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ORIGINAL ARTICLE

Higher incidence of neurotoxicity and skin hyperpigmentation in renal transplant patients treated with polymyxin B

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Background: Toxicity is a major concern related to the clinical use of polymyxin B, and available safety data for renal transplant patients are limited.

Aims: We investigated the safety of polymyxin B and toxicity risk factors in renal transplant patients.

Methods: A prospective study was performed on a group of renal transplant patients who received intravenous polymyxin B between January 2018 and August 2021. Polymyxin B treatment was monitored to evaluate toxicity and risk factors.

Results: A total of 235 courses of polymyxin B were administered to 213 patients. Of these, 121 (51.5%) developed skin hyperpigmentation (SH), 149 (63.4%) developed neurotoxicity and 10 (5.5%) developed acute kidney injury of which 80% was reversible. Risk factors for developing SH included a high total dose by weight (odds ration [OR] 1.31, 95% confidence interval [CI] 1.08–1.60, $P = .008$) and the presence of neurotoxicity (OR 2.86, 95% CI 1.56–5.26, $P = .001$). Neurotoxicity manifested during the first 2 days of treatment. Neurotoxicity occurred most commonly in women (OR 3.84, 95% CI 1.82–8.10, $P < .0001$), and the presence of SH (OR 1.98, 95% CI 1.13–3.46, $P = .016$) was also an independent risk factor.

Conclusions: Neurotoxicity and SH are the two major adverse effects of polymyxin B in renal transplant patients, which may limit its clinical use.

KEYWORDS
neurotoxicity, polymyxin B, renal transplant patients, safety, skin hyperpigmentation

1 | INTRODUCTION

Polymyxins are a group of polypeptide antibacterial agents that were first identified in the 1940s.[1,2] Despite their distinct activity against gram-negative bacteria, their use has been discontinued for many years owing to their toxicity.[3,4] However, with the emergence of multidrug-resistant (MDR) gram-negative bacteria, polymyxins have re-emerged as alternatives against such MDR organisms.[5–7] Polymyxin B and E (colistin) are the only two compounds in this family that have been used in clinical practice, and polymyxin E was widely used previously. However, because of its more predictable pharmacokinetics and rapid antimicrobial activity, polymyxin B has become favoured by clinicians.[8,9]

Like other polymyxins, nephrotoxicity and neurotoxicity are the most common adverse events associated with polymyxin B.[3,10] However, owing to limited clinical experience, the incidence and predictors of these adverse reactions remain controversial. Recent studies in critical care unit (ICU) patients have shown that nephrotoxicity rates range widely from 10 to 60%.[3,4] Some studies found that a higher dosage and concomitant use of other nephrotoxic drugs were associated with an increased risk of nephrotoxicity, while others found a significant relationship between baseline renal

Principal Investigator statement The authors confirm that the Principal Investigator for this paper is Yangang Zhou and that she had direct clinical responsibility for patients.

function and acute kidney injury (AKI).[11–13] Neurotoxicity was less common (7–27%) in earlier studies and usually manifests as dizziness, muscle weakness, facial and peripheral paraesthesia, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia and neuromuscular blockade.[4,14] Nevertheless, Liu and Crass recently reported higher neurotoxic adverse reactions in both healthy subjects (85%) and patients with cystic fibrosis (100%).[15,16] Compared to highly sedated patients in earlier studies, these patients were conscious and presented a better capacity to perceive the symptoms of neurotoxicity, which might be the reason for the higher incidence rates. In addition, intravenous polymyxin B treatment was recently found to cause skin hyperpigmentation (SH), and the D-phenylalanine residue at position 6 might be the critical structure involved in this reaction, but the incidence and mechanism of this effect are still unknown.[17,18]

Renal transplant patients are at an increased risk of developing MDR gram-negative infections due to immunosuppression, frequent antibiotic use and healthcare exposure. Hence, they are at an increased need for polymyxin B treatment.[19,20] However, there is little data regarding the rates and spectrum of polymyxin B toxicity in renal transplant patients.[21] Our previous study showed that polymyxin B was more likely to accumulate in renal transplant patients with much lower clearance than in other patients, which might lead to more toxicity.[22] Moreover, since neurotoxicity and SH caused by polymyxin B are considered to be dose-dependent, patients with impaired renal function are at higher risk of developing these adverse effects.[14,17] The primary objective of our study was to evaluate the safety of polymyxin B in renal transplant patients, with a particular focus on nephrotoxicity, neurotoxicity and SH. The secondary objective was to assess the risk factors for these side effects.

What is already known about this subject

- Toxicity is a major concern related to the clinical use of polymyxin B, especially nephrotoxicity.
- Previous studies have found a low incidence of neurotoxicity in patients treated with polymyxins, but two recent studies reported relatively higher neurotoxic adverse reactions in both healthy subjects (85%) and patients with cystic fibrosis (100%).
- Intravenous polymyxin B treatment was recently found to cause skin hyperpigmentation (SH), but the incidence and mechanism of this effect are still unknown.

