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Effect of Renal Filtration Function on Polymyxin B Pharmacokinetics in Patients with Sepsis

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Summary

The aim of this study was to investigate pharmacokinetics of polymyxin B (PMB) in patients with sepsis and preserved or impaired renal function.

Methods. A two-center, prospective, randomized study enrolled patients with sepsis. Blood samples for analysis were collected in a steady state (SS) to assess the pharmacokinetics of PMB. PMB concentration in the patients' serum was measured using a direct competitive ELISA to verify the achievement of target area under the concentration-time curve (AUC_{24}) value of 50–100 mg×h/L.

Results. The study included 34 patients with sepsis receiving PMB therapy who were distributed into two groups based on their glomerular filtration rate (GFR): patients with impaired renal function (GFR < 80 mL/min, $N = 17$), and with preserved renal function (GFR ⩾ 80 mL/min, $N = 17$). The mean AUC_{24} value in 34 patients was 64.02 ± 11.64 mg×h/L, the median volume of distribution was 31.53 (23.79–43.72), and the median clearance was 3.72 (2.73–4.85). In patients with preserved renal function, the median AUC_{24} was 48.38 mg×h/L, and the SS concentration was 2.02 mg/mL. In patients with impaired renal function, the AUC_{24} was 71.78 mg×h/L, and the SS concentration was 2.99 mg/mL. The clearance of PMB differed considerably depending on GFR: the median clearance in patients with GFR < 80 mL/min was 3.28 L/h versus 4.97 L/h in patients with GFR > 80 mL/min ($P = 0.012$). In 14 of 17 patients with reduced renal function, the AUC_{24} values fell in the range of 50–100 mg×h/L. In the group with preserved and increased renal function, only 7 of 17 patients reached the target range, and in 53% of patients (9 of 17), the exposure to PMB was below the therapeutic level (AUC_{24} < 50 mg×h/L).

Conclusion. Renal function affects the clearance of PMB and, consequently, the achievement of the target therapeutic range. Standard dosing regimens do not provide achieving the target concentrations of antibiotic in all patients, as some patients with preserved renal function have insufficient PMB exposure, while patients with impaired renal function have enhanced exposure, increasing the risk of drug failure or toxicity. To ensure the effectiveness and safety of treatment, regular therapeutic PMB concentrations monitoring and individual dose adjustments are necessary, especially in patients with altered renal function.

Keywords: renal filtration function; polymyxin B; polymyxin B pharmacokinetics; sepsis; antibacterial therapy

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Polymyxins, colistin and polymyxin B (PMB) are polypeptide antibiotics with a unique mechanism of action that involves disrupting the integrity of the outer membrane of gram-negative bacteria, which enhances the activity of other classes of antibacterial drugs. This class of antibiotics was commonly used in clinical practice for treatment of infections caused by multydrug resistant (MDR) *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacteriaceae* strains since the 80s of the last century. Most invasive gram-negative infections currently remain sensitive to PMB, which explains its effectiveness [1]. The «International consensus

guidelines for the optimal use of the polymyxins» [2] recommend to observe the following pharmacokinetic (PK) parameters during treatment of infections caused by MDR gram-negative bacteria: AUC_{24h}=50–100 mg×h/L (area under the serum PMB concentration curve at steady state (SS) over 24 hours), which corresponds to C_{ss}=2–4 mg/l (average steady-state concentration). The recommended AUC_{24h} range is a predictor of maximum clinical efficacy with minimal likelihood of toxic events. According to prevailing consensus PMB exposure exceeding 100 mg×h/L increases the risk of adverse reactions, mainly acute renal injury [3]. However, a study by Z. Yu, et al., involving 312 patients, showed that there was no correlation between an increase in AUC_{24h} > 100 mg×h/L and the incidence of acute kidney injury, and that mortality increased at AUC_{24h} < 50 mg×h/L [4]. However, the criteria for achieving PMB clinical efficacy have not yet been established [5].

Critical conditions, such as sepsis, are accompanied by serious pathophysiological alterations that lead to significant changes in pharmacokinetics. The presence of chronic concomitant pathology can exacerbate pathophysiological changes, significantly affecting the pharmacokinetics of antibacterial agents.

