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ARTICLE

Assessing the predictive performance of population pharmacokinetic models for intravenous polymyxin B in critically ill patients

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Abstract

Polymyxin B (PMB) has reemerged as a last-line therapy for infections caused by multidrug-resistant gram-negative pathogens, but dosing is challenging because of its narrow therapeutic window and pharmacokinetic (PK) variability. Population PK (POPPK) models based on suitably powered clinical studies with appropriate sampling strategies that take variability into consideration can inform PMB dosing to maximize efficacy and minimize toxicity and resistance. Here we reviewed published PMB POPPK models and evaluated them using an external validation data set (EVD) of patients who are critically ill and enrolled in an ongoing clinical study to assess their utility. Seven published POPPK models were employed using the reported model equations, parameter values, covariate relationships, interpatient variability, parameter covariance, and unexplained residual variability in NONMEM (Version 7.4.3). The predictive ability of the models was assessed using prediction-based and simulation-based diagnostics. Patient characteristics and treatment information were comparable across studies and with the EVD ($n = 40$), but the sampling strategy was a main source of PK variability across studies. All models visually and statistically underpredicted EVD plasma concentrations, but the two-compartment models more accurately described the external data set. As current POPPK models were inadequately predictive of the EVD, creation of a new POPPK model based on an appropriately powered clinical study with an informed PK sampling strategy would be expected to improve characterization of PMB PK and identify covariates to explain interpatient variability. Such a model would support model-informed precision dosing frameworks, which are urgently needed to improve PMB treatment efficacy, limit resistance, and reduce toxicity in patients who are critically ill.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Polymyxin B is a narrow therapeutic index antibiotic with high interpatient variability administered to patients who are high risk and critically ill. Accurate dosing can be challenging, prompting the development of population pharmacokinetic (POPPK) models that account for patient heterogeneity and the remaining unexplained variability between patients. However, it is uncertain which models best account for interpatient and residual variability and would therefore be most useful for guiding polymyxin B dosing in patients who are critically ill.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can one or more of the published polymyxin B POPPK models be used for model-informed precision dosing in populations of patients who are critically ill?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study uses an external validation data set of patients who are critically ill to assess the predictive ability of existing population PK models to determine their utility for model-informed precision dosing of polymyxin B and explores sources of bias in the models based on study design.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study tells us which published models may best guide model-informed precision dosing of polymyxin B and best practices for designing new clinical studies to develop POPPK models for individualized polymyxin B dosing.

INTRODUCTION

The treatment of patients who are critically ill remains challenging because of the unabating global increase in antimicrobial resistance, regarded as one of the three greatest threats to human health.[1] This threat has been further amplified by the increased incidence of infections caused by multidrug-resistant (MDR) gram-negative pathogens and dwindling therapeutic options for these pathogens.[2–4] Polymyxins, an "old" antibiotic class, reemerged into clinical use in the 1990s as a last-line therapy against MDR gram-negative pathogens.[5,6] Polymyxin B is a cyclic lipopeptide[7] with dosing guided by the relationship between unbound drug exposure, as indicated by the area under the unbound plasma concentration–time curve (*f*AUC), and the minimum inhibitory concentration (MIC) of the infecting pathogen, that is, *f*AUC/MIC.[8,9] The risk of nephrotoxicity in patients is also associated with the plasma exposure (area under the plasma concentration–time curve [AUC]).[10,11]

Polymyxin B has a narrow therapeutic window that necessitates optimization of its exposure to maximize its bactericidal effect while minimizing the potential for the emergence of resistance[8–12] and polymyxin-associated adverse effects, notably nephrotoxicity.[13,14] Pathophysiological changes in patients who are critically ill (e.g., immune status, organ failure, comorbidity, comedication) can introduce pharmacokinetic (PK) variability,[13,15] making it difficult to predict polymyxin B PK exposure. Population PK (POPPK) approaches have enabled the development of models describing both predictable (interpatient variability) and random unexplained variability to provide the necessary framework for dose individualization.[16] Well-developed POPPK models characterize responses in a "typical" patient as well as the range of likely responses, taking the influence of patient heterogeneity on PK into consideration.[17] Such POPPK models are essential for model-informed precision dosing (MIPD) dose individualization and optimization. Current polymyxin B dosing recommendations, aimed at improving clinical efficacy and reducing toxicity, are provided in the published polymyxin B dosing guidelines.[13]

POPPK models based on PK data collected from clinical studies with adequate numbers of patients combined with well-informed sampling strategies can accurately characterize drug PK.[18–20] Patient (demographic and clinical) characteristics assist in defining the study population and determining the statistically or clinically influential characteristics that can help explain PK variability within the studied population.[21] Current knowledge regarding polymyxin B PK is largely based on clinical experience and observational POPPK data collected from healthy volunteers or during routine

clinical care of patients who are critically ill. These data have enabled the development of POPPK models that relate observed polymyxin B concentrations to administered doses and identify significant covariate relationships that describe sources of variability in these populations.[11,22–26] Such POPPK models can be used to develop an MIPD framework for precision dosing.[16,27] Before this step, it is important to consider the study design (patient population, dosing regimen, and sampling strategy) used to develop each model. Furthermore, as performed for other narrow therapeutic antibiotics,[28–30] evaluation of the predictive performance and generalizability of POPPK models must be performed via validation assessments using "external" data sets obtained from separate groups of patients from those used to develop the model.[31]

The objective of this study was to review and externally validate published polymyxin B POPPK models to determine whether they can be used for MIPD in patients who are critically ill. POPPK data from an ongoing observational clinical study for polymyxin B in patients who are critically ill (NCT02682355) was used as the external validation data set.[32]

METHODS

Review of published POPPK studies

The PubMed, MEDLINE, and Embase databases were searched to identify published POPPK analyses of polymyxin B using the following keywords: "polymyxin B" [AND] "pharmacokinetics" [AND] ("population" [OR] "model"). The search included studies published in English between May 1, 1986, and May 10, 2021. Included POPPK models were those developed using the following: (1) polymyxin B PK data from adult patients who are critically ill; (2) a compartmental, parametric modeling approach; and (3) polymyxin B sample quantification performed via a chromatographic method. POPPK models were excluded if (1) polymyxin B was administered via a nonintravenous route, (2) the model description was insufficient/inadequate to fully reproduce the model, or (3) the model was developed based on data from patients with cystic fibrosis (CF) or healthy volunteers.

