid, intra-abdominal drainage fluid, etc.) plus clinical signs of infection with negative blood culture. For infections requiring removal of the source of infection (catheter-related bacteremia or intra-abdominal infections, etc.), we had performed adequate source control before using antibiotics. Source control included removing or replacing the catheter/drain placement or removing infected fluid and tissue.

Clinical cure with PMB was defined as improved signs and symptoms from the infection onset to the end of therapy and negative culture from the same site. The 30-day all-cause mortality rate referred to the percentage of LT recipients who died from any cause within 30 days after starting PMB treatment. Microbiological eradication was defined as the absence of the initially isolated pathogen from the site of index infection. Additionally, the incidence of nephrotoxicity, neurotoxicity, and hyperpigmentation of PMB was reviewed from medical records. The Kidney Disease Improving Global Outcome (KDIGO) guideline was used to determine PMB-associated AKI based on serum creatinine (SCr) level increase by 0.3 mg/dL within 48 hours or a 50% increase from baseline.[7] The severity of AKI was categorized as stage 1 (increase in SCr level by 1.5 fold or ≥0.3 mg/dL), stage 2 (increase in SCr level by two fold), and stage 3 (increase in SCr level by 3 fold or ≥4 mg/dL or the initiation of renal replacement therapy).[7] Neurotoxicity was defined as any dizziness, weakness, facial and oral numbness, peripheral neuropathy, and confusion during PMB therapy that was not present at the start of therapy. Hyperpigmentation referred to significant darkness of the skin compared to the skin colour before PMB treatment. The von Luschan Color Scale was used to assess changes in skin tone every week from the initial treatment of PMB.

2.3 | Statistical analysis

SPSS version 19.0 (IBM crop., Armonk, NY, USA) was used to perform all statistical analyses. Normal and non-normal distributed continuous

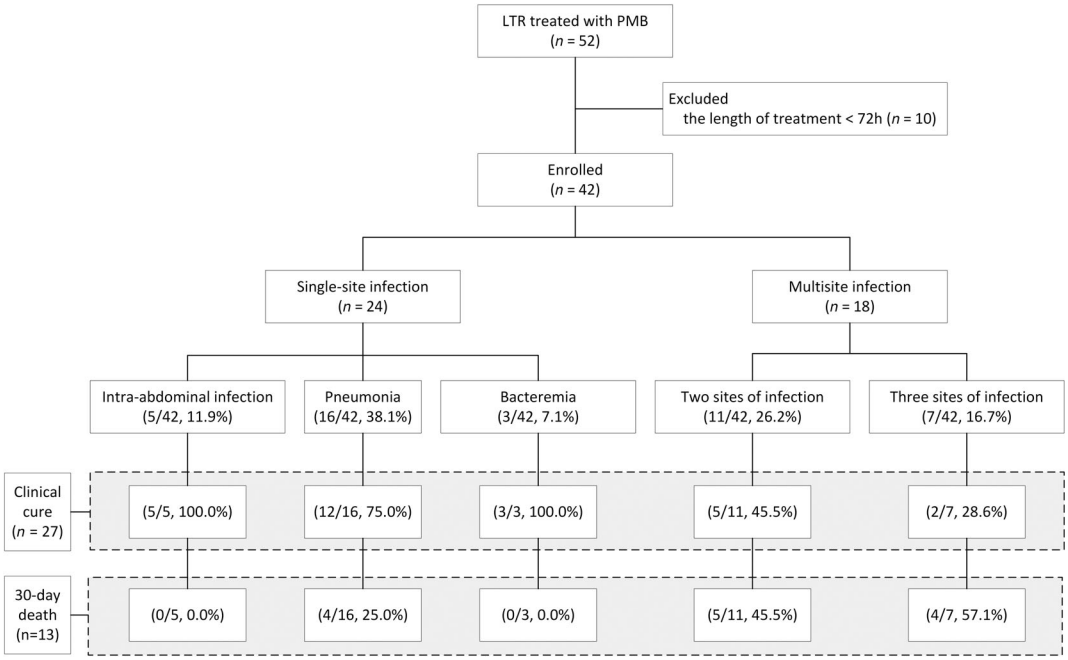

FIGURE 1 Flowchart of the inclusion process of LTRs. LTR, liver transplantation recipient; PMB, polymyxin B

variables were compared using independent sample *t*-test and Mann–Whitney *U* test, respectively. Categorical variables were compared using the Chi-square test or Fisher's exact test. A forward logistic regression model was adopted to analyse independent risk factors affecting clinical cure with PMB and 30-day all-cause mortality. $p < 0.05$ was considered statistically significant.