Excess body weight, endothelial dysfunction, massive capillary leakage syndrome, and extensive infusion therapy can modify the volume of distribution (V_d). Changes in drug clearance (CL) occur due to increased renal clearance, impaired renal function, and the use of extracorporeal treatments and extracorporeal life support (ECLS). Additionally, changes in the blood plasma protein composition, including hypoalbuminemia, can increase V_d due to increased circulating free drug fraction leading indirectly to increased clearance [6].

Demographic data (patient weight and age), biochemical parameters (albumin and creatinine concentrations), and SOFA scores as organ dysfunction measure in sepsis are considered as covariates in the analysis of PK parameters [7]. Most often, PMB dosing is based on the patient's body weight. In a review of 10 PMB PK studies, plasma albumin levels were not considered as a significant covariate [8]. Kidney function statistically significantly affects PK parameters [9]. For example, at a glomerular filtration rate (GFR) of >80 ml/min, adequate plasma concentration of colistin (structurally similar to polymyxin) was attained in less than 40% of cases even at the maximum recommended daily dose because of active renal excretion [10].

Dose-dependent nephrotoxicity is a major PMB –associated side effect [11, 12]. It has been established that PMB accumulates in the renal cortex [13]. Although PMB is mainly eliminated by non-renal routes (mostly via biliary exretion) [14], the excretion of unchanged antibiotic in the urine can vary significantly among individuals, ranging from 0.98% to 17.4% [15].

The choice of the optimal PMB dosing regimen is still a matter of debate, even for susceptible pathogens with MIC (minimum inhibitory concentration) ⩽2 mg/L. The narrow therapeutic window requires a balance between therapeutic efficacy and the risk of complications. Previously, a study of PMB PK in patients with ECMO support showed that the recommended standard dosing regimens of 2.5–3.0 mg/kg/day were adequate, and no increase in dosage was required [16]. PMB-associated nephrotoxicity requires monitoring of patient's kidney function, but according to some researchers, renal dysfunction is not an indication for dose adjustment [17, 18]. Other researchers conclude that it is necessary to reduce doses in renal failure, but in severe infections caused by microorganisms with PMB MICs of ⩾2 mg/L, they allow the use of a high daily dose of 200 mg/day [19], as reduction of the dose increases the rate of fatal outcomes. All studies show significant interindividual variability in PMB PK. A comparative study of PMB PK in patients with preserved and impaired renal function is noteworthy, demonstrating that renal function contributes to PMB clearance [20]. All of the above indicates the need to implement the principles of personalized medicine into the prevention, diagnosis, and treatment of patients in critical conditions [21].

In recent years, the number of PMB PK studies has increased significantly. In a 2024 review analyzing 22 studies conducted since 2008, 14 reports from China were included [7]. The main cohort consisted of patients with a normal weight (for example, in one of the largest studies, the average weight of patients (N=486) was 70 kg), with a recommended PMB dose of 1.5–3.0 mg/kg/day [3]. A greater weight (>80 kg) was considered obesity, and published data on such patients are limited [22].

In this study, we investigated the PK of PMB and analyzed the relationship between PK parameters and renal function in patients with sepsis in Moscow hospitals, who were predominantly elderly (>60 years) and overweight (BMI ⩾28).

The aim of this study was to investigate pharmacokinetics of polymyxin B (PMB) in patients with sepsis and preserved/impaired renal function.

Materials and Methods

Study design and patients. A two-center, prospective, randomized study was conducted at MEDSI Clinical Hospital No. 1 in 2021–2022 and at the National Medical Research Center, Medical and Rehabilitation Center of the Russian Ministry of Health in 2025. The study inclusion criteria for patients were as follows: diagnosis of sepsis caused by MDR gram-negative microorganisms according

to the Sepsis-III criteria, PMB therapy lasting at least 48 hours, and age over 18 years. The exclusion criteria for the study were pregnancy and ECLS use (renal replacement therapy, extracorporeal membrane oxygenation). The patient recruitment scheme for the study is shown in Fig. 1.