What this study adds

- Neurotoxicity and SH are the two major adverse effects of polymyxin B in renal transplant patients, which may limit its clinical use.
- Although the mechanisms of neurotoxicity and SH require further investigation, they are possibly associated with each other.
- When lower doses were administered, nephrotoxicity was not a significant adverse effect in renal transplant patients.

2 | METHODS

2.1 | Study design and patients

This single-centre prospective cohort study was performed in the second Xiangya Hospital of Central South University (Changsha, China), a tertiary-care teaching hospital. Between January 2018 and August 2021, renal transplant patients (age ≥18 years) who received intravenous polymyxin B were eligible for the study, and their treatment courses were carefully monitored throughout polymyxin B therapy. Adverse reactions, except AKI, were evaluated using the Naranjo Adverse Drug Reaction Probability Scale.[23] When the score was greater than 5, adverse effects were considered to be associated with polymyxin B. In addition, all patients who experienced adverse effects from polymyxin B were followed up in the hospital after polymyxin B therapy until the reactions were completely cleared or the patient had been discharged or died. For the nephrotoxicity analysis, in patients who received two courses of polymyxin B therapy, only the first one was analysed and patients were excluded if they (1) received polymyxin B for a period of <48 hours or (2) were on renal replacement therapy at baseline. AKI was assessed using the RIFLE criteria and determined using the highest serum creatinine (Cr) level during polymyxin B treatment compared with the baseline serum Cr value.[24] This study was approved by the Ethics Committee of Second Xiangya Hospital (No. ChiCTR1900022231). All patients provided signed informed consent.

2.2 | Variables and definitions

The following data were collected from each of the included patients: age, sex, weight, time after transplantation, comorbidities such as diabetes and cardiovascular disease, creatinine clearance (CrCL), use of other nephrotoxic drugs or nephrotoxic contrast, vasoactive drugs and mechanical ventilation during polymyxin B treatment, and renal replacement therapy before and during polymyxin B treatment. Data on the use of polymyxin B, including daily dose, daily dose by weight, treatment duration, total dose and total dose by weight, were also collected.

CrCL was calculated according to the Cockcroft-Gault equation, and basal indices were defined as values measured on the day polymyxin B was initiated. Diagnoses of infections were based on clinical

TABLE 1 Demographic data for 235 renal transplant patients who received polymyxin B therapy

Variable	Values[a]
Age (years)	43 (IQR 34, 51, range 12–70)
Male	173 (73.6%)
Weight (kg)	60.2 (IQR 50, 68.9, range 35.1–100)
Time after transplantation	0 (0–100)
≦3 months	149
3–12 months	46
>12 months	40
Cardiovascular disease (n = 213)	119 (56.1%)
Diabetes mellitus (n = 213)	30 (14.2%)
Albumin (g/L)	31.5 (IQR 29.2, 35.5, range 22.7–43.2)
Baseline creatinine clearance (mL/min)	31.9 (IQR 11.8, 46.8, range 3.9–106.2)
Haemodialysis during therapy	38 (16.2%)
Mechanical ventilation	8 (3.4%)
Polymyxin B daily dose (mg)	80 (IQR 80, 100, range 40–200)
Polymyxin B daily dose by weight (mg/kg/day)	1.4 (IQR 1.1, 1.6, range 0.5–3.0)
Polymyxin B treatment duration (days)	9 (IQR 6, 11, range 1–52)
Polymyxin B total dose (mg)	640 (IQR 400, 1000, range 40–3640)
Polymyxin B total dose by weight (mg/kg/day)	11.0 (IQR 7.2, 15.7, range 0.6–74.1)
Other nephrotoxic drugs	
Vancomycin	1 (0.4%)
Aminoglycosides	12 (5.1%)
Loop diuretics	73 (31.1%)
Amphotericin B	32 (13.6%)
NSAIDs	16 (6.8%)
Osmotic contrast	6 (2.6%)
Immunosuppressant	198 (84.2%)
Glucocorticoid	214 (91.1%)
ACEI/ARB	32 (13.6%)
SMZ-TMP	41 (17.4%)
Aciclovir/ganciclovir	72 (30.6%)
Vasoactive drugs	27 (11.5%)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SMZ-TMP, sulfamethoxazole trimethoprim.

[a]Categorical data are number (%) of subjects, continuous data are expressed as median (IQR, range).

features and bacterial isolation. Clinical cure was defined as the total or partial resolution of signs and symptoms of infection at the end of polymyxin B treatment.

2.3 | Statistical analysis

All statistical analyses were performed using Statistical Package Social Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-squared test. Continuous variables were expressed as median (interquartile [IQR], range), tested for normality of distributions using the Kolmogorov-Smirnov test, and then compared using the Mann-Whitney U test. Variables with a P value <.05 in univariate analysis were included in a logistic regression model for multivariate analysis. The time to onset of SH in the stratified cohorts was compared using Kaplan–Meier survival analysis and the log-rank test.

