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Population Pharmacokinetic Modeling Using Polymyxin B Free Plasma Concentrations From Published Reports and Evaluation of Dosage Regimens Based on Monte Carlo Simulation in Critically Ill Patients

You Zheng, MD[1,2], Baohua Xu, MD[1,2], Shengyang Chen, MD[1,2], Maobai Liu, MD[1], Huiping Huang, MD[1,2], Jingting Wang, MD[3], and Xuemei Wu, PhD[1]

Abstract

A population pharmacokinetic (pop PK) model of polymyxin B was developed using nonlinear mixed-effects (NONMEM) modeling based on free plasma concentrations to determine whether dose adjustment is required in critically ill patients. One thousand pharmacokinetic profiles for virtual patients with a body weight of 70 kg were simulated using Monte Carlo simulation at different dose scenarios, and area under the concentration–time curve of free drug (fAUC) was computed. The probability of target attainment (PTA) at each minimum inhibitory concentration (MIC) was calculated using fAUC/MIC as a pharmacokinetic/pharmacodynamic (PK/PD) index. The final population PK model was a 2-compartment model. PTA showed that 3.5 mg/kg/day regimens of polymyxin B effectively achieved the fAUC/MIC target of 10 (one $\log_{10}$ kill) against *Pseudomonas aeruginosa* strains with MIC of 1 mg/L or less (PTA, 90.7% or greater), while the dose regimen were ineffective against strains with an MIC of 2 mg/L or greater (PTA, 56.9% or less). For *Klebsiella pneumoniae*, the fAUC/MIC target of 17.4 (one $\log_{10}$ kill) was achieved in more than 90.4% of cases for MIC of 0.5 mg/L or less with 3 mg/kg/day regimens. However, the PTA decreased dramatically as MICs increased above 1 mg/L (PTA, 56.1% or less). The polymyxin B dosage regimen of 3.5 mg/kg/day and 3 mg/kg/day are sufficient to treat *P. aeruginosa* infections with an MIC of 1 mg/L or less and *K. pneumoniae* infections with an MIC of 0.5 mg/L or less, respectively. The current recommended dose (1.5–3 mg/kg/day) of polymyxin B appears inadequate to attain the PK/PD target for therapeutic efficacy against infections caused by *P. aeruginosa* and *K. pneumoniae* isolates when MIC is above the values.

Keywords

Monte Carlo simulation, pharmacokinetic/pharmacodynamic (PK/PD) index, polymyxin B, population pharmacokinetics, probability of target attainment

Polymyxin B is a peptide antibiotic obtained from the fermentation product of *Bacillus polymyxa* and was first used clinically in the 1950s.[1] However, it was replaced by other, safer antibacterial drugs due to its nephrotoxicity and neurotoxicity in the 1970s.[2] With the emergence of multidrug-resistant gram-negative pathogens, polymyxin B has been reintroduced as a treatment of last resort. Polymyxin B has rapid bactericidal activity against multidrug-resistant gram-negative bacteria such as *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* in vitro.[3] The recommended dose of polymyxin B is 1.5–3.0 mg/kg/day (1 mg of polymyxin B is equivalent to 10,000 IU).[4] However, there is no definite recommended dose for infectious diseases caused by different bacteria.[5] Polymyxin B can only be administered based on the prescriber's experience or intuition.

Two polymyxins are currently available, polymyxin B and colistin (polymyxin E).[6] Studies on polymyxin's pharmacokinetic/pharmacodynamic (PK/PD) index were conducted using a mouse infection model, including neutropenic murine thigh and lung infection models.[7,8] The area under the concentration–time curve of free drug to minimum inhibitory concentration (MIC) ratio (fAUC/MIC) obtained from the thigh infection model was recognized as the best PK/PD index that could predict bacterial killing by polymyxins. Because polymyxin B and colistin have very similar chemical structures and essentially the same potency and antibacterial spectrum in vitro, the PK/PD index of colistin can be adopted by polymyxin B.[9]

[1]Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
[2]School of Pharmacy, Fujian Medical University, Fuzhou, Fujian, China
[3]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA

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Corresponding Author:
Xuemei Wu, PhD, Department of Pharmacy, Fujian Medical University Union Hospital, 29 Xinquan Rd., Gulou District, Fuzhou, Fujian 350001, China.
Email: wuxuemei@fjmu.edu.cn

The plasma-free drug fraction (f_u) of polymyxin B was set at 0.42 in several studies,[9,10] according to Sandri's report. However, in this report, 0.42 represented the median f_u of polymyxin B, with a range between 0.26 and 0.64 and a sizeable interindividual variability.[11] The population pharmacokinetics (popPK) model of polymyxin B was developed using either total plasma concentrations or free drug plasma concentrations derived from total concentration multiplied by 0.42.[9–13] No popPK studies were established using actual free plasma concentrations of polymyxin B. Since only unbound drug can permeate into target tissues or organs, the pharmacological activity of a drug usually depends on the free concentration in the blood rather than the total drug concentration.[14] Moreover, the significant variation in protein levels among individual critically ill patients results in large differences in the free fraction of polymyxin B.[11,15] Therefore, the reported popPK studies of polymyxin B cannot reflect the actual therapeutic effect.