Independent external validation data set

Polymyxin B PK and demographic data were collected from adult patients who are critically ill and enrolled in an ongoing, observational, multisite polymyxin B clinical study (https://clinicaltrials.gov/ct2/show/study/NCT02682355) conducted at Singapore General Hospital (Outram Road, Singapore), Hospital Moinhos de Vento (Porte Alegre, Brazil), and Pontifical Catholic University of Rio Grande do Sul (Porte Alegre, Brazil) from June 2017 to December 2019. The study was approved by the ethical committees at all participating centers. Inclusion criteria were anticipated use of intravenous polymyxin B for 48 h or more following enrollment for the treatment of bacteremia, urinary tract infection, respiratory infections, or sepsis. Patients were excluded if they were diagnosed with CF, were not anticipated to survive beyond 48 h following enrollment, or received concomitant polymyxin B delivered directly into the respiratory tract. No patient in this study was analyzed in previously published polymyxin B POPPK studies. The polymyxin B dose, infusion duration, and dosing interval were at the discretion of the physician caring for each patient and were recorded. Between days 1 and 5, PK plasma samples were collected predose and at nominal times of 0.5, 1, 2, 6, and 12 h after cessation of infusion. Total polymyxin B plasma concentrations were assessed by measuring polymyxin B1 and B2 components in each plasma sample. Individual components were measured using a liquid chromatography–tandem mass spectrometry assay with a lower limit of quantification of 0.05 mg/L and coefficient of variation of 8.42%.[24] Patient age, weight, creatinine clearance (CrCL), Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, sex, race, and renal replacement therapy status were recorded.

External predictive performance evaluation of polymyxin B POPPK models

NONMEM (Version 7.4.3; ICON Development Solutions) was used for external evaluation. R software (Version 4.0.2; R Foundation for Statistical Computing) was used to postprocess NONMEM output and generate graphics. The published POPPK models were employed using reported model equations, parameter values, covariate relationships, interpatient variability, parameter covariance, and unexplained residual variability; the latter, when not reported, was set to values corresponding to the published assay sensitivity and lower limit of quantification. For each model, polymyxin B concentrations were simulated using dosing regimens, sampling times, and covariate information from the EVD.

Prediction-based diagnostics

Based on the observed concentration (C_{obs}) and population prediction (C_{pred}), the prediction error percentage

TABLE 1 Patient characteristics and study design

Model reference	PK study	No. of patients	Age, year	Weight, kg	Creatinine clearance, ml/min	Model reference	Daily dose, mg	Infusion duration range, h	Dose frequency	No. of PK samples (no. of samples per patient)	Model reference	Sampling times	Assay
EVD	External data set	40	60 (18–90)[a]	72 (32.5–122)[a]	62.0 (19.3–322)[a]	EVD	180 (100–300)[a]	1–5	q12h	230 (5.8)	EVD	After end of infusion between days 1 and 5: pre-dose, 0.5, 1, 2, 6, and 12 h	B1 + B2 LLOQ: 0.05 mg/L %CV: 8.39%
M1	Kubin et al.[22]	43	58 (39–69)[b]	78 (59–95)[b]	73 (40–113)[b]	M1	160 (120–240)[b]	1	q12h–q2d	134 (3.1)	M1	On or after day 3: trough and 15–60 min postinfusion	B1 + B2 LLOQ: 100 ng/ml %CV: 5.9%
M2	Manchandani et al.[23]	35	58.7 ± 15.1 (25–89)[c]	57.7 ± 15.6 (36–112)[c]	67 ± 42 (15–175)[c]	M2	119 ± 36.6 (65–240)[c]	1–3	q12h–q.d.	139 (4.0)	M2	Steady state after fourth or greater dose after end of infusion: trough, 1–2 h, 8–12 h, trough	B1 + B2 + B3 + B1-Ile LLOQ: 50 ng/ml %CV: 5.11
M3	Sandri et al.[24d]	24	61.5 (21–87)[a]	62.5 (41–250)[a]	33 (10–143)[a]	M3	150 (80–500)[a]	1–4	q12h–q.d.	192 (8.0)	M3	On or after 48 h of treatment: predose trough, 5 min, 0.5, 1, 2, 4, 8 h after infusion, trough	B1 + B2 LLOQ: 0.05 mg/L %CV: 8.39%
M4	Wang et al.[25]	46	46 (18–94)[a]	70 (45–98)[a]	89.3 (15.6–315.2)[a]	M4	(100–200)[a]	0.5–2	q12h	331 (7.2)	M4	Steady state after 3 days of therapy: predose trough, 0.5, 1, 1.5, 2, 4, 6, and 8 h	B1 + B2 LLOQ: 0.2 mg/L %CV: 13.9%
M5	Wang et al.[11] NRF[e]	37	47.3 ± 17.7[c]	68.6 ± 11.6[c]	123.3 (81.6–315.2)[c]	M5	(100–200)[a]	0.5-2[f]	q12h	462 with RI group (6.6)[g]	M5	Steady state after 3 days of therapy: predose trough, 0 to 1, 2 to 4, and 6 to 10 h after infusion	B1 + B2 LLOQ: 0.2 mg/L %CV: 13.9%
M6	Wang et al.[11] RI[e]	33	54.2 ± 17.5[c]	66.9 ± 11.1[c]	42.0 (15.6–77.6)[c]	M6	(100–200)[a]	0.5-2[f]	q12h	462 with NRF group (6.6)[g]	M6	Steady state after 3 days of therapy: predose trough, 0 to 1, 2 to 4, and 6 to 10 h after infusion	B1 + B2 LLOQ: 0.2 mg/L %CV: 13.9%
M7	Yu et al.[26]	32	63.63 ± 12.92[c]	61.73 ± 11.77[c]	86.58 ± 53.00 (9.12–146.7)[c]	M7	136.6 (100–200)[c]	NR	q12h–q.d.	112 (3.5)	M7	Collected 48 h after starting therapy C_{max} (30 min after infusion ends) and C_{trough} (30 min before start of infusion)	B1 + B2 + B1-Ile LLOQ: 0.1 mg/L %CV: 10%