3 | RESULTS

3.1 | Baseline characteristics of patients

A total of 213 hospitalised patients met the enrolment criteria and 22 patients received two courses of polymyxin B therapy with time intervals of more than 3 months (3–15 months), therefore a total number of 235 courses of polymyxin B therapy were administered to 213 patients between January 2018 and August 2021. The median age of the patients was 44 years (IQR 34–51, range 12–70), 73.6% were male and their median weight was 60.2 kg (IQR 50–68.9, range 35.1–100 kg). Most of the patients (96.2%) had pre-existing renal insufficiency prior to commencement of polymyxin B treatment with a median CrCL of 31.9 mL/min (IQR 11.8–46.8, range 3.9–106.2 mL/min). Twenty-five patients during 38 courses of polymyxin B therapy were on haemodialysis. Of these, 23 patients had renal allograft failure and were permanently on dialysis, and two patients had delayed graft function and renal function subsequently recovered within 2 months. Among all courses, 60% (141/235) had confirmed infection, while 40% (94/235) were administered polymyxin B to prevent the transmission of infection from the donors. Sources of infections included pneumonia (70.2%), urinary tract infection (UTI) (14.9%), primary bloodstream infection (4.3%), skin and soft tissue infection (4.3%), and intra-abdominal infection (3.5%); 2.1% of the patients were treated empirically. The median duration of polymyxin B treatment was 9 days (IQR 6–11, range 1–52 days) and the median polymyxin B dosage was 80 mg/day (IQR 80–100, range 40–200 mg/day). Clinical cure was observed in 64 patients (45.4%) and the 30-day mortality rate was 6.4%. Detailed demographic data are presented in Table 1.

3.2 | Adverse reactions

3.2.1 | Neurotoxicity

Neurotoxicity was observed in 134 patients during 149 (63.4%) courses of polymyxin B therapy, and 15 of the 22 patients who received two courses developed neurotoxicity during both

administrations, while the rest did not develop this adverse effect during either administration. Neurotoxicity manifested mostly during the first 2 days (96.0%), and the most common symptoms were facial and peripheral paraesthesia, skin purities and muscle weakness (Table 2). Three patients developed visual or auditory hallucinations during treatment, and 26 (11.1%) developed visual disturbances and reported unclear vision. No patients developed respiratory failure or apnoea secondary to respiratory muscle paralysis. Nevertheless, discontinuation and reduction in the dosage of polymyxin B due to intolerance to its neurotoxicity, including facial and peripheral paraesthesia, skin pruritus and hallucinations, were required in 15 and 27 treatments, respectively.

TABLE 2 Neurotoxicity of polymyxin B in 235 courses of therapy

Neurotoxicity	Events (n%)
Facial and peripheral paraesthesia	108 (46.0%)
Skin pruritus	71 (30.2%)
Muscle weakness	29 (12.3%)
Visual disturbances	26 (11.1%)
Dizziness	25 (10.6%)
Dysgeusia	19 (8.1%)
Hallucinations	8 (3.4%)
Walking unstable	3 (1.3%)
Dysphagia	2 (0.9%)
Total	149 (63.4%)

Abbreviations: n%, percentage of subjects who reports adverse events out of total subjects enrolled.

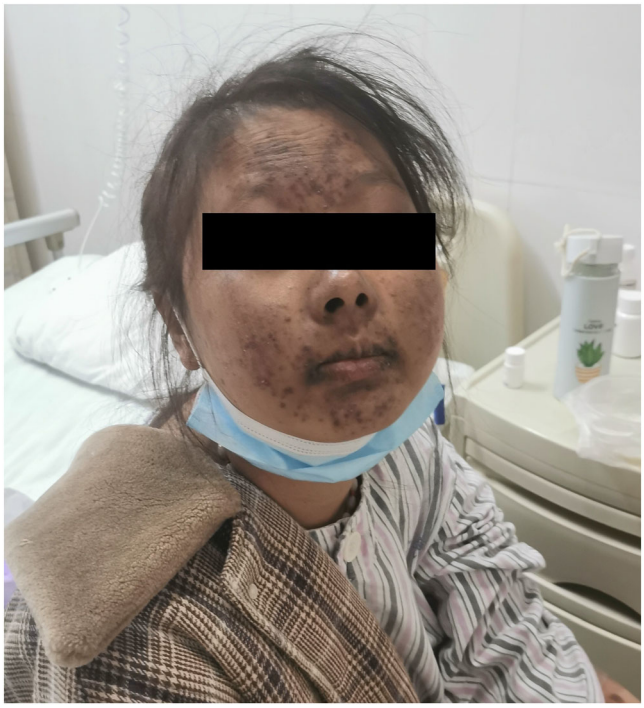

FIGURE 1 Photograph of a patient developing hyperpigmentation on day 4 of polymyxin B treatment

3.2.2 | Skin hyperpigmentation

SH was observed in 121 (51.5%) polymyxin B-treated patients, and the median time to onset of the first observable skin changes was the third day (IQR 3–4, range 1–9 days). Skin changes were noted, particularly on the face (100%) and neck (n = 164, 69.8%) (Figure 1). Furthermore, among the 22 patients who received two courses of polymyxin B therapy, 10 developed SH during both administrations, while the rest did not develop this adverse effect during either administration.