In this study, a popPK model was developed using actual free plasma concentrations of polymyxin B in critically ill patients. One thousand PK profiles at each dose regimen were simulated using Monte Carlo simulation coupled with the final model and estimated parameters. The regimen used for simulation was set at 1.5, 2, 2.5, 3, 3.5, and 4 mg/kg/day. The probability of target attainment (PTA) at each MIC level was calculated. We tried to find a suitable dose regimen that can achieve a PTA of 90% or higher at MIC values of interest, to determine whether dose adjustment is required in critically ill patients.

Methods

Data Search

A search was conducted in the PubMed databases. Search terms were "polymyxin B" and "pharmacokinetics." The literature containing patient-level information for both drug concentration curves and plasma protein binding was selected. "MIC distribution," "gram-negative bacteria," "*Pseudomonas aeruginosa*," and "*Klebsiella pneumoniae*" were used to search the MIC distribution of interested bacteria in the PubMed databases and microbiology website. The search was limited to English only.

Data Set

Only two studies were eligible after screening, and a total of nine critically ill patients were used for modeling.[16,17] If the concentration–time data were shown only in figures, concentration and sampling time were extracted using GetData Graph Digitizer, version 2.26 (GetData Graph Digitizer, 2013, http://getdata-graph-digitizer.com/). The doses administered to each patient were different and ranged from 0.5 to 3.0 mg/kg/day (49.8–250 mg/day). Blood samples were collected in seven patients before the start of 60-min polymyxin B infusion and 60, 90, 120, 180, 360, and 720 min after polymyxin B infusion. In the other two patients, sampling times were 5 min before polymyxin B infusion and 5 min and 0.5, 1, 2, 4, and 8 h after the infusion and before the next dose. The plasma protein binding fraction of polymyxin B was determined by rapid equilibrium dialysis. High-performance liquid chromatography analysis[16] or ultra-performance liquid chromatography–tandem mass spectrometry[17] was used to determine the drug concentration of polymyxin B in the plasma (C_P) and buffer (C_B) reservoirs. The plasma protein binding fraction was calculated as $(1 - C_B/C_P) \times 100\%$, and free drug concentration was determined by blood concentration multiplied by actual f_u.

Population PK Analysis

Free blood concentration was analyzed for popPK modeling using NONMEM software (version 7.5.0, Icon Development Solutions) and Pirana (version 2.9.7, Certara) with the first-order conditional estimation method with interaction. R (version 4.2.1, R Foundation for Statistical Computing) and Xpose 4 (version 4.7.2) software packages were applied to generate diagnostic plots. The structure model selection was evaluated on the basis of objective function value for one- and two-compartment models. Random effects included interindividual variability (IIV) and residual variability (RUV). IIV was modeled using an exponential error model. RUV was modeled using the additive error, the proportional error, the exponential error, and the combined additive–proportional error or additive–exponential error models. The final base model was determined by comparing the objective function values.

Goodness-of-fit plots were used to assess the validity of the popPK model, which included observation concentrations versus individual-predicted concentrations, observation concentrations versus population-predicted concentrations, conditional weighted residuals (CWRES) versus population-predicted concentrations, and CWRES versus time after dose. The sampling importance resampling (SIR) method was applied for parameter evaluation with 500 sampling data as well as 500 resampling data to obtain the final set of parameter vectors via successive iterations. Confidence intervals (CIs) around the parameters were also computed based on this set of parameter vectors. In addition, the prediction-corrected visual predictive check was used to evaluate the performance of the final model. One thousand replicates were calculated from the Monte Carlo simulation. Then, the 90% CIs of the 5th, 50th, and 95th percentiles of the simulated

concentrations were visually compared with actual observed data.

Monte Carlo Simulation and PTA Calculation

The target values used for PTA analysis were derived from PK/PD studies of systemically administered colistin or polymyxin B against infections caused by *P. aeruginosa* or *K. pneumoniae* in mouse thighs.[7,8] The median target values for *P. aeruginosa* and *K. pneumoniae* (10.0 and 17.4 [one $\log_{10}$ kill]) were chosen to avoid significant bias in the final results, which was in line with other, similar studies.[9] One thousand PK profiles were simulated using Monte Carlo simulation coupled with the final model and estimated parameters. Body weight–based dose regimens in adults weighing 70 kg were set at 1.5, 2, 2.5, 3, 3.5, and 4 mg/kg/day. The infusion rate was 50 mg/h. From each of the 1000 sets of simulated PK profiles, the AUC of free polymyxin B was calculated using dose/central clearance (CL). The fAUC/MIC is the most predictive PK/PD index for polymyxin.[18–20] To better understand the efficacy of various dose regimens in infection with different MICs of pathogens, we calculated the PTA of fAUC/MIC across the MIC distribution. The dose regimen was considered appropriate if PTA was 90% or greater.