Abbreviations: B1, polymyxin B1; B1-Ile, polymyxin B1-isoleucine; B2, polymyxin B2; %CV, percentage coefficient of variation; C_{max}, maximum (peak) plasma drug concentration; C_{trough}, trough concentration; EVD, external validation data set; LLOQ, lower limit of quantification; NR, not reported; NRF, normal renal function subpopulation; PK, pharmacokinetic; q.d., every day; q2d, every 2 days; q12h, every 12 h; RI, renal insufficiency subpopulation.

[a]Data represent the median (range).

[b]Data represent the median (interquartile range).

[c]Data represent the mean ± standard deviation (range).

[d]APACHE II score median (range): 21.5 (10–29).

[e]M5 and M6 differentially compared and modeled two patient subsets from a single study ($N = 70$) based on renal function.

[f]Assumed to be the same as M4.[25]

[g]Number of samples per patient were calculated from the sum of patients and samples in the single study ($N = 70$). Number of samples collected from each patient subset were not reported.

(PE%) and absolute prediction error percentage (APE%) were calculated using Equations (1) and (2), respectively:

$$\mathrm{PE}(\%) = \frac{C_{pred} - C_{obs}}{C_{obs}} \times 100\% \quad (1)$$

$$\mathrm{APE}(\%) = \left| \frac{C_{pred} - C_{obs}}{C_{obs}} \right| \times 100\% \quad (2)$$

The median prediction error (MDPE) and the median absolute prediction error (MDAE) were used to evaluate the accuracy and precision of the predictive performance, respectively. The PE% within ±20% (F_{20}) and the PE% within ±30% (F_{30}) were calculated as joint predictors of accuracy and precision.[33] Predictive performance of candidate models was considered satisfactory if |MDPE| ≤ 20%, MDAE ≤ 20%, $F_{20} \geq 30\%$, and $F_{30} \geq 45\%$.[33] Further prediction-based diagnostics using Bayesian forecasting are described in the Supplementary Methods.

Simulation-based diagnostics

The predictive performance of each POPPK model was evaluated by performing Monte Carlo simulations (MCS; $n = 1000$) in NONMEM using patient characteristics, dosing, and the sampling scheme from the EVD. The prediction-corrected visual predictive check (pcVPC)[34] profiles were used to visually assess if prediction-corrected simulations generated by a candidate model deviated from prediction-corrected observed data. This helped determine if intrapatient and interpatient variability were sufficiently specified in each model to reproduce the central trend and variability in the EVD while accounting for differences in dosing and patient covariates.

Normalized prediction distribution errors (NPDE) based on MCS were used to assess if the model-simulated concentrations followed a normal distribution.[35,36] The mean and variance of the NPDE calculated using the Wilcoxon signed-rank test and Fisher test for variance, respectively, were used to ascertain if the models correctly described the observed PK data. Skew and kurtosis of the NPDE were used to assess normality using the Shapiro–Wilk test. In addition, the NPDE versus time from most recent dose and versus predicted concentration plots for each model were visually inspected.

PK profile comparison

To directly compare the different model-predicted PK profiles, a dosing regimen based on median dosing information across studies was simulated for a standardized patient. Dosing was simulated for 3 days to simulate steady-state PK. Simulated PK from each model was plotted and visually inspected. Sampling times reported in each study were included in the plots to visually assess the impact of PK sampling schemes on PK characterization. AUC of the simulated concentration profile over the dose interval (AUC_τ) was calculated for each model using the linear trapezoidal rule in R using the "pmxTools" package (Version 1.2.1).

RESULTS

Literature search and review of published POPPK analyses

Seven polymyxin B POPPK models based on POPPK data from six studies in patients who were critically ill were included for external evaluation (referred to as M1 to M7).[11,22–26] Two studies were conducted at multiple sites (M2 and M3). Dosing information, PK sampling strategy, and patient characteristics for each study are described in Table 1, whereas patient demographics, that is, mean/median age (46–63 years), weight (58–78 kg), and CrCL range (33–123 ml/min) are visualized in Figure S1. Of note, one study separately modeled then compared two patient subsets based on renal function: patients with normal renal function, M5, and those with renal insufficiency, M6. In addition, M4 studied a subset of patients from M5 and M6. All studies excluded patients on renal replacement therapy with the exception of M3, which included 2/24 (8.3%) patients on renal replacement therapy. Liquid chromatography–mass spectrometry assays were used in all studies to determine polymyxin B concentrations.