3 | RESULTS AND DISCUSSION

3.1 | Demographic and clinical characteristics

A total of 52 LTRs were identified from the electronic medical records and excluded 10 recipients with a length of treatment of fewer than 72 h (Figure 1). There were 24 cases of single-site infections, including bacteremia (3/42, 7.1%), intra-abdominal infection (5/42, 11.9), and pneumonia (16/42, 42.9%). The remaining 18 recipients developed multisite infections. Among them, there were three cases of bacteremia combined with pneumonia, three cases of pneumonia combined with intra-abdominal infection, two cases each of bacteremia combined with intra-abdominal infection and pneumonia combined with urinary tract infection, and one case of bacteremia combined with urinary tract infection. There were also seven LTRs with more than two sites of infection. All LTRs had no MDR GNB infection before transplantation.1

Table 1 summarizes the demographic and clinical characteristics of the study. Most recipients were male (31/42, 73.8%), the average age was 54.2 ± 13.4 years, and the average weight was 64.7 ± 14.6 kg. Liver tumours were the most common indications for liver transplant (20/38, 52.6%), followed by hepatitis B virus-related decompensated cirrhosis (9/38, 23.7%). The average Acute Physiology and Chronic Health Evaluation (APACHE) II score and Charlson comorbidity score were 22.5 ± 7.4 and 4.7 ± 2.0, respectively. The incidence of septic shock was 52.4%, and the percentage of patients receiving mechanical ventilation, renal replacement therapy (RRT), vasoactive drugs, or calcineurin inhibitors (CNI) before PMB initiation was 59.5%, 33.3%, 61.9%, and 50.0%, respectively.

3.2 | Microbiological characteristics and PMB therapy

A total of 86 bacterial strains were isolated; 53.5% (46/86) were *Acinetobacter baumannii*, and 45.3% (39/86) were *Klebsiella pneumoniae*. All isolated strains were resistant to carbapenems but displayed susceptibility to PMB. The MICs of PMB were ≤0.5 mg/L (58/86, 67.6%).

All LTRs with MDR GNB infection were treated with a combination of PMB-containing regimens. Eleven of these recipients were switched to PMB after failure of conventional anti-infective therapy. In most cases, PMB was combined with tigecycline (15/42, 35.7%), beta-lactam/beta-lactamase inhibitors (16/42, 38.1%) or high-dose carbapenems (26/42, 61.9%); 61.9% of LTRs received two-drug combinations, and 38.1% received three to four-drug combination therapy. PMB was administrated in a loading dose of 2.5 mg/kg, and then 2.3 ± 0.4 mg/kg as the average daily maintenance dose for a median duration of 13.5 days (range, 8.0–18.0 days). The median time from the onset of infection to the initial treatment was 27.0 h (range, 4.0–96.0 h).

3.3 | Outcomes

Clinical cure with PMB was observed in 27 recipients (64.3%), and the 30-day all-cause mortality rate was 31.0% (13/42). The percentage of

TABLE 1 Characteristics and outcomes of liver transplant recipients treated with polymyxin B against multidrug-resistant Gram-negative bacteria infections