Results

Demographic Data

A total of nine patients who contributed to 63 polymyxin B plasma concentrations were included in the study. Each patient contributed an average of seven clinical samples. The demographic and clinical data are shown in Table 1.

Table 1. Demographic and Clinical Data

Characteristic	Values
Sex[a]	
Male	4
Female	5
Age[b]	59.4 (18.33)
Weight[b]	86.67 (58.40)
APACHE II score[b]	23.4 (2.45)
Dialysis[a]	
No	7
Yes	2
Coadministered antibiotic(s)[a]	
Meropenem	2
Levofloxacin	1
Ceftazidime	2
Aztreonam	1
Vancomycin	2
Trimethoprim-sulfamethoxazole	2
Ciprofloxacin	1

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.
[a] Presented as patient number.
[b] Presented as median (standard deviation).

Microbiological Information

MIC distribution of polymyxin B obtained from the SENTRY surveillance program (Sader, personal communication, 2015) and two other studies,[21,22] which included 3961 *P. aeruginosa* strains and 4178 *K. pneumoniae* strains, is shown in Table 2. MICs ranged between 0.125 and 16 mg/L for *P. aeruginosa*, and 0.25–16 mg/L for *K. pneumoniae*.

Population PK Model

The final popPK model was a two-compartment model with no covariates included due to the limited patient size. IIV and RUV were described by the exponential model and additive model, respectively. The PK parameters were estimated, as shown in Table 3.

The goodness-of-fit plots for the final model are shown in Figure 1. The plots of observation concentrations versus individual-predicted concentrations and observation concentrations versus population-predicted concentrations indicated no structural bias. The plot of CWRES versus population-predicted concentrations and CWRES versus time after dose showed a random distribution around zero, and most of the plasma concentrations were scattered within −2 to 2, showing that the structure of the final model was not biased and that the model was acceptable.

The estimates of the SIR method are presented in Table 3. The estimates of the final model were similar to the median estimates of the SIR, and they were within the 95% CI from the SIR analysis, which did not include zero.

The prediction-corrected visual predictive check plot (Figure 2) showed that almost all the observed values were located within the 5th and 95th percentiles, indicating that the prediction from the model reproduced the central trend and variability in the observed data.

Probability of Target Attainment Calculation

The results of PTA analyses are shown in Figure 3. For *P. aeruginosa* (Figure 3a), the regimens of 3.5 mg/kg/day effectively achieved the fAUC/MIC target of one $\log_{10}$ kill (fAUC/MIC index, 10) against strains with an MIC of 1 mg/L or less (PTA, 90.7% or greater), while the dose regimen was ineffective against strains with an MIC of 2 mg/L or greater (PTA, 56.9% or less).

For *K. pneumoniae* (Figure 3b), the fAUC/MIC target of 17.4 (one $\log_{10}$ kill reduction) was achieved in more than 90.4% of cases for MICs of 0.5 mg/L or less with 3-mg/kg/day regimens. However, the PTA decreased sharply as MICs increased above 1 mg/L (PTA, 56.1% or less).

Table 2. MIC Distribution of Polymyxin B for *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*

	MIC (mg/L)							
Strain	0.125	0.25	0.5	1	2	4	8	≥16
P. aeruginosa	3	32	123	1905	1876	8	2	12
K. pneumoniae	1	43	2407	1570	37	31	40	111

Abbreviation: MIC, minimum inhibitory concentration.

Table 3. Population Parameter Estimates for the Final popPK Model

Parameters	Estimate	RSE (%)	Shrinkage (%)	SIR median (95% CIs)
TVCL/L/h	10.6	20	—	10.6 (6.7–14.9)
TVV1/L	33.1	38	—	33.8 (11.8–59.5)
TVV2/L	89.0	29	—	89.2 (42.5–146.5)
TVQ/L/h	33.9	27	—	34.4 (14.7–52.2)
IIV				
CL	0.38	36	0	0.39 (0.084–0.68)
V1	1.31	44	0.34	1.39 (0.21–2.44)
V2	0.21	36	27	0. 21 (0.052–0.37)
Q	0.43	23	11	0. 43 (0.23–0.62)
RUV				
Additive	0.0062	17	25	0.0062 (0.0040–0.0087)

Abbreviations: CIs, confidence intervals; CL, central clearance; IIV, interindividual variability; Q, intercompartment clearance; RSE, relative standard error; RUV, residual variability; TV, typical value; V1, central volume of distribution; V2, peripheral central volume of distribution.