The clinical study of PMB PK in intensive care patients was approved by the Independent Ethics Committees of MEDSI group of companies (commission meeting protocol No. 29 dated April 15, 2021) and the National medical research center for intensive care of the Ministry of Health of the Russian Federation (commission meeting protocol No. 061 dated January 22, 2025). Voluntary informed consent to participate in the study was obtained from patients or their legal representatives. On the first day, all patients received a PMB loading dose at a rate of 2.5–3.0 mg/kg intravenously once (PMB therapy is recommended to start with a loading dose of 2.0–2.5 mg/kg) [2].

A population pharmacokinetic study in critically ill patients showed that after the first dose of the regimen of 1.25 mg/kg every 12 hours, PMB plasma concentration achieved ~56–70% of the SS concentration values [15]. It was calculated using Monte Carlo simulation, that at a loading dose of 2.0 mg/kg, PMB concentration would be 76–94% of the values observed at steady state [15]. Further PMB therapy was administered twice daily at a dose of 75–150 mg (2.5–3.0 mg/kg/day). The drug was dissolved in 5% glucose and administered intravenously over one hour using a syringe dispenser. The PMB MIC were obtained based on isolates susceptibility testing using the VITEK® 2 automatic analyzer (bioMérieux, France). GFR was estimated using the Cockcroft-Gault equation [23].

Blood sampling. To assess PK PMB at steady state, blood samples were collected before drug administration and then 1.1, 1.5, 2, 3, 5, 9, and 12 hours after the start of the 1-hour infusion. Blood samples were centrifuged at 1600×g for 10 min, the separated serum was immediately frozen and stored at –20°C for 10–90 days prior to analysis.

Solid-phase competitive enzyme-linked immunosorbent assay (ELISA). PMB concentration in serum samples was evaluated using a direct competitive enzyme — linked immunosorbent assay (ELISA) according to previously described method [16, 24]. Sample preparation included preliminary deproteinization of serum samples using 5% trichloroacetic acid. After centrifugation, the supernatant was diluted 100-fold with an assay buffer consisting of 0.15 M phosphate — buffered saline (pH 7.2) containing 0.05% Tween 20. The results of the subsequent immunoassay were available after 1.5–2 hours.

Pharmacokinetic and statistical analysis. Based on the results obtained from measuring PMB concentration in patients' serum, the PK parameters were calculated with Lixoft SAS 2024 software (France) using a non-compartmental method.

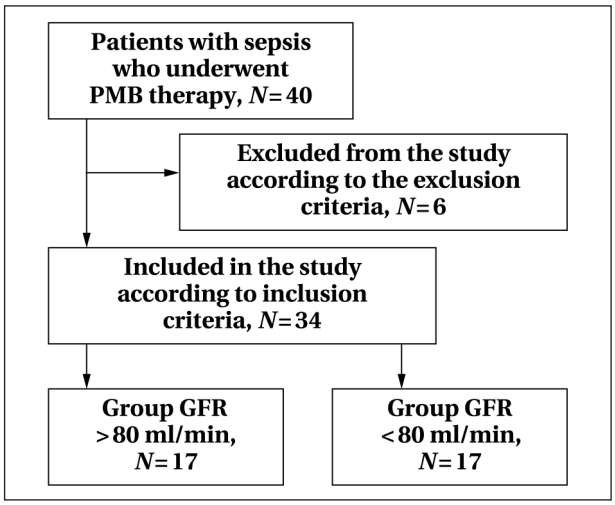

Fig. 1. Patient recruitment scheme for the study.

Primary data analysis and visualization were performed using Microsoft Office Excel 2019 and GraphPad Prism 9 software. Qualitative variables were described statistically as absolute and relative data. The normality of data distribution was assessed using the Shapiro–Wilk test. For quantitative variables, the mean *(M)* and standard deviation *(SD)* were calculated, as well as the median *(Me)* and interquartile range (IQR). Differences between groups with normal distribution of quantitative data were analyzed using Student's *t*-test and Mann–Whitney test for quantitative data that did not follow a normal distribution. Welch's *T*-test was used to determine the statistical difference between the means of two groups with different dispertion. The relationship between two quantitative parameters was assessed using Spearman's correlation. A level of $P < 0.05$ was accepted as the criterion for statistical significance for intergroup comparisons. The data were statistically processed using IBM SPSS Statistics v. 28.0 software.

Study endpoints. The primary endpoint of the study was the frequency of achieving the target AUC_{24} 50–100 mg×h/L at steady state in each group of patients. The secondary endpoints were: PMB distribution volume and clearance, albumin concentration, and median patient weight.