The median daily doses ranged from 119 to 160 mg/day. M4, M5, M6, and M7 reported fixed polymyxin B dosing. All models were based on intravenous administration of polymyxin B with linear first-order elimination. Infusion durations, when reported, ranged from 0.5 to 4 h. Across all studies, polymyxin B was most commonly administered twice daily; however, four studies included patients dosed daily or once every 2 days. M3 had the largest polymyxin B daily dose range resulting from the high dose administered to a 250 kg patient. The number of patients, PK samples per patient, and total PK samples used to develop each model are compared in Figure S2. M3, M4, M5, and M6 used intensive sampling (six or more samples per patient), collected 150 or more PK samples, and described polymyxin B PK using a two-compartment model. Conversely, M1, M2, and M7 collected fewer than 150 PK samples with four or fewer samples per patient and described polymyxin B PK with a one-compartment model.

Table 2 details the models. Patient characteristics that were significant predictors of polymyxin B PK variability were included in three models. Total body weight was included in M3 as a predictor of variability for both the volume of distribution and clearance. Renal function (CrCL) was a predictor of variability for clearance in M4 and M7. Typical clearance values across studies ranged from 1.58 (M6) to 2.5 (M2) L/h. The typical volume of distribution ranged from 17.6 L (sum of compartment volumes for central and peripheral in M6) to 34.4 L (volume of central compartment in M1). Across studies, the mean (percentage coefficient of variation [%CV]) population estimate for volume of distribution for the one-compartment and two-compartment models was 29.7 L (27%) and 20.8 L (25%), respectively, indicating moderate interstudy variability, whereas the mean population estimate for clearance for the one-compartment and two-compartment models was 2.15 L/h (23%) and 1.86 L/h (14%), respectively, indicating a relatively small interstudy variability. Interpatient variability (%CV) was generally higher for volume parameters than clearance across models, ranging from 16% (M1) to 88% (M5) and 13% (M7) to 51% (M6), respectively (M7 did not estimate interpatient variability for volume).

External validation data set cohort

The EVD included 230 PK samples from 40 patients who were critically ill: 22 male patients; 27 White, four Black, and nine Asian patients; and eight patients on renal replacement therapy. The median (range) of the age, weight, CrCL, and APACHE II score was 60 years (18–90), 72 kg (32.5–122), 62.0 ml/min (19.3–322), and 17 (0–41), respectively. Patients received polymyxin B doses from 100 to 300 mg/day twice daily as intravenous infusions for 1 to 5 h. All patients were sampled between days 1 and 5, except for two patients sampled on days 6 and 11.

Assessment of the predictive performance of published polymyxin POPPK models

Prediction-based diagnostics

The residual unexplained variability was not reported for M2 and was assumed to have a combined error model based on the reported assay description: 0.05 mg/L additive error and 5.11% proportional error.

Figure 1 displays the observed EVD versus population-predicted concentrations when each model was implemented in NONMEM. The PE% for each model is shown in Figure 2. Accuracy and precision measures generated for each model from the prediction errors are provided in Table 3. All models had an MDPE < 0, indicating median underprediction of the observed plasma concentrations in the EVD. M7 had an MDPE closest to 0 (−16.3%) and the lowest MDAE (32.0%), indicating that this model had better accuracy and precision of population estimates, respectively, than the other models. In addition, M7 had the best relative accuracy and precision as characterized by an F_{20} of 31.1% and an F_{30} of 46.5%. M4 and M6 were the second and third most predictive models based on these values, respectively.

Simulation-based diagnostics

pcVPC plots of prediction-corrected plasma polymyxin B concentrations versus time since last polymyxin B dose (Figure 3) indicated systematic underprediction of the EVD by all models. The deviation of the prediction-corrected confidence intervals of the observed data from the simulated data across all percentiles demonstrated that the PK parameters of all candidate POPPK models were unable to describe EVD PK. Although simulated data for M4 and M6 were within the 90% prediction interval of observed data at the 5th and 95th percentiles, these models underpredicted the EVD at the 50th percentile, indicating slight misspecification of parameter estimates. Large deviations between observed and simulated data at specific confidence intervals demonstrated that intrapatient and interpatient variability were inadequately described, as in the case of the 5th percentile in M7.

NPDE distributions were not normally distributed for any model (Figure S3, Table S1), indicating that these models poorly described the EVD when accounting for intrapatient and interpatient variability. However, M4, M5, and M6 had NPDE distributions within expected confidence intervals at early timepoints, indicating that these models adequately characterized the EVD immediately following polymyxin B administration (Figure S4). Only M4 predicted the EVD well across the dosing interval based on NPDE plots. However, when assessing NPDE relative to predicted concentration (Figure S5), M4 poorly characterized the EVD at low concentrations, and no model characterized the EVD well across the predicted concentration range.

PK profile comparison

The dosing regimen used to explore differences in predicted PK profiles across studies was a 75 mg polymyxin B dose infused for 2 h every 12 h. A 71 kg patient with a CrCL of 71.9 ml/min was used to standardize the PK profile based on patient characteristics across the evaluated models. Figure 4 shows PK curves simulated for