Discussion

To the best of our knowledge, this is the first study to establish a popPK model of polymyxin B based on actual free drug concentration in critically ill patients. PK profiles of 1000 virtual patients were simulated using Monte Carlo simulation at different dose regimens. PTA of polymyxin B against *P. aeruginosa* and *K. pneumoniae* was plotted over the MIC distribution based on the fAUC/MIC. The results suggested that the 3.5 and 3.0 mg/kg/day of polymyxin B had PTA exceeding 90% at MICs up to 1.0 and 0.5 mg/L for *P. aeruginosa* and for *K. pneumoniae*, respectively. Higher doses are required for *P. aeruginosa* and *K. pneumoniae* infections with MICs exceeding the above values.

A two-compartment model can adequately describe the disposition of polymyxin B. CL was 10.6 L/h for free polymyxin B in plasma, which was 3.7–9 times higher than the results[12,13] using the total polymyxin B concentrations (range, 1.18–2.86 L/h). Considering that the f_u of polymyxin B in this study was 0.195 ± 0.125 (range, 0.076–0.512), and the total concentrations are 1.95- to 13.16-fold higher than free concentrations, it is reasonable to obtain a higher CL. For the value of V1 (33.1L), it is 5.32 times higher than in the study by Wang et al.[23] and 2.94 times higher than in the study by Wang et al.[13] The V2 of 89 L was also higher than the research reported previously,[13,23,24] indicating that free polymyxin B might have more tissue distribution.

Because only nine patients were included in this study, covariate modeling was not performed. For small sample data sets, the bootstrap method is not applicable to validate the performance of the final popPK model.[25] It has been suggested that the SIR method performs better than the bootstrap for parameter evaluation of small sample data sets,[26] with the advantage of being free of distributional assumptions and not requiring repeated parameter estimation. The estimates of the final model were similar to the median estimates of the SIR. They were within the 95% CI from the SIR analysis, suggesting that the NONMEM parameter estimates of the models were unbiased.

The bacterial MIC distribution was derived from the studies of van der Heijden et al.[21] and Vaara et al.,[22] as well as the SENTRY surveillance program. *P. aeruginosa* isolates with an MIC of 1 and 2 mg/L accounted for 48.1% (1905/3961) and 47.4% (1876/3961) of the total number, respectively. The corresponding value for *K. pneumoniae* with an MIC of 0.5 and 1 mg/L was 57.6% (2407/4178) and 36.1% (1570/4178), respectively. Given that the total number of bacterial strains is large, it can prevent the bias caused by single research or limited sample size.

The currently recommended maximum dose is 3.0 mg/kg/day. Monte Carlo simulation indicated the maximum dose regimen was effective against *K. pneumoniae* strains with an MIC of 0.5 mg/L or less (PTA, 90. 4 or greater). The PTA was only 56.1% when MIC was 1 mg/L. For *P. aeruginosa* infections, the higher dose of 3.5 mg/kg/day is needed to reach the target PTA for patients with an MIC of 1 mg/L or less (PTA, 90.7% or greater), with a PTA of 56.9% when MICs were 2 mg/L. We also calculated the dose of polymyxin B to reach 90% or greater PTA for *P. aeruginosa* infections with an MIC of 2 mg/L and *K. pneumoniae* infections with and MIC of 1 mg/L. The doses needed were increased to 7.0 and 6.0 mg/kg/day, respectively. Because more than 3.0 mg/kg/day of polymyxin B is too high and lacks clinical data on safety, combination therapy or alternative drugs should be considered for severe infections caused by such pathogens.

A popPK model using total concentrations with AUC/MIC greater than 50 as the target value shows