3.2.3 | Nephrotoxicity

Among the 213 patients, five received polymyxin B for less than 48 hours and 25 patients were on renal replacement therapy at the beginning of polymyxin B treatment, thus a total of 183 therapies were eligible for nephrotoxicity analysis. According to the RIFEL criteria, AKI occurred in 10 (5.5%) patients and was categorised as risk (50.0%) and injury (50.0%); the baseline CrCL of these patients was 41.4 mL/min (IQR 17.7–65.4, range 9.7 to 84.0 mL/min) and the mean time to AKI development was 6 days (IQR 4–9, range 2–19 days). Most patients (80.0%) recovered within 25 days of polymyxin B discontinuation.

3.2.4 | Other adverse reactions

Nine cases of nausea or vomiting were reported in nine subjects. One male patient discontinued polymyxin B treatment on the third day because of intolerable vomiting, and the others recovered within 2 days after the therapy without additional treatment. Desquamation was observed in three patients, which occurred mainly around the lips. Lip balm seemed to be helpful in alleviating this effect and all patients recovered after 3 days of cessation. Severe pain at the injection site was reported by 14 patients and most of them had to replace the indwelling venous needle every other day because of phlebitis.

3.3 | Risk factors for adverse reactions

The univariate analysis for neurotoxicity is shown in Table 3. In multivariate analysis, female sex (odds ratio [OR] 3.84, 95% confidence interval [CI] 1.82–8.10, $P < .0001$) and concurrence with SH (OR 1.98, 95% CI 1.13–3.46, $P = .016$) were independent risk factors for neurotoxicity. Polymyxin B treatment (daily dose, duration, total dosage and daily dose by body weight) was not significantly associated with neurotoxicity. Subgroup analysis among patients with different baseline

TABLE 3 Univariate analysis of the predictors for polymyxin B-induced neurotoxicity

Variables	Neurotoxicity[a] (n = 149)	No neurotoxicity[a] (n = 86)	OR (95% CI)
Demographic paremeters			
Female	52 (34.9%)	10 (11.6%)	4.07 (1.94–8.54)
Age (years)	42.4 (9.1)	42.9 (9.5)	0.99 (0.97–1.02)
Weight (kg)	59.5 (10.5)	61.5 (10.3)	0.99 (0.97–1.01)
Comorbidities			
Hypertension	85 (57.0%)	45 (52.3%)	1.21 (0.71–2.06)
Diabetes mellitus	23 (15.4%)	10 (11.6%)	1.39 (0.63–3.07)
Clinical conditions			
Baseline CrCL (mL/min)	32.3 (22.3)	31.1 (23.8)	1.00 (0.99–1.01)
Haemodialysis during therapy	25 (16.8%)	15 (17.4%)	0.95 (0.47–1.93)
Albumin (g/L)	32.1 (4.1)	31.6 (4.4)	1.02 (0.96–1.09)
Concurrence with skin hyperpigmentation	87 (58.4%)	34 (39.5%)	2.15 (1.25–3.69)
Polymyxin B treatment			
Daily dosage (mg)	80.3 (20.6)	81.0 (19.1)	0.99 (0.98–1.01)
Daily dosage by body weight (mg/kg)	1.4 (0.4)	1.4 (0.4)	1.19 (0.64–2.22)
Duration (day)	9.2 (6.8)	9.7 (5.2)	0.99 (0.95–1.03)
Total dosage (mg)	725.5 (533.9)	791.0 (534.4)	1.00 (0.99–1.00)
Total dosage (mg/kg)	12.6 (9.8)	13.8 (11.0)	0.99 (0.96–1.02)
Combination therapy			
Amikacin	3 (2.0%)	9 (10.9%)	0.18 (0.05–0.67)
Nephrotoxic contrast	4 (2.7%)	2 (2.3%)	1.16 (0.21–6.46)
Diuretics	42 (28.2%)	32 (37.2%)	0.66 (0.38–1.16)
Vasoactive agents	15 (10.1%)	12 (13.9%)	0.69 (0.31–1.55)
Tacrolimus	112 (75.2%)	63 (73.3%)	1.10 (0.60–2.20)
Cyclosporine	16 (10.7%)	9 (10.4%)	1.03 (0.43–2.44)
Mycophenolate mofetil	107 (71.8%)	61 (70.9%)	1.04 (0.58–1.88)
Prednisone	134 (89.9%)	80 (93.0%)	0.67 (0.25–1.80)

Abbreviations: CI confidence interval; OR, odds ratio; CrCL, creatinine clearance.
[a]Categorical data are number (%) of subjects, continuous data are expressed as mean (standard deviation).