TABLE 2 Model summary of published POPPK Polymyxin B models

Model reference	Modeling software	Structural model	Parameter values and covariate relationships	Interpatient variability (%)	RUV
M1	Monolix 2016R1 (SAEM)	1 CMT	CL (L/h) = 2.37 V (L) = 34.4	CL = 37.7 V = 15.7	Add = 0.00693 mg/L Prop = 23.3%
M2	ADAPT 5 (MLEM)	1 CMT	CL (L/h) = 2.5 V (L) = 34.3	CL = 43.8 V = 47.8 Cov = 12.8	
M3	S-ADAPT (1.57) (MCPEM)	2 CMT	CL (L/h) = 1.87 × (BW/70) V1 (L) = 6.35 × (BW/70) V2 (L) = 22.3 × (BW/70) Q (L/h) = 9.86 × (BW/70)	CL = 32.4 V1 = 73.3 V2 = 70.1 Q = 50.4	Add = 0.05 mg/L Prop = 8.39%
M4[a]	Phoenix NLME (7.0)	2 CMT	CL (L/h) = 1.79 × (CRCL/105.9)$^{0.362}$ V1 (L) = 6.22 V2 (L) = 11.92 Q (L/h) = 13.52	CL = 0.208 V = 0.318 V2 = 0.690 Q = 1.508 Corr V–CL = 0.713 Corr V–V2 = 0.667 Corr CL–V2 = 0.571	Prop = 11%
M5[a]	Phoenix NLME (7.0)	2 CMT	CL (L/h) = 2.19 V1 (L) = 6.87 V2 (L) = 11.97 Q (L/h) = 13.83	CL = 0.22 V = 0.78 V2 = 0.32 Q = 0.68 Corr V–CL = 0.57 Corr V–V2 = 0.83 Corr CL–V2 = 0.76	Prop = 13%
M6[a]	Phoenix NLME (7.0)	2 CMT	CL (L/h) = 1.58 V1 (L) = 6.98 V2 (L) = 10.57 Q (L/h) = 10.28	CL = 0.26 V = 0.38 V2 = 0.74 Q = Fixed Corr V–CL = 0.75 Corr V–V2 = 0.46	Prop = 10%
M7	NONMEM (7.4)	1 CMT	CL (L/h) = 1.59 × (CRCL/80)$^{0.408}$ V (L) = 20.5	CL = 13 V = Fixed	Prop = 40.5%

Abbreviations: Add, additive residual unexplained error; BW, body weight; CL, total body clearance; CMT, compartment; Corr, parameter correlation; Cov, parameter covariance; CRCL, creatinine clearance; MCPEM, Monte Carlo parametric expectation maximization; MLEM, maximum likelihood expectation maximization; Prop, proportional unexplained error; Q, intercompartmental clearance; RUV, residual unexplained variability; SAEM, stochastic approximation expectation maximization; V, volume of distribution; V1, typical volume of central compartment; V2, typical volume of peripheral compartment.

[a]Interpatient variability is represented by the log-normal variance of population means.

each model with nominal sampling times of each study marked with a circle. Four of the five models that predicted high maximum (peak) plasma drug concentration (C_{max}) were two-compartment models with robust sampling early in the distribution phase, whereas the two models that predicted low C_{max} values were one-compartment models with sparse sampling during the same period. M3, M4, M5, and M6, studies with intensive sampling during the distribution phase, described the PK using a two-compartment model. The AUC_{τ} for the two-compartment models (%CV, 15%) varied less compared with the one-compartment models (%CV%, 79%).

DISCUSSION

This is the first study to systematically evaluate the predictive performance of published POPPK models for polymyxin B by external validation. A previous analysis examined bias in five polymyxin B POPPK models by calculating the predicted AUC based on the population clearance estimates.[37] However, the analysis did not account for the random variability predicted by these models nor for the potential sources of bias. Our work helps assess the rigor of existing population analyses to determine (i) if the study designs were appropriate to identify a covariate relationship, (ii) if an identified

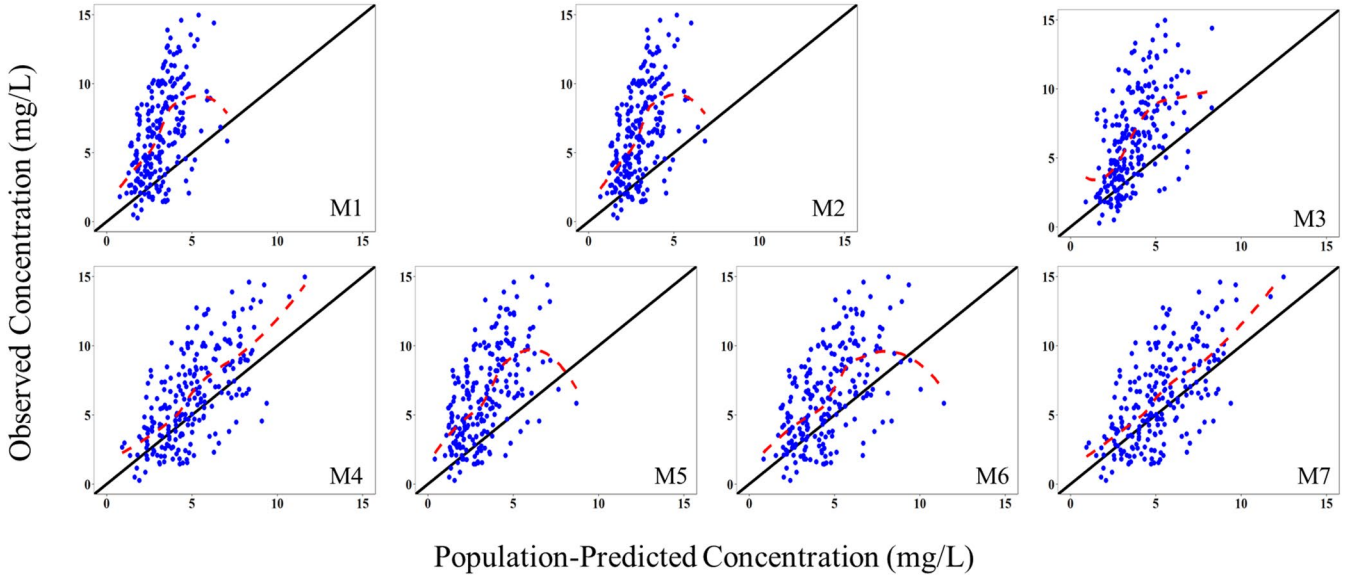

FIGURE 1 Observed versus predicted PK. The observed polymyxin B concentration (mg/L) is plotted against the population-predicted polymyxin B concentration (mg/L) for each of the seven models (denoted M1 through M7). Data points are depicted as blue circles and the line of unity as a black line. A locally estimated scatterplot smoothing–transformed line (red) depicts the local trends of the data.