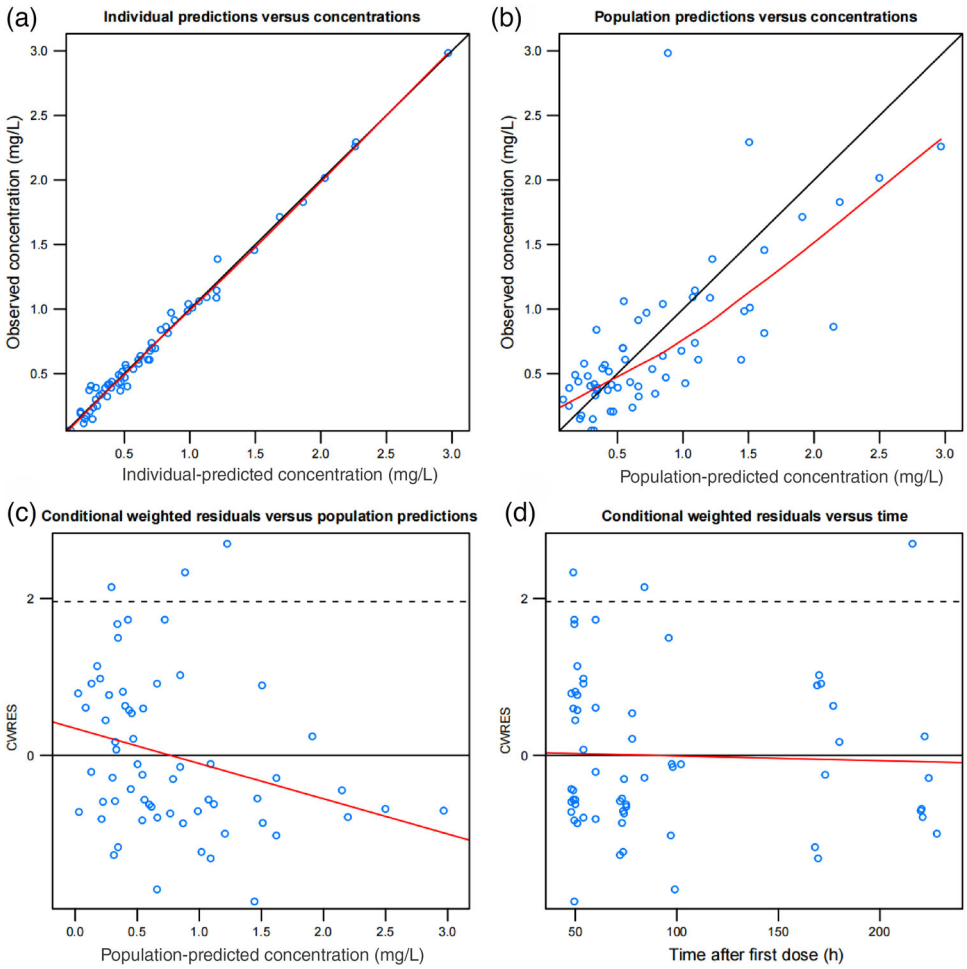


Figure 1. Diagnostic goodness-of-fit plots of the final model. (a) Observed concentrations versus individual-predicted concentrations. (b) Observed concentrations versus population-predicted concentrations. (c) CWRES versus population-predicted concentrations. (d) CWRES versus time after dose. The red line represents a locally weighted least-squares regression; the solid black line represents the identity line; the dots represent the observed data. Abbreviation: CWRES, conditional weighted residuals.

that 3 mg/kg/day is sufficient to treat all bacterial infections with an MIC of 0.5 mg/L or less (PTA, greater than 99%), which is consistent with the present study (PTA, greater than 90.4%).[24] Considering that different bacteria exhibit varying responses to the same drug, it would be more reasonable to use different target values (fAUC/MIC). We also developed a popPK model using total concentrations and simulated 1000 virtual patients to calculate AUCs. According to the reported[11] unbound fraction range of 0.26–0.64 (median, 0.42), the fixed f_u (0.26, 0.42, and 0.64) was used for the PTA analysis. The PTA for *P. aeruginosa* (target value, 10) with MIC 1 mg/L was 92.7%, 91.9%, and 92.3% with polymyxin B regimens of 2.5, 1.5, and 1 mg/kg/day, respectively. The PTA for *K. pneumoniae* (target value of 17.4) with an MIC of 0.5 mg/L was 90.7%, 95.2%, and 95.4% with polymyxin B regimens of 2, 1.5, and 1 mg/kg/day, respectively. The results indicated that the dose required to achieve the target PK/PD index was more than two times between the patients with a high f_u and low f_u. Fixed f_u does not capture the variation in protein levels among individuals in critically ill patients, which may result in a big gap between the recommended dose and the required dose. Therefore, it is more accurate to use the actual free concentrations for dose recommendation than to use fixed f_u.

PTA indicated that high-dose polymyxin B was more effective in treating multidrug-resistant bacterial infections, which is consistent with the observation in the clinical study. Xia et al.[27] investigated the efficacy of polymyxin B in carbapenem-resistant gram-negative organism infections. The clinical effective rate and bacterial clearance rate of the 2.5-mg/kg/day group were higher than the 1.5- or 2-mg/kg/day group. However, with the recommended dose of 1.5–2.5 mg/kg/day, the overall effective rate and bacterial clearance rate is less than 50% (49.72% and 42.0%), with the 28-day all-cause mortality rate higher, at 59.1%. The results seem in line