Variable	Total ($n = 42$)
Male, *n* (%)	31 (73.8)
Age (years)	54.2 ± 13.4
Weight (kg)	64.7 ± 14.6
Causes of transplantation ($n = 38$)[a]	
Tumour, *n* (%)	20 (52.6)
Hepatitis B virus, *n* (%)	9 (23.7)
Graft failure, *n* (%)	3 (7.9)
Alcoholic cirrhosis, *n* (%)	2 (5.3)
Other, *n* (%)	4 (10.5)
Clinical characteristic	
Meld-Na before liver transplant ($n = 38$)	17.0 (9.5–26.0)
APACHE II score	22.5 ± 7.4
Charlson comorbidity index	4.7 ± 2.0
Charlson comorbidity index ≥3, *n* (%)	37 (88.1)
Pitt bacteremia score ($n = 16$)	4.4 ± 2.8
Mechanical ventilation, *n* (%)	25 (59.5)
RRT before PMB administration, *n* (%)	14 (33.3)
Concomitant vasoactive drugs, *n* (%)	26 (61.9)
Concomitant CNI, *n* (%)	21 (50.0)
Septic shock, *n* (%)	22 (52.4)
Baseline laboratory variable	
Haemoglobin (g/L), Median (IQR)	87.5 (78.0–98.0)
PLT (10^9/L), Median (IQR)	62.5 (30.5–125.3)
WBC (10^9/L), Median (IQR)	9.0 (4.6–15.4)
PCT (ng/mL), Median (IQR)	2.7 (1.0–11.4)
CRP (mg/L), Median (IQR)	64.9 (47.5–90.0)
BUN (mmol/L), Median (IQR)	15.3 (8.4–27.0)
SCr (μmol/L), Median (IQR)	81.0 (56.8–142.5)
ALB (g/L), Median (IQR)	35.0 (31.0–40.0)
TB (μmol/L), Median (IQR)	39.2 (21.4–155.1)
ALT (U/L), Median (IQR)	82.0 (27.8–244.8)
AST (U/L), Median (IQR)	38.0 (26.0–107.3)
Infection and PMB therapy	
Infection pathogens, *n* (%)	
Acinetobacter baumannii	46 (53.5)
Klebsiella pneumoniae	39 (45.3)
Pseudomonas aeruginosa	1 (1.2)
Single-site infection, *n* (%)	24 (57.1)
Bacteremia	3 (7.1)
Intra-abdominal infection	5 (11.9)
Pneumonia	16 (38.1)
Multisite infections, *n* (%)	18 (42.9)
Bacteremia ± Pneumonia	3 (7.1)
Bacteremia ± Intra-abdominal infection	2 (4.8)
Bacteremia ± Urinary tract infection	1 (2.4)
Pneumonia ± Intra-abdominal infection	3 (7.1)
Pneumonia ± Urinary tract infection	2 (4.8)
Bacteremia ± Pneumonia ± Intra-abdominal infection	6 (14.3)
Bacteremia ± Pneumonia ± Urinary tract infection	1 (2.4)
Primary bacteremia, *n* (%)	8 (50.0)
Secondary bacteremia, *n* (%)	8 (50.0)
Donor liver	4 (25.0)
Abdominal	3 (18.8)
Respiratory	1 (6.2)
PMB therapy	
Loading dose (mg/kg)	2.4 ± 0.3
Daily maintaining dose (mg/kg)	2.3 ± 0.4
Duration of therapy (days), Median (IQR)	13.5 (8.0–18.0)
Time to treatment initiation (hours), Median (IQR)	27.0 (4.0–96.0)
Combination therapy, *n* (%)	
Two-drug combinations	26 (61.9)
Three or four-drug combinations	16 (38.1)
Outcome	
Clinical cure, *n* (%)	27 (64.3)
30-day all-cause mortality, *n* (%)	13 (31.0)
Microbiological eradication, *n* (%)	26 (61.9)
Time to microbiological eradication, Median (IQR)	4.0 (3.0–7.0)
Adverse drug reaction	
Acute kidney injury, *n* (%)	16 (57.1)
Stage 1, *n* (%)	6 (21.4)
Stage 2, *n* (%)	3 (10.7)
Stage 3, *n* (%)	7 (25.0)
Renal failure LTRs who needed RRT, *n* (%)	6 (21.4)
PMB dose adjustment, *n* (%)	12 (28.6)
Neurotoxicity, *n* (%)	2 (4.8)
Skin hyperpigmentation, *n* (%)	7 (16.7)

Note: Data are presented as mean ± SD, median (interquartile range, IQR), or number [%].
Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNI, calcineurin inhibitors; CRP, C-reactive protein; BUN, blood urea nitrogen; PMB, polymyxin B; PLT, platelet; WBC, white blood cell; PCT, procalcitonin; RRT, renal replace therapy; SCr, serum creatinine; TB, total bilirubin.
[a]Liver transplant recipients readmitted to intensive care unit ($n = 4$).