Results

The study included 34 patients with sepsis receiving PMB therapy, who were divided into two groups ($N=17$) according to their GFR. The cutoff value was set at GFR = 80 ml/min [10, 20], with a median GFR for all patients ($N=34$) of 80.7 ml/min (46.5; 125.4). The study included adults (aged 30 up to 89 years old), men and women. Most patients in both groups were men (12/17 and 10/17). The median age in the group of patients with reduced

Table 1. Demographic and clinical characteristics of patients.

Parameters	Glomerular filtration rate, ml/min		*P*
	>80, *N*=17	<80, *N*=17	
	Values		
Gender			
Males, *N* (%)	12 (71)	10 (59)	0.632*
Females, *N* (%)	5 (29)	7 (41)	
Age, years	64 (57; 68)	70 (64; 76)	0.039
Weght, kg	100 (80; 110)	80 (70; 100)	0.022
BMI	33.9 (27.7; 34.0)	28.0 (24.0; 31.1)	0.015
Isolated bacteria			
Klebsiella pneumoniae, N	3	8	
Acinetobacter baumannii, N	7	4	
Pseudomonas aeruginosa, N	1	2	
Mixed flora	6	3	
SOFA	7 (6; 8)	8 (5; 10)	0.715
Total protein, g/l	52.5 (46.8; 59.6)	53.0 (49.0; 60.6)	0.710
Albumin, g/l	26.6 (23.8; 30.0)	26.8 (24.4; 28.2)	0.559
Bilirubin, μmol/L	12.3 (9.6; 32.3)	13.7 (10.5; 28.7)	0.967
Creatinine, μmol/L	72.0 (53.0; 89.0)	175.0 (103.5; 272.5)	<0.001
GFR, ml/min	123.0 (89.2; 159.6)	42.3 (24.3; 64.4)	<0.001

Note. Data are presented as absolute values for qualitative variables — *N* (%), and as *Me* (IQR) *f*or quantitative variables, where *Me* is the median and IQR is the interquartile range; * — *Z*-test of proportions.

GFR was 70 years (range 56– 89 years) with a median body weight of 80 kg (range 64–100 kg). The median age and weight in the group with GFR >80 ml/min were 64 years (range 35–85 years) and 100 kg (range 75–140 kg). Sepsis was mainly caused by carbapenem-resistant strains of *K. pneumonia* (*N*=11), *A. baumannii* (*N*=11), or *P. aeruginosa* (*N*=3), and by multiple pathogens with MIC ⩽ 1 μg/mL in 9 patients. Secondary bacterial pneumonia was diagnosed in 71.9% of cases, bloodstream infection — in 7 cases, and abdominal infection — in 2 patients. Based on the SOFA score, these two groups of patients did not differ in terms of organ dysfunction, total protein, albumin, or bilirubin levels. Patients in both groups differed significantly in terms of creatinine concemtrations and GFR ($P<0.001$). Demographic and clinical data are shown in Table 1.

The patients' (*N*=257) steady-state serum antibiotic concentrations are presented in Fig. 2.

The mean AUC_{24} for 34 patients at steady state was 64.02 ± 11.64 mg×h/L, the median distribution volume was 31.53 (23.79; 43.72), and the median clearance was 3.72 (2.73; 4.85). Preliminary analysis of the data allowed to establish relationships and evaluate the effect of various covariates (age, body weight, SOFA, creatinine clearance, bilirubin, total protein, and albumin levels) on main PK parameters (AUC_{24}, V_d, and CL). Of all the data analyzed, a relationship was found for some pairs. An inverse correlation was established between the volume of distribution and albumin concentration (r_s=–0.355, P=0.039), as well as a significant direct correlation between GFR and clearance (r_s=0.427, P=0.012). The dose-normalized AUC depended on direct correlation with SOFA (r_s=0.453, P=0.007). The relationship between these variables is shown in Fig. 3