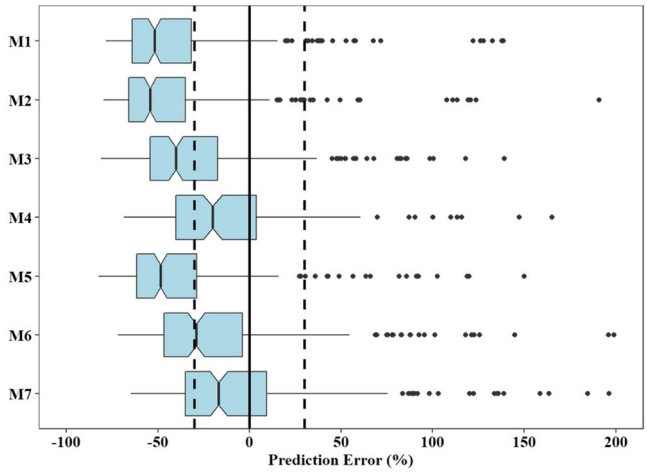

FIGURE 2 Prediction errors. Boxplots of the prediction error (x-axis) for each model (y-axis). Solid vertical line represents 0% prediction error. Dashed vertical lines represent ±30% prediction error. Notches on the boxplots represent the 95% confidence intervals of the median prediction error for each model (denoted M1 through M7). Black dots represent prediction errors that are beyond 1.5-fold of the interquartile range.

TABLE 3 Precision and accuracy assessment of published POPPK models of polymyxin B

Model reference	MDPE (%)	MDAE (%)	F_{20} (%)	F_{30} (%)
M1	−51.8	54.3	7.46	13.6
M2	−54.0	56.2	8.77	13.6
M3	−40.1	44.4	26.2	27.6
M4	−20.1	32.8	29.4	43.9
M5	−48.5	50.6	12.3	19.3
M6	−27.8	37.8	24.1	35.5
M7	−16.3	32.0	31.1	46.5

Note: F_{20} fraction of values within ±20% prediction error, and F_{30} fraction of values within ±30% prediction error.

Abbreviations: MDPE, median prediction error; MDAE, median absolute prediction error; POPPK, population pharmacokinetic.

covariate relationship was appropriate, and (iii) the bias in interindividual and residual variability. This analysis assists in identifying models that are useful for exploring "what if" scenarios for informing polymyxin B dosing.[17] Based on our analysis, all seven published polymyxin B POPPK models evaluated did not adequately describe the observed polymyxin B PK in the EVD. We explored differences in study design, number of patients, sampling strategy, and patient characteristics between studies as potential factors that could influence model development and performance.

POPPK models based on studies with relatively large patient populations and an informed sampling strategy (six or more plasma samples per patient) characterized polymyxin B PK of the EVD better overall. Optimal sampling over the distribution phase improved the assessment of the number of compartments needed to effectively characterize polymyxin B PK and the interindividual variability.[18,19,38] Two-compartment models characterized polymyxin B PK best: M4 and M6 were based on data from studies that used robust and intensive sampling, resulted in better characterization of interpatient variability, and identified covariance relationships. However, M4 reported