LTRs who achieved clinical cure also survived at 30 days was 92.6% (25/27). Of the recipients who died, only nine cases (69.2%) were attributable to infection, and the rest died from malignant arrhythmia, pneumothorax, and multiple organ failure. Compared to uncured LTRs, the rates of mechanical ventilation, RRT, and use of vasoactive drugs were significantly lower in cured recipients. Additionally, recipients

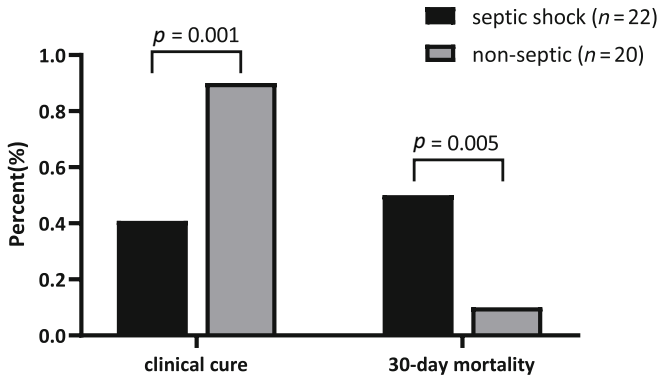

FIGURE 2 Comparison of clinical cr and 30-day mortality of polymyxin B between the LTRs with septic shock and non-septic groups. Clinical cure in the septic shock group was 40.9% (9/22), compared to 90.0% (18/20) in the non-septic group ($p = 0.001$). The 30-day mortality in the septic shock group was 50.0% (11/22), compared to 10.0% (2/20) in the non-septic group ($p = 0.005$).

with septic shock had a lower clinical improvement rate (40.9% vs. 90.0%, $p = 0.001$) and a higher 30-day all-cause mortality rate (50.0% vs. 10.0%, $p = 0.005$) than recipients without septic shock (Figure 2).

Microbiological eradication was observed in 26 recipients (61.9%) (13 with pneumonia, 3 with bacteremia, 2 with intra-abdominal infection, and others with multisite infections), and the median time from initial treatment to microbiological eradication was 4.0 days (range, 3.0–7.0 days).

Due to 14 LTRs receiving renal replacement therapy (RRT) before PMB administration, only 28 recipients received nephrotoxicity assessment. The incidence of AKI was 57.1% (16/28), stage 1 was 21.4%, and stage 3 was in six recipients who required RRT. Twelve patients received an adjusted dose. Before discharge, eight patients had a normal renal function, and one patient had no renal function improvement. Seven patients died during PMB treatment and failed to be observed for renal function recovery.

The incidence of neurotoxicity and hyperpigmentation was 4.8% (2/42) and 16.7% (7/42), respectively. After PMB discontinuation, neurotoxicity disappeared. Except for two recipients who died during the treatment, the skin tone of the other recipients gradually recovered after a few months of PMB discontinuation.

Logistic regression analysis showed that APACHE II score (OR, 1.203; 95% CI, 1.016 to 1.423, $p = 0.032$) was an independent risk factor of 30-day all-cause mortality, whereas RRT (OR, 0.128; 95% CI, 0.019 to 0.860, $p = 0.034$) was independent risk factor affecting clinical cure with PMB (Table 2).

4 | DISCUSSION

Bacterial infections are the most common complication among solid organ transplant (SOT) recipients and are associated with higher mortality.[8] Throughout the first year after SOT, MDR GNB infection rose

TABLE 2 Univariate and multivariate analysis of factors associated with clinical cure and 30-day mortality in the 42 liver transplant recipients treated with polymyxin B