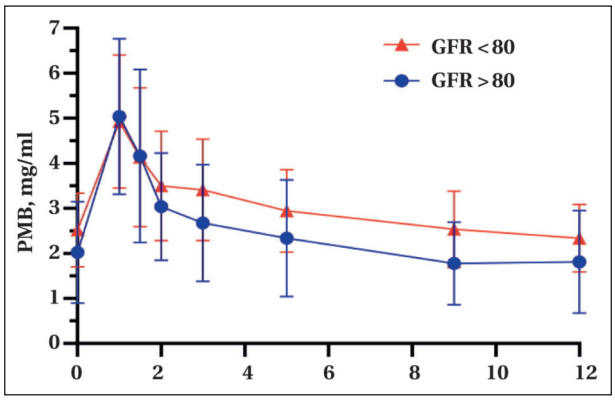

Fig. 2. PMB SS pharmacokinetic profile in patients with sepsis (*N*=34).
Note. Concentration is presented as the mean value ± standard deviation (*N*=17).

Since the albumin concentration and SOFA severity score in patients in both groups were comparable, and the differences in GFR were statistically significant ($P<0.001$), the analysis of PK data in the groups was continued in more detail. PK parameters were calculated based on individual plasma PMB concentrations at different time-points (Table 2).

In patients with preserved renal function, the median AUC_{24} value was 48.38 mg×h/L, and the SS concentration was 2.02 mg/mL. In the group with reduced renal function, the median AUC_{24} value reached 71.50 mg×h/L, and the SS concentration was 2.99 mg/mL. After normalizing the AUC_{24} values by dose, the level of differences between the groups increased statistically (from P=0.027 to P=0.01). At the same time, the PMB C_{max} in patients from both groups was similar — 5.1 mg/mL (P=.931). The PMB volume of distribution was slightly lower in

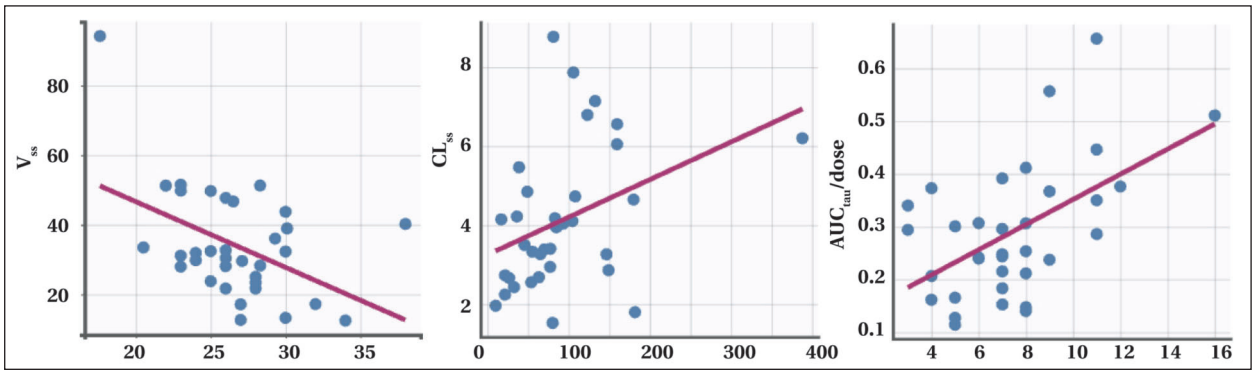

Fig. 3. PMB SS pharmacokinetic profile in patients with sepsis (*N* = 34).
Note. Concentration is presented as the mean value ± standard deviation (*N* = 17).

Table 2. PMB SS PK parameters in patients with different glomerular filtration rates.

Parameters	Glomerular filtration rate, ml/min		*P*
	>80, *N* = 17	<80, *N* = 17	
AUC_{24}, mg×h/L	48.38 (39.42; 65.90)	71.50 (59.60; 79.44)	0.027
AUC_{24}/dose, mg×h/L	0.25 ± 0.15	0.33 ± 0.09	0.010
C_{max}, mg/L	5.11 ± 1.96 (2.24–9.67)	5.09 ± 1.42 (2.35–8.34)	0.931
C_{ss}, mg/L	2.02 (1.70; 2.66)	2.99 (2.48; 3.33)	0.027
CL, l/h	4.97 ± 2.07 (1.52–8.77)	3.28 ± 0.95 (1.96–5.46)	0.012
V_d, L	32.71 (29.22; 48.22)	28.29 (21.71; 34.12)	0.114
T_{max}, h	1.17 ± 0.16	1.19 ± 0.18	0.694