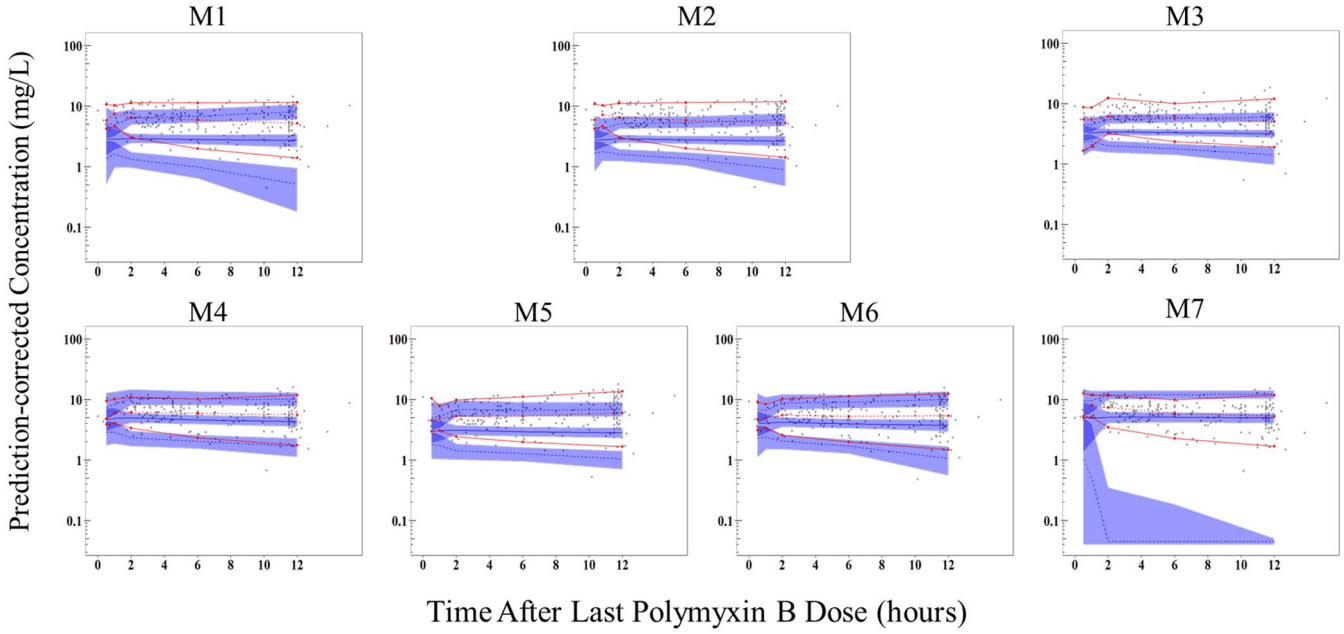

FIGURE 3 Prediction-corrected visual predictive checks of the simulations. A total of 1000 Monte Carlo simulations of the pharmacokinetics of polymyxin B for each model (denoted M1 through M7) were run using the external validation data set. The 5th, 50th, and 95th percentiles of prediction-corrected simulated data and prediction-corrected observed data over time are plotted relative to the most recent polymyxin B dose. The prediction-corrected observed data are represented by gray dots. Confidence intervals of the 5th, 50th, and 95th percentiles of the prediction-corrected observed data are represented by red lines. Confidence intervals of the 5th, 50th, and 95th percentiles of the prediction-corrected simulated data are represented by blue lines. The 90% prediction interval around each prediction-corrected simulated confidence interval are represented by the blue-shaded regions

extremely high variability for the intercompartment clearance parameter Q (122%), with no explanation (such as patient characteristics) provided that might explain this high variability. Despite intensive sampling, M6 could not identify covariates explaining interpatient variability given the small patient sample size ($N = 33$). M2 had the highest bias among the seven models, probably attributable to the study design and sampling strategy. Of the three samples collected per patient, the first sample was obtained up to 2 h following the end of infusion and likely resulted in an overall lower observed C_{max} and concentration-time profile.

The two-compartment models had more consistent measurements of AUC_{τ} (based on %CV), however, discrepancies in sampling strategies between the two groups of model structures resulted in differences in simulated C_{max}, AUC_{τ}, and volume estimates. Robust sampling during the distribution phase, as seen in M3, M4, M5, and M6, resulted in lower volume estimates and a more descriptive, consistent characterization of PK between peak and trough concentrations. M3 had lower simulated PK concentrations over the distribution phase 3 h after dosing compared with M4 and M6. This is because M3 had larger intercompartmental clearance and a tissue compartment volume, V2, nearly double that of M4, M5, and M6. Differences in the volume estimates may be attributed to differences in protein binding between studies. However, protein binding was only reported in M3 (median, 58%). Comparatively, the one-compartment models, M1 and M2 with sampling later in the distribution phase combined with sparse sampling, estimated a higher volume of distribution and therefore predicted a lower drug exposure with greater AUC_{τ}. However, M7, another one-compartment model with reduced sampling in the distribution phase, had a lower volume estimate and had higher simulated C_{max} and AUC_{τ} inconsistent with M1 and M2. A sparse and ill-informed sampling strategy combined with small sample size makes characterization of polymyxin B PK and interpatient variability challenging.[18–20]

Based on our assessment of the prediction-based diagnostics, M7 best predicted population PK of the EVD before taking PK variability into account. The next best predictors of population PK were the two-compartment models M4 and M6. Bayesian forecasting, which assesses the influence of observed concentrations on model predictability, found M4 and M6 best predicted observed PK of the EVD. Based on the simulation-based diagnostics (pcVPC plots and NPDE analysis), which take interpatient and unexplained variability into account, all of the reviewed models underpredicted the EVD and deviated from the observed PK. M4 and M6 extensively