CrCLs (<30, 30–50, >50 mL/min) indicated the same risk factors of neurotoxicity (data not shown).

The univariate analysis for SH is shown in Table 4, where the total dosage, daily dosage, total dosage by weight, duration and concurrence with neurotoxicity were significant predictors for SH. When these variables were included in the multivariate logistic regression model, the independent predictors for SH were total dosage by weight and neurotoxicity (Table 5). The time to onset of SH between patients with and without neurotoxicity is shown in Figure 2, and was remarkably earlier in the neurotoxicity group ($P = .002$).

Risk factors for AKI were not considered because of the very low incidence of renal injury.

4 | DISCUSSION

Our study showed higher incidence of neurotoxicity and SH in renal transplant patients using intravenous polymyxin B, and a significant correlation between neurotoxicity and SH. However, the incidence of nephrotoxicity was comparatively low.

The high incidence of polymyxin B neurotoxicity in our study is in accordance with two recent studies in healthy Chinese subjects and patients with cystic fibrosis but is much higher than that reported in earlier studies (63.4% *vs* 7–27%).[3,4] The main causes of this discrepancy might be the retrospective settings and the sedated critically ill patients in most previous studies, which make the adverse neurotoxic effect difficult to detect and possibly underestimated. Notably, in contrast to benign and well-tolerated peripheral neurotoxicity, over half of our patients complained of severe paraesthesia and skin pruritus, and 42 of them needed to reduce the dosage or discontinue the therapy. It seems that neurotoxicity is more intolerable in renal transplant patients, and the concomitant use of other neurotoxic medications such as tacrolimus, cyclosporine A (CsA) and glucocorticoids might explain this finding. Interestingly, a higher incidence (14.5%) of CNS toxicities such as visual disturbances and hallucinations was observed in our patients. Intravenous injection of polymyxin B is seldom

TABLE 4 Univariate analysis of the predictors for polymyxin B induced SH

Variables	With SH[a] (n = 121)	Without SH[a] (n = 114)	OR (95% CI)
Demographic parameters			
Female	38 (31.4%)	24 (21.0%)	1.72 (0.95–3.10)
Age (years)	41.6 (11.5)	43.7 (10.6)	0.98 (0.96–1.00)
Weight (kg)	58.6 (13.8)	61.9 (11.7)	0.98 (0.96–1.00)
Comorbidities			
Hypertension	67 (55.4%)	63 (55.3%)	0.99 (0.59–1.67)
Diabetes mellitus	13 (10.7%)	20 (17.5%)	1.97 (0.83–3.75)
Clinical conditions			
Baseline CrCL (mL/min)	33.7 (23.2)	30.0 (22.0)	1.01 (0.99–1.02)
Haemodialysis during therapy	21 (17.4%)	18 (15.8%)	0.84 (0.43–1.67)
Albumin (g/L)	32.0 (4.1)	31.8 (4.3)	1.02 (0.96–1.08)
Concurrence with neurotoxicity	87 (71.9%)	62 (54.4%)	2.15 (1.25–3.69)
Polymyxin B treatment			
Daily dosage (mg)	81.7 (18.0)	79.4 (21.9)	1.0 (0.99–1.01)
Daily dosage by body weight (mg/kg)	1.44 (0.4)	1.3 (0.4)	2.02 (1.09–3.73)
Duration (day)	11.1 (7.0)	7.6 (4.7)	1.13 (1.06–1.20)
Total dosage (mg)	908.8 (631.1)	582.1 (329.5)	1.00 (1.00–1.00)
Total dosage (mg/kg)	16.2 (12.4)	9.7 (5.6)	1.11 (1.06–1.16)
Combination therapy			
Amikacin	8 (6.6%)	4 (3.5%)	1.95 (0.57–6.65)
Nephrotoxic contrast	1 (0.8%)	5 (4.4%)	0.18 (0.02–1.58)
Diuretics	33 (27.3%)	41 (36.0%)	0.67 (0.38–1.16)
Vasoactive agents	10 (8.3%)	17 (14.9%)	0.51 (0.23–1.18)
Tacrolimus	86 (71.1%)	89 (78.1%)	0.69 (0.38–1.25)
Cyclosporine	13 (10.7%)	12 (10.5%)	1.02 (0.45–2.35)
Mycophenolate mofetil	85 (70.2%)	83 (72.8%)	0.88 (0.50–1.56)
Prednisone	107 (88.4%)	107 (93.8%)	0.50 (0.19–1.29)

Abbreviations: CI confidence interval; CrCL, creatinine clearance; OR, odds ratio; SH, skin hyperpigmentation.
[a]Categorical data are number (%) of subjects, continuous data are expressed as mean (standard deviation).

