Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens

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Background. Polymyxin B is a last-line therapy for multidrug-resistant gram-negative bacteria. There is a dearth of pharmacokinetic data to guide dosing in critically ill patients.

Methods. Twenty-four critically ill patients were enrolled and blood/urine samples were collected over a dosing interval at steady state. Polymyxin B concentrations were measured by liquid chromatography–tandem mass spectrometry. Population pharmacokinetic analysis and Monte Carlo simulations were conducted.

Results. Twenty-four patients aged 21–87 years received intravenous polymyxin B (0.45–3.38 mg/kg/day). Two patients were on continuous hemodialysis, and creatinine clearance in the other patients was 10–143 mL/min. Even with very diverse demographics, the total body clearance of polymyxin B when scaled by total body weight (population mean, 0.0276 L/hour/kg) showed remarkably low interindividual variability (32.4% coefficient of variation). Polymyxin B was predominantly nonrenally cleared with median urinary recovery of 4.04%. Polymyxin B total body clearance did not show any relationship with creatinine clearance ($r^2 = 0.008$), APACHE II score, or age. Median unbound fraction in plasma was 0.42. Monte Carlo simulations revealed the importance of initiating therapeutic regimens with a loading dose.

Conclusions. Our study showed that doses of intravenous polymyxin B are best scaled by total body weight. Importantly, dosage selection of this drug should not be based on renal function.

Keywords. polymyxins; pharmacokinetics; dose selection; plasma protein binding; urinary recovery.

The burgeoning multidrug resistance among gram-negative bacteria, combined with a paucity of new antibiotics, has led to the reemergence of polymyxins [1, 2]. There are 2 polymyxins used clinically, polymyxin B and colistin (ie, polymyxin E) [1, 2]. Both antibiotics were first used clinically in the late 1950s but were largely abandoned in the 1970s due to toxicity; however, they were reintroduced to the therapeutic arsenal in the last decade due to resistance to all other antibiotics [1–4].

Pharmacokinetics (PK)/pharmacodynamics (PD) of antibiotics is critical for optimizing their dosage regimens to maximize efficacy and minimize toxicity and resistance. Almost all modern PK studies on polymyxins are for colistin that is administered parenterally as its inactive prodrug, colistin methanesulfonate (CMS) [5]. In contrast, polymyxin B is available for direct parenteral administration, that is, as the antibacterial entity [2].
Recent PK studies have highlighted that the conversion of CMS to colistin occurs very slowly and incompletely in vivo [6, 7]. Therefore, current PK findings for CMS/colistin cannot be extrapolated to polymyxin B.

There are no scientifically based dosing guidelines for polymyxin B due to the lack of solid PK information. Reports on the PK of polymyxin B in humans have been limited to a small number of studies with 20 patients in total [8–11]. Even though a population PK study was reported in 9 adult patients [9], only 2 serum samples were collected from each patient and, unfortunately, only polymyxin B1 was measured, an approach leading to the potential for bias in defining polymyxin B PK. Furthermore, no urine samples were collected in that study and, therefore, urinary recovery and renal clearance of polymyxin B could not be obtained [9]. Importantly, the applicability of that study [9] to critically ill patients is limited. Hence, there is an urgent need to investigate the PK of polymyxin B in critically ill patients and to optimize its clinical use. In this study, we developed a population PK model for polymyxin B after intravenous administration in 24 patients with various degrees of renal function. Our aim was to identify patient factors influencing the PK and thereby allow proposing of dosage regimens to achieve a desired target plasma polymyxin B concentration. The study also provides important new information on the renal handling of polymyxin B that assists in understanding the potential for this antibiotic to cause nephrotoxicity.

PATIENTS AND METHODS

Patients and Ethics
The study was approved by the Ethical Committees of Hospital de Clínicas de Porto Alegre, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Hospital Nossa Senhora da Conceição, Brazil, and Monash University, Australia. Informed consent was obtained from all patients or their legal representatives. The decision to administer polymyxin B and its dosing regimen was made by the attending physician. From March 2011 to January 2012, 24 patients (aged ≥18 years) who received intravenous polymyxin B were included; the noncompartmental PK data of 2 patients on continuous venovenous hemodialysis (CVVHD) have been reported [11].