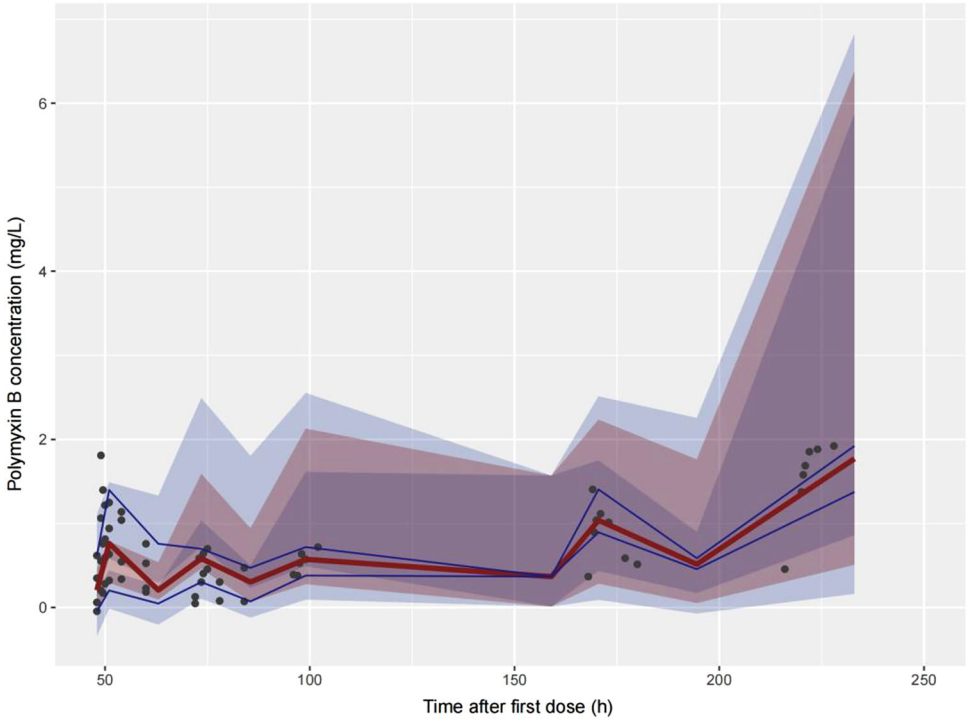


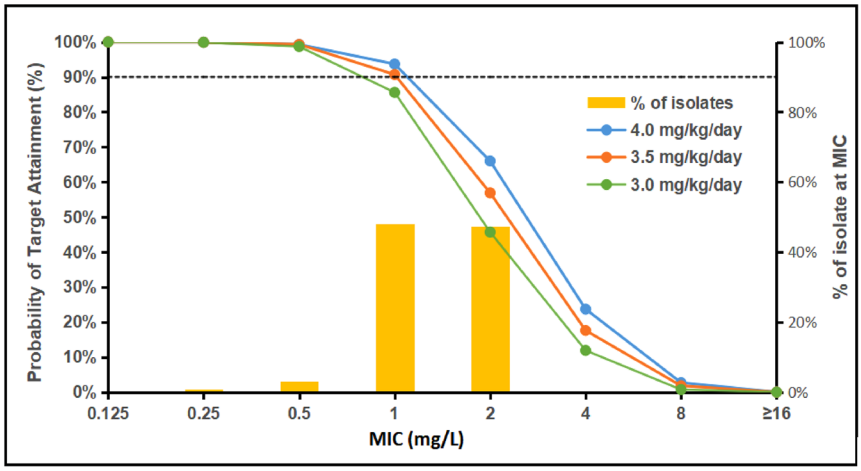
Figure 2. The prediction-corrected visual predictive check of the final model. Solid dots represent the observed concentrations. The solid lines represent the 5th (lower blue), 50th (red), and 95th (upper blue) percentiles of the observed data. The shaded areas represent the 90% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated concentrations, respectively.

with the lower PTA obtained when using a dose of less than 3 mg/kg/day in the current study. Another study[28] also suggested that 200 mg/day or greater of polymyxin B was associated with a lower risk for in-hospital mortality. There is a large proportion of isolates with an MIC of 2 mg/L or greater for *P. aeruginosa* and an MIC of 1 mg/L or greater for *K. pneumoniae* (Table 2). For the infections caused by the strain with higher MIC, the dose to reach the PTA above 90% is much higher than the recommended dose. The lower PTA achieved under the dose of 3 mg/kg/day might give an alternative explanation for the higher mortality observed in the above studies.

Although high doses of polymyxin B are beneficial for treatment, its side effects should not be ignored. The main side effects of polymyxin B are nephrotoxicity and neurotoxicity. The incidence of polymyxin B–related nephrotoxicity is 4%–60%.[29] Most studies support that the side effects tend to increase with higher doses, with a few exceptions. In the study conducted by Rigatto et al.,[30] ≥150 mg/day of polymyxin B was associated with a greater risk of developing any degree of acute renal failure. The probability of developing acute renal failure significantly increased with doses between 150 and 199 mg/day. Zhang et al.[31] observed that a polymyxin B daily dose was an independent risk factor for nephrotoxicity. However, John et al.[32] showed that high doses of polymyxin B (250 mg/day or greater or 3.0 mg/kg/day or greater) had a low incidence of infusion-related severe adverse events with an acceptable safety profile. The study conducted by Elias et al.[28] also demonstrated that a doses of polymyxin B of 200 mg/day or greater was associated with a higher incidence of severe renal impairment, but 200 mg/day or greater of polymyxin B was not associated with mild or moderate renal impairment as expected.