Variable	Clinical cure			Adjusted		30-day mortality			Adjusted	
	YES ($n = 27$)	NO ($n = 15$)	*p*	Odds ratio (95% CI)	*P*	YES ($n = 13$)	NO ($n = 29$)	*P*	Odds ratio (95% CI)	*p*
APACHE II score	21.1 ± 7.3	24.9 ± 7.3	0.111			27.6 ± 7.0	20.2 ± 6.5	**0.002**	**1.203 (1.016–1.423)**	**0.032**
Charlson comorbidity index	4.3 ± 2.2	5.5 ± 1.5	0.073			5.9 ± 1.7	4.2 ± 2.0	**0.014**		
Mechanical ventilation, *n* (%)	12 (44.4)	13 (86.7)	**0.008**			11 (84.6)	14 (48.3)	**0.027**		
Renal replace therapy, *n* (%)	7 (25.9)	13 (86.7)	**0.000**	**0.128 (0.019–0.860)**	**0.034**	11 (84.6)	9 (31.0)	**0.001**	**9.253 (0.922–92.905)**	**0.059**
Concomitant vasoactive drugs, *n* (%)	11 (40.7)	15 (100.0)	**0.000**			13 (100.0)	13 (44.8)	**0.002***		
Concomitant CNI, *n* (%)	14 (51.9)	7 (46.7)	0.747			5 (38.5)	16 (55.2)	0.317		
Septic shock, *n* (%)	9 (33.3)	13 (86.7)	**0.001**			11 (84.6)	11 (37.9)	**0.005**		
First-line therapy, *n* (%)	17 (63.0)	14 (93.3)	0.075*			11 (84.6)	20 (69.0)	0.492*		
PMB dose adjustment, *n* (%)	10 (37.0)	2 (13.3)	0.203*			2 (15.4)	10 (34.5)	0.370*		
Loading dose (mg/kg)	2.4 ± 0.3	2.5 ± 0.4	0.203			2.5 ± 0.4	2.4 ± 0.3	0.400		
Daily maintaining dose (mg/kg)	2.2 ± 0.4	2.4 ± 0.3	0.172			2.4 ± 0.4	2.3 ± 0.4	0.295		
Duration of therapy (days)	14.0 (9.0–18.0)	10.0 (4.0–18.0)	0.236			10.0 (4.0–14.5)	14.0 (10.0–18.5)	0.056		
Time to treatment initiation (hours)	29.0 (4.0–144.0)	26.0 (4.0–33.0)	0.189			22.0 (3.0–39.5)	27.0 (4.5–120.0)	0.374		
Combination therapy (*n*>2)	9 (33.3)	7 (46.7)	0.394			7 (53.8)	9 (31.0)	0.287*		

Note: The bold values provided in Table 2 refers to $p < 0.05$.
*Continuity correction.

dramatically from 4.8% to 38.8% over the last decade,[3] but the treatment options remained very limited. The guidelines or consensus recommend the combination therapy based on PMB, but there was no study evaluating PMB application in LTRs. Hence, the present study retrospectively analysed the efficacy and safety of PMB against MDR GNB infection in LTRs for the first time.

In our study, clinical cure with PMB was observed in 27 recipients (64.3%), consistent with previous literature.[9,10] The failure of treatment might be related to the timing of treatment initiation, the MIC of PMB, multisite infection, and severe sepsis. A previous study pointed out that delayed active treatment initiation was associated with poorer outcomes of severe GNB bloodstream infections.[11] Therefore, we administered PMB as early as possible, and the median time from the onset of infection to the targeted therapy was 27 h.

Recent studies also found that the MIC of a drug is an essential factor affecting the efficacy. Even if PMB was sensitive and all patients were given a weight-based dosage strategy, the probability of target attainment (PTA) of PMB would decrease with the increase of MIC value.[12] Besides, in our study, multisite infections accounted for 42.9%, with a clinical cure rate of 38.9%, which is less than the overall cure rate (64.3%). One research also showed that the 30-day mortality rate of patients with multisite infections was much higher.[13]

To obtain better drug efficacy, it is essential to optimize the therapeutic dose and strategy of PMB. Initiating with a loading dose was necessary to achieve efficacious exposure as soon as possible. Without a loading dose, exposure on day 1 was mostly one-third lower than on day 4.[14] The current dosing strategy is a weight-based regimen based mainly on the population pharmacokinetics study by Sandri.[14] However, other studies suggested that weight might not be an accurate predictor of PMB pharmacokinetic.[12,15,16] Elias and colleagues' research showed that a higher daily dose (≥200 mg/day) of PMB for severe infection could reduce in-hospital mortality.[17] We adopted a weight-based regimen in our practice, but a relatively higher PMB dose might have been a better choice for critically ill recipients. When deciding a dosage regimen, the PMB MIC of the pathogen must be considered.