Polymyxin B Administration and Sample Collection
Blood samples were collected after ≥48 hours of treatment with polymyxin B (sulfate; Polymyxin B for Injection, Eurofarma, Brazil). Collection of urine samples was possible for 17 of the patients. Polymyxin B was administered by short-term infusions (60–240 minutes) every 12 hours (23 patients) or every 24 hours (1 patient). In each patient, 8 blood samples (3 mL each) were collected immediately before starting the infusion, 5 minutes, and 0.5, 1, 2, 4, and 8 hours after completing the infusion and immediately before the next infusion. Blood samples were centrifuged for 10 minutes (4000 g), and the plasma samples were immediately stored at −80°C until analysis. Urine was collected across the dosage interval (0–6 hours and 6–12 hours for 12-hourly dosing; 0–6 hours, 6–12 hours, and 12–24 hours for 24-hourly dosing) and the volumes were recorded; 5 mL of each collection was stored at −80°C pending analysis.

Binding of Polymyxin B in Plasma
Plasma protein binding of polymyxin B was determined by rapid equilibrium dialysis [11]. For each patient, 3 plasma samples were pooled (pH adjusted to 7.4) and 1 mL was dialyzed against an equal volume of isotonic phosphate-buffered saline (pH 7.4) at 37°C for 4 hours. Polymyxin B concentrations were determined (described below), and unbound fraction in plasma (fu) was calculated as the ratio of the concentration in buffer to that in plasma.

Quantification of Polymyxin B Concentrations
Polymyxin B (base) concentrations in samples were quantified by monitoring both polymyxin B1 and B2 using a validated ultraperformance liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay [11]. Analysis of independently prepared quality control samples indicated good reproducibility (coefficients of variation ≤8.39%) and accuracy (measured concentrations ≤10.0% from target concentrations). The limit of quantification was 0.05 mg/L.

Pharmacokinetic Analysis
Nonlinear mixed-effects modeling of polymyxin B population PK was performed utilizing the S-ADAPT platform (version 1.57) with the Monte Carlo parametric expectation maximization algorithm [12]. The SADAPT-TRAN program was used for pre- and postprocessing [13, 14]. One-, 2-, and 3-compartment models were explored for the polymyxin B plasma concentration-time profiles with linear or nonlinear (saturable) elimination. These models were fit to the data for all patients simultaneously. The interindividual variability was assumed to be log-normally distributed. Candidate covariates that were explored for their possible effect on polymyxin B disposition included the following: body size (total body weight [TBW] and lean body weight [LBW]), sex, age, creatinine clearance (CrCL), serum albumin concentration, and APACHE II score on total body clearance (CL) of polymyxin B; and body size (TBW and LBW) on volume of distribution. CrCL was calculated using the Cockcroft-Gault equation with LBW [15]. For model evaluation, plots of observed versus individual-fitted and observed versus population-fitted polymyxin B concentrations, the normalized prediction distribution error, and the objective function in S-ADAPT were utilized. Polymyxin B renal clearance...
(CL\textsubscript{R}) was calculated as the amount recovered in urine during the urine collection period divided by the area under the plasma concentration-time curve (AUC) across the same period. Because only unbound drug in plasma is filtered at the glomeruli, the clearance of polymyxin B by glomerular filtration (CL\textsubscript{GF}) was estimated as \(fu \times \text{GFR}\) (where GFR is glomerular filtration rate from CrCL) [16]. The percentage of polymyxin B reabsorbed from tubular urine was calculated as \(100 \times (1 - \frac{\text{CLR}}{\text{CLGF}})\); the percentage of water reabsorbed was similarly determined as \(100 \times (1 - \frac{\text{urine flow rate}}{\text{GFR}})\). The number of milligrams per day of polymyxin B filtered at the glomeruli was calculated by multiplying the polymyxin B average steady-state plasma concentration (Css,avg, mg/L) with its filtration clearance (CL\textsubscript{GF}/day); the milligrams of polymyxin B per day reabsorbed by the renal tubular cells was then estimated from the percentage of the filtered polymyxin B that was reabsorbed.