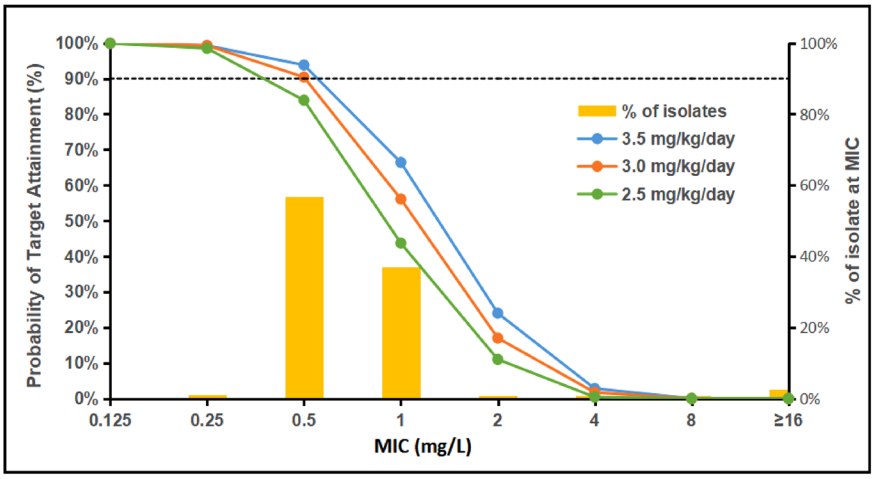
There are several limitations in this study. First, due to the smaller patient size, a shorter sampling time window of 12 h, and difference in patient population (two patients on continuous venovenous hemodialysis), the built popPK model is not so convincing, and the possible effect of the covariate on popPK parameters cannot be examined. Because the current model was developed on the basis of a digitized data set that was derived from figures with a log-scale *y* axis in the literature, errors in extracting the data via digitization might result in the inaccuracy of the model. However, the results can give us an insight into the reconsideration of the efficacy of the recommended dose of polymyxin B. In addition, free plasma concentration cannot reflect the drug level in the infectious region. Substantial regional susceptibility differences and the bacterial species involved must be taken into account when using the results.[9] Finally, we hypothesized that the PK/PD index for polymyxin B would be similar to that of colistin for *P. aeruginosa*, but there is no

(a)



Dose(mg/kg/day)	fAUC/MIC index of *P. aeruginosa*	PTA (%)	
		MIC ≤1 mg/L	MIC ≥2 mg/L
3.0	10	≥ 85.6	≤ 45.7
3.5	10	≥ 90. 7	≤ 56. 9
4.0	10	≥ 93. 7	≤ 66.0

(b)



Dose (mg/kg/day)	fAUC/MIC index of *K. pneumoniac*	PTA (%)	
		MIC ≤0.5 mg/L	MIC ≥1 mg/L
2.5	17.4	≥ 83.9	≤ 43.7
3.0	17.4	≥ 90. 4	≤ 56. 1
3.5	17.4	≥ 93.8	≤ 66.4

Figure 3. Probability of target attainment versus *Pseudomonas aeruginosa* (a) and *Klebsiella pneumoniae* (b) over a range of MIC values in critically ill patients. The right *y* axis is the percentage MIC distribution of polymyxin B. Abbreviations: fAUC, concentration–time curve of free drug; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

experimental evidence to support this. Polymyxin B can also treat infections caused by *A. baumannii* and *Escherichia coli*. We did not perform PTA analysis for these two pathogens due to a lack of MIC distribution of polymyxin B for *A. baumannii* and the PK/PD indexes of polymyxin B for *E. coli*.

Conclusions

A popPK model was successfully established to characterize the PK parameters of unbound polymyxin B. The use of actual free plasma concentrations may account for the variation in protein levels among individuals in critically ill patients. Monte Carlo simulation and PTA suggested that a higher dose of polymyxin B than the recommended dose might be sufficient to achieve the therapeutic effect in critically ill patients. Future study is needed to evaluate the PK of polymyxin B with a larger population and establish a robust popPK model based on polymyxin B free concentration, as well as find the significant covariates that impact PK. In addition, the side effects of high-dose polymyxin B should be investigated.

Author Contribution

All authors contributed to the study conception and design. Xuemei Wu, You Zheng, and Maobai Liu participated in research design and method execution. You Zheng and Baohua Xu analyzed the data, drafted the manuscript, and performed the analysis with constructive discussions. Huiping Huang and Shengyang Chen contributed to data analysis and plotting. Xuemei Wu and Jingting Wang polished the language. All authors read and approved the final manuscript.