Note. Values are presented as mean ± standard deviation (range) and *Me* (IQR), where *Me* is the median and IQR is the interquartile range.

the group with reduced renal function (28.29 L vs. 32.71 L), but the differences between the groups were statistically insignificant ($P = 0.114$). Clearance values were normally distributed across groups and differed statistically significantly. In the group of patients with GFR < 80 ml/min, the median clearance value was 3.28 L/h, compared to 4.97 L/h in the group of patients with GFR > 80 ml/min ($P = 0.012$). The parameters of total PMB exposure (AUC_{24}) in individual patients showed significant differences (Fig. 4).

In 14 of 17 patients with reduced renal function, AUC_{24} values were in the range of 50–100 mg×h/L. Among patients with normal renal function and hyperfiltration, only 7/17 attained the target range, while in 53% of patients (9/17) PMB exposure did not reach therapeutic efficacy levels (AUC_{24} < 50 mg×h/L).

Discussion

PMB exposure was assessed depending on GFR and renal function. PK was described using a non-compartmental model, which allowed the obtained data to be evaluated.

The PMB pharmacokinetics was described in 34 patients with sepsis, divided into 2 groups depending on renal function (GFR > 80 and < 80 ml/min). Despite differences between the groups in terms of median body weight and age of patients ($P < 0.05$), most of them were overweight (median weight 90 kg, BMI ⩾ 28) and elderly (over 60 years old). Previously, patients with such demographic data had not been described. In a similar study in 2021, patients with increased body weight (> 90 kg) had a mean age of 52 years [22]. In another study, the mean body weight of 23 elderly people was 70 kg [25], and the mean age was 73 years.

The mean AUC_{24} for all patients at steady state was 64.02 ± 11.64 mg×h/L, which is within the target range (50–100 mg×h/L). However, in some patients (2/34, 5.9%), PMB exposure exceeded the toxicity threshold (> 100 mg×h/L), and in 11/34 (32.4%) patients, it was insufficient (< 50 mg×h/L), which increased the risk of treatment failure. The median values of distribution volume and clearance in the respective groups (31.53 L and 3.72 L/h), taking into account the heterogeneity of patients, were comparable to those described earlier [18, 26].

Similar levels of total distribution volume (32.71 and 28.29 L) were found in both groups, which can be explained by a comparably low albumin concentration (26.6 and 26.8 g/L) and similar median weight of patients (80 and 100 kg). Despite achieving virtually identical C_{max} in all patients, the mean AUC_{24} (48.38 mg×h/L) in the group with preserved renal function was lower than in the group with impared renal function (71.50 mg×h/L), reflecting insufficient exposure. Even more significant differences ($P = 0.01$) between these categories of patients were found when