TABLE 5 Multivariate analysis of the predictors for polymyxin B-induced SH

Variables	Adjusted OR (95% CI)	*P*
Daily dosage by body weight (mg/kg)	0.31 (0.08–1.14)	0.077
Total dosage (mg)	1.00 (1.00–1.00)	0.608
Total dosage (mg/kg)	1.31 (1.08–1.60)	0.008
Duration (day)	0.87 (0.73–1.04)	0.129
Concurrence with neurotoxicity	2.86 (1.56–5.26)	0.001

Abbreviations: CI confidence interval; OR, odds ratio.

considered to cause CNS toxicities because of its negligible concentration in the cerebrospinal fluid.[25,26] However, in the 1970s, research on rabbits showed that polymyxin B was highly concentrated in the brain tissue in an inactive form.[27,28] Further studies are needed to explore the distribution of polymyxin B in the human central nervous system and its subsequent neurotoxicity.

Logistic analysis found a significant association between female sex and a higher incidence of neurotoxicity ($p < .0001$), which is consistent with the tendency in healthy subjects.[16] These results indicate that polymyxin B-induced neurotoxicity might be a gender-dependent adverse event, but the mechanism is not yet clear. It is suggested that polymyxins may induce neuromuscular blockade by interfering with the receptor site and blocking the release of acetylcholine to the synaptic gap.[29] Further research is warranted to investigate whether females are more sensitive to this process, thus leading to more neurotoxic events.

The relationship between polymyxin B dosage and neurotoxicity remains unclear. Our results showed that neurotoxicity was not significantly correlated with polymyxin B treatment, which might be due to negligible dose differences (mostly 80–100 mg/day) among our patients. However, neurotoxicity symptoms in 18 patients were remarkably alleviated after reducing the polymyxin B dosage.

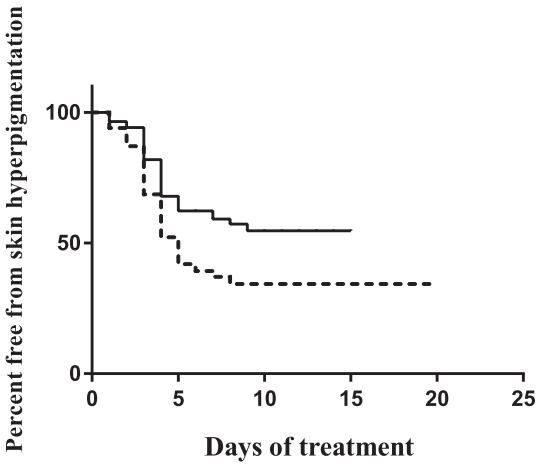

FIGURE 2 Comparison of skin hyperpigmentation onset between neurotoxicity and non-neurotoxicity patients (log rank $P = .002$). The continuous line represents patients who did not developed neurotoxicity and the broken line represents patients who developed neurotoxicity

Moreover, Liu et al[16] also found that the incidence of polymyxin B neurotoxicity was higher in subjects who received a 1.5 single mg/kg dose compared with those in the low dose (0.75 mg/kg) group. Consequently, although polymyxin B dosage was not a predictor for neurotoxicity in our study, it is still possible that polymyxin B induces neurotoxicity in a dose-dependent manner and further research is needed to investigate this exposure-toxicity relationship.

Another important finding of our study was the increased SH. SH was recently first noticed as a side effect of polymyxin B by Knueppel,[30] after which more cases have been reported.[31–34] Several mechanisms may be involved in polymyxin B-induced SH: (1) polymyxin B directly activates histamine release and melanin; (2) polymyxin B regulates the skin inflammation process related to the activation of melanocytes, such as Langerhans cell hyperplasia and dermal IL-6 overexpression; and (3) polymyxin B increases melanin production by inducing oxidative stress.[18,34] The main cause of the higher rate of SH in our study (51.5% *vs* 8–15%) might be the impaired renal function in most of our patients, which impedes the clearance of melanin and therefore increases pigmentation. Furthermore, in our study, a higher polymyxin B dosage was independently associated with an increased risk of SH and the number of incidences increased significantly within the first 5 days of treatment. This finding indicates that polymyxin B-induced SH is likely to be dose-dependent, and when a threshold concentration is reached, it causes pigmentation. However, determining whether a reduction in dosage can reduce the occurrence of SH requires further verification. Moreover, according to our results, neurotoxicity and skin hyperpigmentation were significantly related to each other. The underlying mechanism is unclear, but since oxidative stress and mitochondrial dysfunction are involved in both toxicities, this might be one of the reasons for this correlation.[35,36]