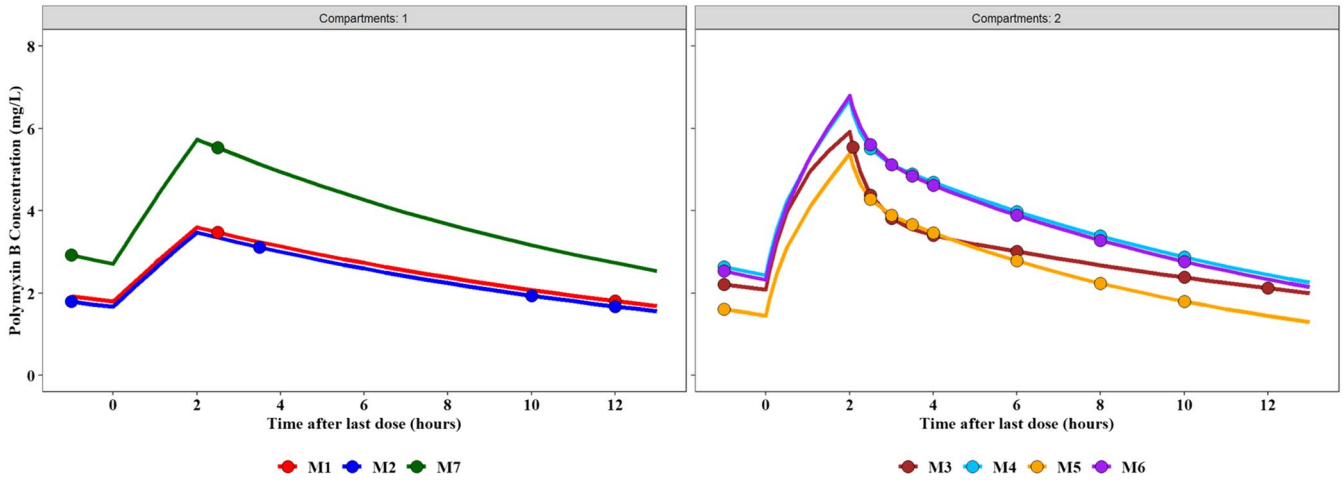

FIGURE 4 Pharmacokinetic (PK) profile comparison. A median dose regimen of 75 mg 2-h infusions of polymyxin B every 12 h for 3 days was simulated in each model (denoted M1 through M7) in a standardized patient. PK was simulated to steady state after the sixth dose on day 3. PK curves represent the population-predicted value without variability for each model. The number of PK samples collected per patient are parenthesized for each model. Points represent the sampling scheme from each study design as described in the literature. The predicted maximum (peak) plasma drug concentration range for one-compartment (left) and two-compartment (right) models with the given dose regimen and sampling scheme are 3.11–5.53 mg/L and 4.28–5.60 mg/L, respectively. The predicted area under the plasma concentration–time curve of the simulated concentration profile over the dose interval range for one-compartment (left) and two-compartment (right) models were 17.7–74.0 mg/L·h and 19.7–28.6 mg/L·h, respectively

characterized the interpatient variability and PK parameter covariance, allowing them to predict the PK of the EVD better when random variability was included. Most published polymyxin B models reviewed here did not identify any covariates that could adequately describe the interpatient variability. Although M4 and M6 characterized random interpatient variability for each PK parameter, random variability for some parameters was greater than 85%. Inclusion of additional patient covariates for these PK parameters would help explain the random variability and increase POPPK model utility. This highlights the importance of effectively characterizing PK variability for models intended for clinical use: models with poor accounting of variability are ineffective for describing PK in patients that diverge from "typical."[17]

In addition to using patient information to describe PK differences within a study, the differences in drug characteristics within a study should be explored and reported as potential sources of variability. For example, polymyxin B has two main components (B1 and B2), which account for >80% of the total composition.[7] A previous analysis of the composition of polymyxin B at 1 mg/L from four different manufacturers found significant differences between B1 and B2 forms despite total polymyxin B concentrations not being significantly different.[39] PK characteristics of the two main polymyxin B components, when administered individually to Sprague-Dawley rats, were different. Plasma protein binding for B1 was higher compared with B2; however, there were no significant ($p > 0.05$) differences with regard to total clearance, volume of distribution, and the elimination half-life.[40] Most studies reviewed here employed assays that measured polymyxin B composition as the sum of B1 and B2. The assay used in M2 measured polymyxin B1 isoleucine and polymyxin B3 in addition to B1 and B2. This interstudy assay disparity may have an impact on the interpretability of the PK parameters described in these models. Future studies should consider polymyxin B composition as well as the major components measured by the assay.

Appropriateness of the external data set to assess each model needs consideration in light of the high degree of bias and imprecision found across the published models. Dosing in the clinical study used to generate the EVD was comparable with dosing described in the published models and is, therefore, an unlikely source of bias or imprecision. M3 incorporated body weight as a covariate, with a body weight range similar to the EVD (excluding the 250 kg patient in M3), enabling comparison of impact of weight on dosing. M4 and M7 reported CrCL as a clearance covariate, and the CrCL ranges in these studies were comparable with the CrCL range in the EVD. This indicates that EVD patient demographic and clinical factors were reflective of patient covariates identified while building these models. However, the clinical relevance of CrCL as a covariate needs to be taken into consideration given that polymyxin B has low renal excretory clearance and it is unclear if renal function impacts polymyxin B exposure.[11,24,41,42] As mentioned previously, disease

severity measurements such as APACHE II scores may explain some patient variability between studies, but M3 was the only study to report them. Descriptive patient demographics were recorded in each study, but additional information, such as measures of disease severity, was not reported in five of six studies, nor was it reportedly explored as a covariate. Therefore, disease severity was not used in this analysis. Disease severity, especially in patients who are critically ill, can impact PK in several ways as a result of altered fluid balance, clearance, and/or protein binding, leading to changes in volume compartment distribution.[15]

An additional limitation of this study is the ability to interpret the published models: not all publications provided methods and clear model descriptions. Despite using assay sensitivity information to describe residual unexplained variability for M2, the overall analysis was marginally impacted because several model assessment criteria used population-predicted concentrations and typical patient values (MDPE and MDAE), which are not affected by residual unexplained variability. In addition, infusion duration was not reported in M7. This may have limited our ability to assess potential sources of bias or imprecision; however, missing information did not impact the predictive analyses performed here.

Current polymyxin B POPPK models for patients who are critically ill described in the literature characterize the external data set inadequately, hence these models may be not suitable for *a priori* dose determination. Bayesian forecasting can improve individual patient PK characterization to optimize the dosing regimen based on the concentrations measured (observed) in the patients *a posteriori*.[43,44] However, no model was able to predict polymyxin B concentrations at high (>10 mg/L) concentrations, which is vital to prevent polymyxin-associated nephrotoxicity. The lack of alignment of these published population analyses with the aim of dosing polymyxin B appropriately in patients who are critically ill combined with their poor predictive performance emphasizes the need to develop such a POPPK model. The development of this POPPK model should be based on well-powered studies in the patient population of interest with an informed optimal PK sampling strategy to identify clinically as well as statistically relevant covariates that can adequately characterize polymyxin B PK and help explain interindividual variability within the studied population to dose polymyxin B appropriately. A large, ongoing, observational clinical study to assess the PK of polymyxin B in patients who are critically ill (NCT02682355) will provide the PK data necessary to develop a robust POPPK model for MIPD.

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CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.O.H. and G.G.R. wrote the manuscript. R.L.N., M.H.S., A.P.Z., A.M.S., A.L.K., B.P.Z.C., C.J.K., M.T.Y., J.L., K.S.K., and G.G.R. designed the research. P.O.H. performed the research. P.O.H., J.W., J.L., K.S.K., and G.G.R. analyzed the data.

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