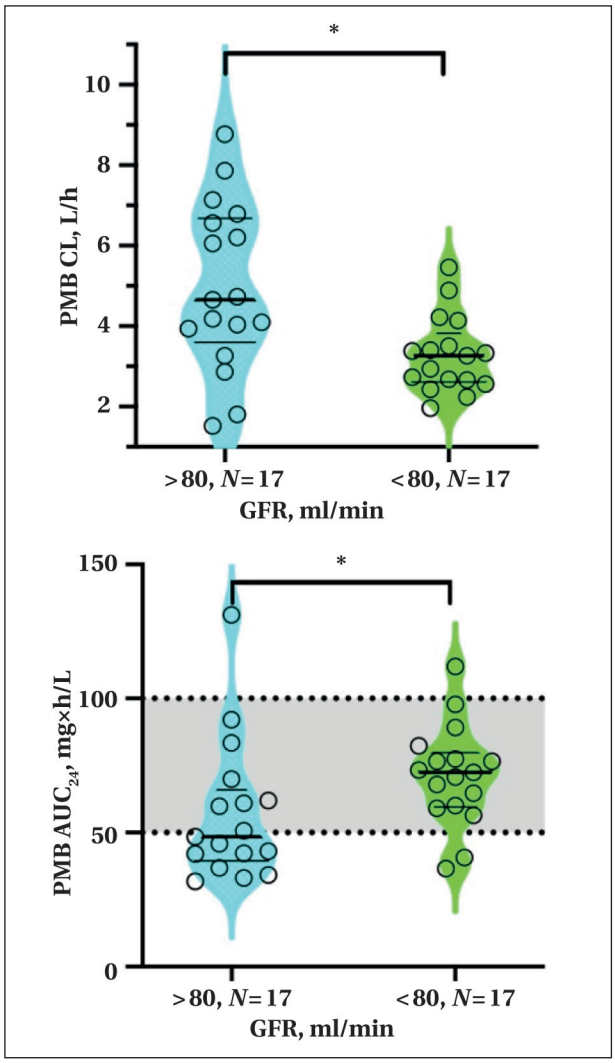

Fig. 4. Comparison of PMB clearance (CL) and exposure (AUC_{24}) depending on glomerular filtration rate (GFR).
Note. Data are presented as mean values ± standard deviations. * — $P < 0,05$.

comparing AUC values normalized to the daily dose (AUC_{24}/dose). Previously, researchers noted a similar fact: the area under the curve in patients with impared renal function was slightly higher vs patients with normal function (creatinine clearance ranged from 15 to 175 mL/min), although the statistical differences between the groups were insignificant [26].

The PK analyzis revealed that PMB clearance in patients with GFR < 80 mL/min was significantly lower ($P = 0.012$) compared to patients with preserved renal function (3.28 vs. 4.97 L/h), leading to significant increase in exposure ($P = 0.027$). In a PK study based on a two-compartment model, among 70 patients weighing 66–68 kg at PMB maintenance dose from 50 to 100 mg, clearance in patients with normal renal function was also significantly higher compared to patients with renal impairment (2.19 L/h compared to 1.58 L/h, respectively, $P < 0.001$). Moreover, AUC_{24} was significantly higher in patients with acute renal failure than in patients without renal impairment (108.66 ± 70.10 mg×h/L vs. 66.18 ± 34.79 mg×h/L; $P = 0.001$) [17].

Unlike most previous studies, including ours [20], focusing on PK estimatiom in patients with impaired renal filtration [4, 18], the present study makes emphasis on PMB inefficacy in patients with preserved renal function (GFR > 80 ml/min). Thus, failure to attain the minimum target AUC_{24} (50 mg×h/L) with the risk of treatment failure, was documented in 52.3% of patients (9/17) with preserved renal function, and only in 11.8% of patients (2/17) with impaired renal function. Higher AUC_{24} (> 100 mg×h/L) fraught with toxic manifestations, was documented in 2 patients — one from each group (5.9%). Therefore, in 58.8% (10/17) of patients with preserved renal function and in 17.6% (3/17) of patients with reduced filtration, AUC_{24} did not attain the target values (Fig. 3).

Impaired renal function comes with increased exposure to PMB due to decreased drug clearance and, conversely, renal hyperfiltration can lead to decreased antibiotic exposure. Thus, among patients ($N = 9$) with GFR > 120 ml/min, the median values of AUC_{24}, clearance, and volume of distribution were 45.76 mg×h/L (39.42; 76.73), 6.05 l/h (3.06; 6.78), and 40.24 L (26.6; 48.72), respectively. Similar data were obtained in patients with lower body weight [3]. In the present study, in more than half of the cases, patients with GFR > 80 ml/min had AUC_{24} values less than 50 mg×h/L. The target range of AUC_{24} = 50–100 mg×h/L was not attained, and most likely, such patients require dose adjustments, which is consistent with the observations of other researchers who call into question the concept of non-renal clearance of this antibiotic [18].

Limitations of the study. Preliminary registration of the prospective study on Clinical Trials platform and calculation of patient sample size were not done.

Conclusion

Thus, adherence to standard PMB dosing regimens, even taking into account the administration of a loading dose, does not always ensure that the target drug exposure is attained, which may be due to significant individual differences in PK in patients with sepsis.

It has been established that renal function significantly affects the pharmacokinetics of PMB in patients with sepsis: a decrease in renal function

increases drug exposure, while in preserved renal function drug exposure may be insufficient to achieve a therapeutic effect, especially in patients with increased body weight.

As a result, therapeutic drug monitoring is necessary to control therapy not only in patients with decreased renal function, but also in those with preserved renal clearance.

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