Nephrotoxicity is a major concern related to the clinical use of polymyxin B, according to previous studies.[12,13,37] However, the nephrotoxicity of polymyxin B in our study was low (6.4%). The most important reason for the reduced incidence might be the considerably low daily dosage (median 80 mg/day) used and the relatively short duration (9.4 ± 6.3 days) in this study. It has been shown that the daily dosage of polymyxin B and treatment duration are correlated with nephrotoxicity. Patients who received over 150–200 mg/day of polymyxin B were more likely to have AKI,[12] while other studies also found that cumulative polymyxin B use is significantly related to renal dysfunction and patients who received polymyxin B treatment for more than 15 days were more prone to nephrotoxicity.[11–13,38] Moreover, another reason for the low nephrotoxicity rate observed might be the less concomitant use of other nephrotoxic drugs in our study, especially vancomycin and aminoglycosides, which are considered to induce nephrotoxicity.[39]

This study had a few limitations. First, we only recorded the incidence of SH without classifying skin colour on a professional scale, therefore we could not assess the severity of this adverse effect. Second, the follow-up time in our study was the duration of the hospital stay, which was not long enough to record the time needed to recover from SH.

5 | CONCLUSION

In summary, our study demonstrated a considerably high incidence of neurotoxicity and SH caused by polymyxin B in renal transplant patients, and acute neurotoxicity may be the primary use limiting toxicity of polymyxin B in these patients. Moreover, our results indicate that neurotoxicity and SH are significantly correlated, which might benefit the investigation of the mechanisms of these adverse reactions. Further research is warranted to investigate the safety and exposure-toxicity relationship of polymyxin B.

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COMPETING INTERESTS

None of the authors have conflicting interests that interfere with the integrity of the content of the article.

AUTHOR CONTRIBUTIONS

Y.Z. and Y.L. supervised and participated the entire procedure, reviewed the data and drafted the manuscript. X.X., L.S., G.L. and B.S. conducted the clinical visit and collected the data. T.T. and H.Y. conducted the statistical analysis. B.Z. and P.X. contributed to the conception of the work and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author on reasonable request.