### Monte Carlo Simulations of Dosage Regimens

Simulations with between-subject variability (BSV) were performed for various clinically relevant dosage regimens scaled by TBW. The regimens were as follows: (1) 1.25 mg/kg as a 1-hour infusion every 12 hours; (2) 2 mg/kg as a 2-hour infusion loading dose followed 12 hours later by 1.25 mg/kg as a 1-hour infusion every 12 hours; (3) 1.5 mg/kg as a 1-hour infusion every 12 hours; (4) 2.5 mg/kg as a 2-hour infusion loading dose followed 12 hours later by 1.5 mg/kg as a 1-hour infusion every 12 hours; (5) continuous infusion of 2.5 mg/kg/24 hours; and (6) 2 mg/kg as a 2-hour infusion loading dose immediately followed by continuous infusion of 2.5 mg/kg/24 hours. For each dosage regimen, 5000 virtual subjects were simulated using NONMEM software (version VI, level 1.2) [17].

### RESULTS

Demographic data of the 24 intensive care patients are presented in Table 1. TBWs ranged from 41 kg to 110 kg in 23 patients, and 1 patient was extremely obese at 250 kg. A large range of renal functions was observed. The physician-selected dose of polymyxin B was 0.45–3.38 mg/kg/day; 23 patients received the drug every 12 hours, whereas the patient who was prescribed the lowest daily dose received it every 24 hours.

Plasma polymyxin B concentration-time profiles arising from the physician-selected dosage regimens are presented in Figure 1. The AUC over a day (AUC\textsubscript{0–24 hours}) from the population PK analysis was 66.9 ± 21.6 mg/hour/L (range, 16.4–117 mg/hour/L), and therefore the average steady-state plasma concentration (Css,avg) ie, AUC\textsubscript{0–24 hours}/24 hours) was 2.79 ± 0.90 mg/L (range, 0.68–4.88 mg/L). The polymyxin B concentrations from the 2 CVVHD patients [11] were within the range of concentrations observed in non-CVVHD patients (Figure 1).

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.5 (21–87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Total body weight, kg</td>
<td>62.5 (41–250)</td>
</tr>
<tr>
<td>Lean body weight, kg</td>
<td>46.0 (29–99)</td>
</tr>
<tr>
<td>Estimated creatinine clearance (mL/min)</td>
<td>33 (10–143)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.5 (10–29)</td>
</tr>
<tr>
<td>Coadministered antibiotic(s)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>With renal replacement therapy</td>
<td></td>
</tr>
<tr>
<td>Continuous renal replacement</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values are median (range) or No. (%).

The time course of polymyxin B concentrations was well described by a 2-compartment disposition model with constant-rate, short-term infusion input and linear (ie, nonsaturable) elimination. The population PK model provided excellent fits to the observed concentration-time profiles for individual patients (Figure 2), and the individual-fitted and population-fitted concentrations were unbiased and adequately precise (Figure 2). As only 12.2% and 5.62% of polymyxin B was

### Figure 1. Plasma concentration-time profiles of polymyxin B in 24 patients. Concentrations from the 2 patients undergoing continuous venovenous hemodialysis [11] are shown by filled symbols.
The concentration-time profiles from all patients (ie, on and not on renal replacement therapy) were successfully described simultaneously with one set of population PK parameter estimates (Table 2). Linear scaling of clearances and volumes of distribution by TBW reduced the unexplained BSV (%CV) by 3.4% for CL and 41.7% for the central volume of distribution (V1). Allometric scaling of CL (scaled by TBW^{0.75}) performed slightly better than linear scaling. Linear and allometric scaling by LBW performed similarly as TBW. For simpler clinical implementation, the results from the model with linear scaling by TBW are reported in Table 2. The BSV in clearance (CV 32.4%, Table 2) was remarkably low in this critically ill patient population with a wide range of body weights and renal functions. After scaling of clearances and volumes of distribution by TBW, the parameter estimates for the 2 patients receiving CVVHD, including the patient with 250-kg TBW, were within the range of estimates from the other patients, as shown for CL in Figure 3. Importantly, neither the unscaled \((P = .68, r^2 = 0.008)\) nor scaled \((P = .22,
$r^2 = 0.068$) polymyxin B CL showed any relationship with CrCL (Figure 3). Furthermore, no relationships were identified between CL of polymyxin B and APACHE II score, sex, age, or serum albumin concentration.