One of the major concerns for PMB use in LTRs is the potential nephrotoxicity and its narrow therapeutic window. AKI is a common complication after liver transplant due to factors related to the recipient, the donor graft, and intraoperative and post-transplant events.[5] In our practice, LTRs were treated with a loading PMB dose of 2.5 mg/kg, followed by 1–1.5 mg/kg infusion every 12 h regardless of whether recipients had renal impairment or received RRT before PMB administration. The incidence of AKI was 57.1%, which was similar to previous studies.[18,19] At present, the optimal dose of PMB in patients with renal insufficiency is still in dispute. Sandri reported that creatinine clearance (CrCL) did not significantly influence the clearance of PMB and suggested that dosing should not be adjusted in the setting of renal impairment and RRT.[14] In contrast, a new study showed that PMB clearance significantly correlated with CrCL and suggested that the dosage of PMB should be decreased by 33% for patients with moderate renal insufficiency ($30 \le CrCL < 60$ ml/min).[15] One study found that a higher daily PMB dose was independently associated with AKI.[20] When sepsis patients with MDR GNB infection were prescribed high-dose PMB (3 mg/kg/day), AKI incidence (58.1%) was higher than those receiving standard-dose PMB. However, decreasing the daily doses of PMB to avoid nephrotoxicity was not a viable option because PMB administration less than 1.5–2.5 mg/kg/day would result in subtherapeutic antibiotic exposure.[21] Such subtherapeutic exposure might have multiple detrimental effects, including the amplification of PMB-resistant subpopulations and compromising clinical outcomes due to inadequate drug exposure.[22–24] In our study, the PMB dose was not adjusted for LTRs with renal insufficiency before initiating treatment. However, for LTRs who developed AKI during the treatment, the dose was slightly reduced to avoid drug overexposure but was still higher than 2 mg/kg/day. After the end of treatment, renal function recovered in half of the patients. The benefits of high-dose PMB and the increased risk of AKI must be weighed against the high mortality associated with MDR GNB infections as treatment failure in septic patients often equates to mortality. Now some scholars emphasize the therapeutic drug monitoring (TDM) of PMB. A case report of an individualized treatment against MDR GNB using TDM-guided medication of PMB demonstrated that timely dose adjustment based on TDM could improve clinical cure and reduce the incidence of acute kidney injury.[25]

The neurotoxicity of PMB is another major concern affecting its use. Neurotoxic effects include circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and speech slurring. In our study, two patients (4.8%) who received PMB developed neurotoxicity. One developed epilepsy and another had lip numbness. The symptoms, however, resolved after PMB withdrawal. Our findings showed that more attention should be towards patients with impaired renal function as they represented a high-risk population.[26]

Finally, skin toxicity due to PMB was monitored regularly in all LTRs. Using von Luschan Color Scale, we were able to find and quantify skin tone changes timely to communicate with patients and provide psychological counselling and humanistic care. The incidence of skin hyperpigmentation in our study was 16.7%, and pigmentations were mostly on the face and neck. Similar to previous reports, skin hyperpigmentation disappeared 3–6 months after PMB discontinuation.[27,28]

Some limitations to the present study should be noted. First, it was a retrospective study which was subject to selection bias and relied on medical record's accuracy. Second, there was no control group to compare the findings. The small sample of LTRs included has also limited the generalization of the concluded clinical data. Further large-sampled clinical trials are required to obtain more reliable results to test the efficacy of TDM dosage regimen for PMB and confirm the advantage of PMB in MDR GNB infections.

5 | WHAT IS NEW AND CONCLUSIONS

This is the first study to evaluate the application of PMB in LTRs. We demonstrated that PMB weight-based dosage regimen could be used against MDR GNB infection in LTRs, with RRT being the independent risk factor for a poor clinical outcome. Throughout the treatment course, toxic reactions should be closely monitored, and the therapeutic dose should be based on the balance of efficacy and toxic reaction.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DISCLOSURES