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REFERENCES

1. Velkov T, Thompson PE, Azad MAK, Roberts KD, Bergen PJ. History, Chemistry and antibacterial spectrum. *Adv Exp Med Biol*. 2019;1145:15-36. doi:10.1007/978-3-030-16373-0_3
2. 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
3. Justo JA, Bosso JA. Adverse reactions associated with systemic polymyxin therapy. *Pharmacotherapy*. 2015;35(1):28-33. doi:10.1002/phar.1493
4. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care*. 2006;10(1):R27. doi:10.1186/cc3995
5. 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. doi:10.1128/AAC.00844-15
6. Falagas ME, Kyriakidou M, Voulgaris GL, Vokos F, Politi S, Kechagias KS. Clinical use of intravenous polymyxin B for the treatment of patients with multidrug-resistant Gram-negative bacterial infections: An evaluation of the current evidence. *J Glob Antimicrob Resist*. 2021;24:342-359. doi:10.1016/j.jgar.2020.12.026
7. Sobieszczyk ME, Furuya EY, Hay CM, et al. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. *J Antimicrob Chemother*. 2004;54(2):566-569. doi:10.1093/jac/dkh369
8. Kwa A, Kasiakou SK, Tam VH, Falagas ME. Polymyxin B: similarities to and differences from colistin (polymyxin E). *Expert Rev Anti Infect Ther*. 2007;5(5):811-821. doi:10.1586/14787210.5.5.811
9. Rigatto MH, Falci DR, Zavascki AP. Clinical use of polymyxin B. *Adv Exp Med Biol*. 2019;1145:197-218. doi:10.1007/978-3-030-16373-0_14
10. Tuon FF, Rigatto MH, Lopes CK, Kamei LK, Rocha JL, Zavascki AP. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. *Int J Antimicrob Agents*. 2014;43(4):349-352. doi:10.1016/j.ijantimicag.2013.12.002
11. Kubin CJ, Ellman TM, Phadke V, Haynes LJ, Calfee DP, Yin MT. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. *J Infect*. 2012;65(1):80-87. doi:10.1016/j.jinf.2012.01.015
12. 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. doi:10.1093/jac/dku561
13. 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. doi:10.1093/jac/dkv014
14. Weinstein L, Doan TL, Smith MA. Neurotoxicity in patients treated with intravenous polymyxin B: Two case reports. *Am J Health Syst Pharm*. 2009;66(4):345-347. doi:10.2146/ajhp080065
15. Crass RL, Al Naimi T, Wen B, et al. Pharmacokinetics of polymyxin B in hospitalized adults with cystic fibrosis. *Antimicrob Agents Chemother*. 2021;65(10):e0079221. doi:10.1128/AAC.00792-21
16. Liu X, Chen Y, Yang H, et al. Acute toxicity is a dose-limiting factor for intravenous polymyxin B: A safety and pharmacokinetic study in healthy Chinese subjects. *J Infect*. 2021;82(2):207-215. doi:10.1016/j.jinf.2021.01.006
17. Lu C, Hou N. Skin hyperpigmentation in coronavirus disease 2019 patients: Is polymyxin B the culprit? *Front Pharmacol*. 2020;11:01304. doi:10.3389/fphar.2020.01304
18. Zou D, Yu H, Li F. The difference between polymyxin B and polymyxin E in causing skin hyerpigmentation. *Front Pharmacol*. 2021;12:647564. doi:10.3389/fphar.2021.647564
19. Pouch SM, Kubin CJ, Satlin MJ, et al. Epidemiology and outcomes of carbapenem-resistant Klebsiella pneumoniae bacteriuria in kidney transplant recipients. *Transpl Infect Dis*. 2015;17(6):800-809. doi:10.1111/tid.12450
20. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*. 2014;58(9):1274-1283. doi:10.1093/cid/ciu052
21. Mostardeiro MM, Pereira CA, Marra AR, Pestana JO, Camargo LF. Nephrotoxicity and efficacy assessment of polymyxin use in 92 transplant patients. *Antimicrob Agents Chemother*. 2013;57(3):1442-1446. doi:10.1128/AAC.01329-12
22. Li Y, Deng Y, Zhu ZY, et al. Population pharmacokinetics of polymyxin B and dosage optimization in renal transplant patients. *Front Pharmacol*. 2021;12:727170. doi:10.3389/fphar.2021.727170
23. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi:10.1038/clpt.1981.154
24. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative w Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212. doi:10.1186/cc2872
25. Pan S, Huang X, Wang Y, et al. Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of polymyxin B for post-neurosurgical intracranial infections due to MDR/XDR *Acinectobacter baumannii*: a retrospective cohort study. *Antimicrob Resist Infect Control*. 2018;7:8. doi:10.1186/s13756-018-0305-5
26. Wang P, Zhang Q, Qin Z, et al. A simple and robust liquid chromatography with tandem mass spectrometry analytical method for therapeutic drug monitoring of plasma and cerebrospinal fluid polymyxin B1 and B2. *Ther Drug Monit*. 2020;42(5):716-723. doi:10.1097/FTD.0000000000000754
27. Kunin CM, Bugg A. Binding of polymyxin antibiotics to tissues: the major determinant of distribution and persistence in the body. *J Infect Dis*. 1971;124(4):394-400. doi:10.1093/infdis/124.4.394
28. Craig WA, Kunin CM. Dynamics of binding and release of the polymyxin antibiotics by tissues. *J Pharmacol Exp Ther*. 1973;184(3):757-765.
29. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann Intern Med*. 1970;72(6):857-868. doi:10.7326/0003-4819-72-6-857
30. Knueppel RC, Rahimian J. Diffuse cutaneous hyperpigmentation due to tigecycline or polymyxin B. *Clin Infect Dis*. 2007;45(1):136-138. doi:10.1086/518706
31. Li YM, Milikowski C, Selvaggi G, Abbo LM, Skiada D, Galimberti F. Polymyxin B-induced skin hyperpigmentation. *Transpl Infect Dis*. 2020;22(5):e13312. doi:10.1111/tid.13312
32. Lahiry S, Choudhury S, Mukherjee A, Bhunya PK, Bala M. Polymyxin B-induced diffuse cutaneous hyperpigmentation. *J Clin Diagn Res*. 2017;11(2):FD01-FD02. doi:10.7860/JCDR/2017/24278.9213

33. Mattos KP, Lloret GR, Cintra ML, et al. Acquired skin hyperpigmentation following intravenous polymyxin B treatment: a cohort study. *Pigment Cell Melanoma Res*. 2016;29(3):388-390. doi:10.1111/pcmr.12468
34. Zheng G, Cao L, Che Z, Mao E, Chen E, He J. Polymyxin B-induced skin hyperpigmentation: a rare case report and literature review. *BMC Pharmacol Toxicol*. 2018;19(1):41. doi:10.1186/s40360-018-0226-1
35. 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
36. Mattos KPH, Cintra ML, Gouvea IR, Ferreira LA, Velho P, Moriel P. Skin hyperpigmentation following intravenous polymyxin B treatment associated with melanocyte activation and inflammatory process. *J Clin Pharm Ther*. 2017;42(5):573-578. doi:10.1111/jcpt.12543
37. John JF, Falci DR, Rigatto MH, Oliveira RD, Kremer TG, Zavascki AP. Severe infusion-related adverse events and renal failure in patients receiving high-dose intravenous polymyxin B. *Antimicrob Agents Chemother*. 2017;62(1):e01617. doi:10.1128/AAC.01617-17
38. 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):e02391. doi:10.1128/AAC.02391-16
39. Bahlis LF, Diogo LP, Lemons D, Klaus D. Risk factors for acute kidney injury in patients treated with polymyxin B at a tertiary care medical center. *J Bras Nefrol*. 2015;37(4):446-450. doi:10.5935/0101-2800.20150071

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