The median unbound fraction in plasma of polymyxin B was 0.42 (range, 0.26–0.64; n = 23) and was independent of concentration ($P > .05$, $r^2 = 0.13$). The mean (±SD) of the AUC for unbound polymyxin B (AUC$_{24}$ hours) was 29.2 ± 12.0 mg hour/L (range, 6.05–60.5 mg hour/L). Urinary excretion data were available from 17 patients. The median percentage of the polymyxin B dose that was excreted unchanged in urine was 4.04% (range, 0.98%–17.4%), and the median renal clearance (CLR) was 0.061 L/hour (range, 0.018–0.377 L/hour). The CLR of polymyxin B was a small percentage of CLGF in every patient (median, 9.7%; range, 0.75%–27.9%). Thus, a large percentage of polymyxin B filtered at the glomerulus was reabsorbed (median, 90.3%; range, 72.1%–99.2%); by comparison, the median percentage of filtered water that was reabsorbed was 96.4% (range, 85.7%–99.0%). There was a trend for the percentage of filtered polymyxin B that was reabsorbed to increase with creatinine clearance; the result being that there was a strong linear relationship ($P < .0001$, $r^2 = 0.90$) between the amount of polymyxin B reabsorbed per day, scaled to the daily dose, to increase with CrCL (Figure 4). The exposure to polymyxin B with various dosage regimens, predicted from the Monte Carlo simulations, is quantified in Table 3.

**DISCUSSION**

This polymyxin B population PK study has made a significant contribution to understanding of how to optimize the clinical use of this important last-line antibiotic in critically ill patients. It is the first study to demonstrate that total body weight is a patient characteristic that influences polymyxin B PK and that the total body clearance, and hence daily dose requirement, of polymyxin B is not affected by kidney function.

Scaling of clearances and volumes of distribution by TBW resulted in unbiased fits for all patients, including the extremely obese patient (250 kg), and an overall reduction in the BSV. Thus, loading and maintenance doses for polymyxin B are best scaled by TBW; this finding informed the manner in which the Monte Carlo simulations were conducted.
Polymyxin B CL scaled by TBW displayed only modest interindividual variability, particularly given the very diverse demographics including sex, age, renal function, and severity of illness. Notably, despite the wide range of renal function across the patients, this patient characteristic was not a determinant of polymyxin B CL (Figure 3). That renal function did not influence polymyxin B CL is in keeping with the fact that only a small percentage of the dose was excreted in urine as unchanged drug, as we have previously reported [8]. Non–renal clearance has also been demonstrated to be the major elimination pathway of polymyxins in rats [16, 18].

As polymyxin B CL was not related to CrCL (Figure 3), its daily doses should not be based on renal function. This contrasts strongly with colistin wherein daily doses need to be tailored to renal function, because the latter is administered as the predominantly renally eliminated prodrug CMS [7]. Decreasing daily doses of polymyxin B for patients with poor renal function may lead to suboptimal plasma exposure, with potentially adverse consequences on clinical and microbiological outcomes and development of resistance. Physicians should balance the risk of polymyxin-induced nephrotoxicity against the benefit of maintaining adequate doses of polymyxin B, particularly in patients with declining renal function. It should be noted that the benefit of higher polymyxin B dosage regimens (≥200 mg/day) on overall hospital mortality remained even for patients who developed moderate or severe renal impairment during therapy [19].

The Monte Carlo simulations indicated that dosage regimens not involving a loading dose resulted in exposure to polymyxin B across day 1 that was substantially lower than the exposure achieved on day 4 (ie, at steady state). It should be noted that even though loading doses have been proposed for CMS, several hours’ delay occurs in the achievement of Cmax of the antibacterial entity colistin because of the slow formation from the prodrug CMS [6, 7, 20, 21]. Our data clearly show the potential PK/PD advantage of polymyxin B versus CMS after intravenous administration and the importance of employing a loading dose to achieve optimal plasma exposure of polymyxin B as soon as possible.

The fAUC/minimum inhibitory concentration (MIC) has been shown to be the most predictive PK/PD index for the in vivo antibacterial activity of colistin [22, 23]. In the thigh infection model, the fAUC/MIC values for 2-log bacterial killing

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**Table 3. Polymyxin B Exposure for 6 Different Dosage Regimens on the First and Fourth Day of Treatment Based on Monte Carlo Simulations**