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Baganate F, Beal EW, Tumin D, et al. Early mortality after liver transplantation: defining the course and the cause. *Surgery*. 2018;164(4):694-704.
2. Barchiesi F, Montalti R, Castelli P, et al. Carbapenem-resistant *Klebsiella pneumoniae* influences the outcome of early infections in liver transplant recipients. *BMC Infect Dis*. 2016;16(1):538.
3. Oriol I, Sabe N, Simonetti AF, et al. Changing trends in the aetiology, treatment and outcomes of bloodstream infection occurring in the first year after solid organ transplantation: a single-Centre prospective cohort study. *Transpl Int*. 2017;30(9):903-913.
4. 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.
5. Durand F, Francoz C, Asrani SK, et al. Acute kidney injury after liver transplantation. *Transplantation*. 2018;102(10):1636-1649.
6. 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.
7. Stevens PE, Levin A. Kidney disease: improving global outcomes chronic kidney disease guideline development work group M. evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825-830.
8. Kritikos A, Manuel O. Bloodstream infections after solid-organ transplantation. *Virulence*. 2016;7(3):329-340.
9. Nelson BC, Eiras DP, Gomez-Simmonds A, et al. Clinical outcomes associated with polymyxin B dose in patients with bloodstream infections due to carbapenem-resistant gram-negative rods. *Antimicrob Agents Chemother*. 2015;59(11):7000-7006.
10. Ismail B, Shafei MN, Harun A, Ali S, Omar M, Deris ZZ. Predictors of polymyxin B treatment failure in gram-negative healthcare-associated infections among critically ill patients. *J Microbiol Immunol Infect*. 2018;51(6):763-769.
11. Liang Q, Huang M, Xu Z. Early use of polymyxin B reduces the mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. *Braz J Infect Dis*. 2019;23(1):60-65.
12. Miglis C, Rhodes NJ, Avedissian SN, et al. Population pharmacokinetics of Polymyxin B in acutely ill adult patients. *Antimicrob Agents Chemother*. 2018;62(3):e01475-e01417.
13. Rigatto MH, Falci DR, Lopes NT, Zavascki AP. Clinical features and mortality of patients on renal replacement therapy receiving polymyxin B. *Int J Antimicrob Agents*. 2016;47(2):146-150.
14. 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.
15. Yu XB, Jiao Z, Zhang CH, et al. Population pharmacokinetic and optimization of polymyxin B dosing in adult patients with various renal functions. *Br J Clin Pharmacol*. 2021;87(4):1869-1877.
16. Manchandani P, Thamlikitkul V, Dubrovskaya Y, et al. Population pharmacokinetics of Polymyxin B. *Clin Pharmacol Ther*. 2018;104(3):534-538.
17. Elias LS, Konzen D, Krebs JM, Zavascki AP. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. *J Antimicrob Chemother*. 2010;65(10):2231-2237.
18. Rigatto MH, Behle TF, Falci DR, et al. Risk factors for acute kidney injury (AKI) in patients treated with polymyxin B and influence of AKI on mortality: a multicentre prospective cohort study. *J Antimicrob Chemother*. 2015;70(5):1552-1557.
19. Dubrovskaya Y, Prasad N, Lee Y, Esaian D, Figueroa DA, Tam VH. Risk factors for nephrotoxicity onset associated with polymyxin B therapy. *J Antimicrob Chemother*. 2015;70(6):1903-1907.
20. Cai Y, Leck H, Tan RW, et al. Clinical experience with high-dose Polymyxin B against Carbapenem-resistant gram-negative bacterial infections-a cohort study. *Antibiotics (Basel)*. 2020;9(8):451.
21. Onufrak NJ, Rao GG, Forrest A, et al. Critical need for clarity in Polymyxin B dosing. *Antimicrob Agents Chemother*. 2017;61(5):e00208-e00217.
22. 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.
23. Pogue JM, Ortwine JK, Kaye KS. Are there any ways around the exposure-limiting nephrotoxicity of the polymyxins? *Int J Antimicrob Agents*. 2016;48(6):622-626.
24. Cannatelli A, Di Pilato V, Giani T, et al. In vivo evolution to colistin resistance by PmrB sensor kinase mutation in KPC-producing *Klebsiella pneumoniae* is associated with low-dosage colistin treatment. *Antimicrob Agents Chemother*. 2014;58(8):4399-4403.
25. Yu X, Pan J, Zhou Z, et al. TDM-guided medication of polymyxin B in a patient with CRKP-induced bloodstream infection: a case report. *Eur J Clin Microbiol Infect Dis*. 2021;40(1):201-204.
26. Myint T, Evans ME, Burgess DR, Greenberg RN. Respiratory muscle paralysis associated with Colistin, Polymyxin B, and muscle relaxants drugs: a case report. *J Investig Med High Impact Case Rep*. 2016;4(1):2324709616638362.
27. Zavascki AP, Manfro RC, Maciel RA, Falci DR. Head and neck hyperpigmentation probably associated with Polymyxin B therapy. *Ann Pharmacother*. 2015;49(10):1171-1172.
28. Zavascki AP, Schuster LF, Duquia RP. Histopathological findings of pigmented lesion and recovery of natural skin colour in a patient with polymyxin B-associated diffuse hyperpigmentation. *Int J Antimicrob Agents*. 2016;48(5):579-580.

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