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Conflicts of Interest

There is no conflict of interest to declare.

Data Availability Statement

All data included in this study are available from corresponding author upon request.

References

1. Tran TB, Velkov T, Nation RL, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? *Int J Antimicrob Agents*. 2016;48(6):592–597.
2. Avedissian SN, Liu J, Rhodes NJ, et al. A Review of the clinical pharmacokinetics of polymyxin B. *Antibiotics (Basel)*. 2019;8(1):31.
3. Zavascki AP, Goldani LZ, Li J, Nation RL. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. *J Antimicrob Chemother*. 2007;60(6):1206–1215.
4. 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.
5. Rigatto MH, Falci DR, Zavascki AP. Clinical use of polymyxin B. *Adv Exp Med Biol*. 2019;1145:197–218.
6. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006-09). *J Antimicrob Chemother*. 2011;66(9):2070–2074.
7. Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. *J Antimicrob Chemother*. 2015;70(12):3291–3297.
8. Landersdorfer CB, Wang J, Wirth V, et al. Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against *Klebsiella pneumoniae* in mouse thigh and lung infection models. *J Antimicrob Chemother*. 2018;73(2):462–468.
9. Bian X, Liu X, Hu F, et al. Pharmacokinetic/pharmacodynamic based breakpoints of polymyxin B for bloodstream infections caused by multidrug-resistant gram-negative pathogens. *Front Pharmacol*. 2021;12:785893.
10. 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.
11. 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.
12. 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.
13. Wang P, Zhang Q, Feng M, Sun T, Yang J, Zhang X. Population pharmacokinetics of polymyxin B in obese patients for resistant gram-negative infections. *Front Pharmacol*. 2021;12:754844.
14. Deng Y, Gu JY, Li X, et al. Does monitoring total and free polymyxin B1 plasma concentrations predict polymyxin B-induced nephrotoxicity? A retrospective study in critically ill patients. *Infect Dis Ther*. 2022;11(4):1591–1608.
15. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.
16. Zavascki AP, Goldani LZ, Cao G, et al. Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis*. 2008;47(10):1298–1304.
17. Sandri AM, Landersdorfer CB, Jacob J, et al. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis. *J Antimicrob Chemother*. 2013;68(3):674–677.
18. Bergen PJ, Li J, Nation RL, Turnidge JD, Coulthard K, Milne RW. Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. *J Antimicrob Chemother*. 2008;61(3):636–642.
19. Bergen PJ, Bulitta JB, Forrest A, Tsuji BT, Li J, Nation RL. Pharmacokinetic/pharmacodynamic investigation of

colistin against *Pseudomonas aeruginosa* using an in vitro model. *Antimicrob Agents Chemother*. 2010;54(9):3783–3789.
20. Tam VH, Schilling AN, Vo G, et al. Pharmacodynamics of polymyxin B against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2005;49(9):3624–3630.
21. van der Heijden IM, Levin AS, De Pedri EH, et al. Comparison of disc diffusion, Etest and broth microdilution for testing susceptibility of carbapenem-resistant *P. aeruginosa* to polymyxins. *Ann Clin Microbiol Antimicrob*. 2007;6:8.
22. Vaara M, Sader HS, Rhomberg PR, Jones RN, Vaara T. Antimicrobial activity of the novel polymyxin derivative NAB739 tested against Gram-negative pathogens. *J Antimicrob Chemother*. 2013;68(3):636–639.
23. Wang P, Zhang Q, Zhu Z, et al. Population pharmacokinetics and limited sampling strategy for therapeutic drug monitoring of polymyxin B in Chinese patients with multidrug-resistant gram-negative bacterial infections. *Front Pharmacol*. 2020;11:829.
24. Miglis C, Rhodes NJ, Avedissian SN, et al. Population pharmacokinetics of polymyxin B in acutely ill adult patients. *Antimicrob Agents Chemother*. 2018;62(3):e01475-17.
25. Dosne AG, Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. *J Pharmacokinet Pharmacodyn*. 2017;44(6):509–520.
26. Dosne AG, Bergstrand M, Harling K, Karlsson MO. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. *J Pharmacokinet Pharmacodyn*. 2016;43(6):583–596.
27. Xia GL, Jiang RL. Efficacy and safety of polymyxin B in carbapenem-resistant gram-negative organisms infections. *BMC Infect Dis*. 2021;21(1):1034.
28. 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.
29. Pogue JM, Tam VH. Toxicity in patients. *Adv Exp Med Biol*. 2019;1145:289–304.
30. 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.
31. Zhang J, Hu Y, Shen X, Zhu X, Chen J, Dai H. Risk factors for nephrotoxicity associated with polymyxin B therapy in Chinese patients. *Int J Clin Pharm*. 2021;43(4):1109–1115.
32. 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*. 2018;62(1):e01617-17.