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 1</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>P&lt;sub&gt;10&lt;/sub&gt;</td>
<td>P&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Day 1</td>
<td>2.59</td>
<td>5.17</td>
</tr>
<tr>
<td>Day 4</td>
<td>4.34</td>
<td>7.09</td>
</tr>
<tr>
<td>2 mg/kg loading as 2-h infusion, followed by 1.25 mg/kg q12h as 1-h infusion&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Day 1</td>
<td>3.06</td>
</tr>
<tr>
<td>Day 4</td>
<td>4.35</td>
<td>7.06</td>
</tr>
<tr>
<td>1.5 mg/kg q12h as 1-h infusion</td>
<td>Day 1</td>
<td>3.11</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.20</td>
<td>8.51</td>
</tr>
<tr>
<td>2.5 mg/kg loading as 2-h infusion followed by 1.5 mg/kg q12h as 1-h infusion&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Day 1</td>
<td>3.95</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.40</td>
<td>8.76</td>
</tr>
<tr>
<td>2.5 mg/kg/d as continuous infusion</td>
<td>Day 1</td>
<td>3.95</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.40</td>
<td>8.76</td>
</tr>
<tr>
<td>2.5 mg/kg loading as 2-h infusion, then 2.5 mg/kg/d as continuous infusion&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Day 1</td>
<td>42.4</td>
</tr>
<tr>
<td>Day 4</td>
<td>48.0</td>
<td>73.9</td>
</tr>
</tbody>
</table>

Abbreviations: AUC<sub>0–24 hours</sub>, area under the plasma concentration-time curve over 24 hours; Cmax, maximum polymyxin B concentration; Cmin, minimum polymyxin B concentration; P<sub>10</sub>, 10th percentile; P<sub>50</sub>, 50th percentile; P<sub>90</sub>, 90th percentile; q12h, every 12 hours.

<sup>a</sup> All values refer to total polymyxin B concentration.

<sup>b</sup> Cmax and Cmin on day 1 and day 4 refer to dose 1 and dose 8. The Cmin on day 1 is the concentration at the end of the first dosage interval.

<sup>c</sup> First maintenance dose administered 12 hours after the loading dose.

<sup>d</sup> Continuous infusion commenced immediately after the loading dose.
Adverse effect [19, 24]. In the present study, urinary excretion of polymyxin B was independently associated with lower hospital mortality [19]. Because 200 mg/day corresponds to 2.5, 2.85, and 3.0 mg/kg per day in patients weighing 80, 70, and 65 kg, respectively, ≥300 mg/day is very likely in accordance with the dosage regimens associated with bactericidal activity of polymyxins, according to the data from mouse infection models [22, 23] and our Monte Carlo simulations (Table 3).

Although renal clearance contributes in a minor way to polymyxin B CL, the processing of the drug within the kidney is extremely important as nephrotoxicity is the major dose-limiting adverse effect [19, 24]. In the present study, urinary excretion and plasma protein binding data were available for 16 patients with a wide range of renal functions. In all of these patients, polymyxin B CL was only a very small percentage of the antibiotic's plasma clearance, indicating that polymyxin B was subject to extensive net tubular reabsorption, as has been reported previously for 4 other patients [8] and for colistin in rats [16]. The trend for the percentage of filtered polymyxin B reabsorbed to increase with CrCL is consistent with the intact nephron hypothesis [25]. The relationship between the percentage of the daily dose that was reabsorbed and CrCL (Figure 4) highlights the degree of exposure of tubular cells to polymyxin B. For example, for a patient with a CrCL ≥100 mL/min, remarkably, an amount equivalent to the daily dose or more was reabsorbed through the tubular cells per day. In the case of a patient with a lower CrCL, the amount reabsorbed per day can still be a substantial percentage of the daily dose, especially given the likely fewer number of functioning nephrons in such a patient [25]. Thus, there is substantial recycling of polymyxin B between tubular urine and the systemic circulation, which results in extensive intracellular exposure to polymyxin B. Our data (Figure 4) suggest that inhibition of tubular reabsorption may serve to decrease the potential for nephrotoxicity.

A potential limitation of our study was the use of CrCL estimated by the Cockcroft-Gault equation, which has not been validated in critically ill patients. Nonetheless, this limitation does not affect our results because there was clearly no relation between renal function and polymyxin B CL. In addition, only 2 patients on renal replacement therapy were included in the population PK analysis. In conclusion, this is the first population PK study demonstrating that doses of intravenous polymyxin B are best scaled by total body weight and should not be based upon renal function. For patients on renal replacement therapy, dosage adjustments are not recommended at this time. Further clinical studies on polymyxin B PK/PD are urgently needed.

Notes

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Potential conflicts of interest. A. P. Z. has received consultancy fees from Pfizer, Eurofarma, and Forest Laboratories. D. R. F. has received consultancy fees from Pfizer. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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