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Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients▽

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With increasing clinical emergence of multidrug-resistant Gram-negative pathogens and the paucity of new agents to combat these infections, colistin (administered as its inactive prodrug colistin methanesulfonate [CMS]) has reemerged as a treatment option, especially for critically ill patients. There has been a dearth of pharmacokinetic (PK) data available to guide dosing in critically ill patients, including those on renal replacement therapy. In an ongoing study to develop a population PK model for CMS and colistin, 105 patients have been studied to date; these included 12 patients on hemodialysis and 4 on continuous renal replacement therapy. For patients not on renal replacement, there was a wide variance in creatinine clearance, ranging from 3 to 169 ml/min/1.73 m^2. Each patient was treated with a physician-selected CMS dosage regimen, and 8 blood samples for PK analysis were collected across a dosage interval on day 3 or 4 of therapy. A linear PK model with two compartments for CMS and one compartment for formed colistin best described the data. Covariates included creatinine clearance on the total clearance of CMS and colistin, as well as body weight on the central volume of CMS. Model-fitted parameter estimates were used to derive suggested loading and maintenance dosing regimens for various categories of patients, including those on hemodialysis and continuous renal replacement. Based on our current understanding of colistin PK and pharmacodynamic relationships, colistin may best be used as part of a highly active combination, especially for patients with moderate to good renal function and/or for organisms with MICs of ≥1.0 mg/liter.

There has been an increasing clinical emergence of multidrug-resistant (MDR) Gram-negative pathogens, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, and this is especially of concern for critically ill patients (19, 30). Infections caused by these organisms are increasingly difficult to treat due to a wide variety of resistance mechanisms. With a paucity of new drugs available to treat infections caused by these MDR organisms, colistin, also known as polymyxin E, which was first introduced in the late 1950s, has reemerged as a treatment of choice and often as the only antibiotic active against these organisms (14, 26, 33). Colistin is available for parenteral administration as colistin methanesulfonate (CMS), an inactive prodrug that is less nephrotoxic than colistin (7, 25). Because it has been more than 50 years since CMS became available for clinical use, it has never been subjected to contemporary drug development procedures. As a result, there are very limited pharmacokinetic (PK) data available to guide appropriate CMS dosage selection, especially in critically ill patients. Early studies, including those used for current product labeling, utilized nonspecific microbiological assays which are not able to differentiate colistin present in biological samples at the time of collection from that formed from CMS *in vitro* during the incubation phase of microbiological assays. Current dosing guidelines therefore are not scientifically based, have been found to be inappropriate, and have led to treatment failure as well as emergence of resistance (1, 6, 20).

The need to administer antibiotics in critically ill patients based upon PK, pharmacodynamic (PD), and toxicodynamic (TD) principles in order to optimize the benefit and minimize the potential for development of resistance has been highlighted recently (30). The relatively recent development of separate assays for colistin and CMS in biological fluids

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(17, 21–22, 32) has provided some insight into the disposition of CMS and formed colistin in small populations of critically ill patients (total of 32) with near-normal renal function (29, 31). The removal of CMS and colistin by continuous renal replacement therapy and intermittent hemodialysis has been assessed in just three critically ill patients (27–28). As a result, there is a major paucity of information on the disposition of the prodrug CMS and formed colistin in critically ill patients across a wide range of renal function. The aims of this study were to develop a population PK model for CMS and colistin in a larger population of critically ill patients with a wider range of renal function more typical of this population, including those receiving renal replacement therapy. This would permit characterization of the patient covariates influencing the disposition of CMS and formed colistin and, by integrating the PK results with literature PD data, development of improved dosing guidelines for use in this difficult-to-treat population. This report presents the results for 105 critically ill patients from an ongoing study that will recruit a total of 238 patients to define the population PK/PD/TD of CMS and formed colistin. The interim dosing suggestions contained herein provide important information for clinicians to assist in the use of intravenous CMS/colistin in this difficult-to-manage population.

MATERIALS AND METHODS

Patients and study design. This was an open-label population PK study conducted at two sites in the United States and one in Thailand. Patients were eligible for enrollment in the study if they were ≥18 years old, receiving CMS as part of their clinical care for treatment of bloodstream infection or pneumonia due to a Gram-negative bacillus lacking susceptibility to all of the antibiotics cefepime or ceftazidime, imipenem or meropenem, piperacillin-tazobactam, and ciprofloxacin or levofloxacin, and had adequate venous access to enable collection of blood for determination of CMS and formed colistin in plasma. Patients who were pregnant or breastfeeding, were concomitantly receiving CMS/colistin or polymyxin B delivered directly into the respiratory tract, or had cystic fibrosis were excluded. Data collected included demographic information, APACHE II (acute physiology and chronic health evaluation II) scores, serum creatinine, comorbidities, use of immunosuppressives, and presence and type of renal replacement (intermittent hemodialysis [HD] or continuous renal replacement therapy [CRRT]). Informed consent was obtained for all patients, and the study was approved by the ethics committee of each institution.

CMS administration. CMS (Colistate [Atlantic Pharmaceutical Co., Bangkok, Thailand], and colistimethate for injection [Paddock Laboratories, Inc., MN and X-Gen Pharmaceuticals, Inc., Big Flats, NY]) was administered intravenously as a short-term infusion (range of infusion durations, 9 to 180 min) every 8 to 24 h according to a dosage regimen determined by the respective treating physician. The dose of CMS was expressed as colistin base activity (CBA); 150 mg CBA is equivalent to approximately 5 million units (MU) of CMS (26) and approximately 400 mg CMS sodium.

Pharmacokinetic sampling. Eight samples of blood (each 3 ml) were collected across a dosage interval on day 3 to 4 of CMS therapy. Samples were collected immediately prior to a dose, at the end of the CMS infusion, and at the following nominal times thereafter: 0.5, 1, 2, 4, 8, and 12 h or immediately prior to the next dose if CMS was not being administered every 12 h. The actual times of CMS administration and blood sampling were recorded. Samples were collected in heparinized blood collection tubes, placed on ice, and centrifuged at 4°C within 1 h of collection. The resulting plasma was stored at −70 to −80°C to prevent *in vitro* conversion of CMS to colistin (11). For patients on either HD or CRRT, the total volume of dialysate collected across a collection interval was measured or calculated from known flow rates. For subjects on HD, "spot" samples of dialysate were collected just after the start of the dialysis session, once every hour during dialysis, and just prior to the end of the session (typically, 4 such samples were collected); blood samples were also collected at the start and end of the session in those cases where the HD occurred on a different day from that for the collection of the eight blood samples mentioned above. For subjects on CRRT, "spot" dialysate samples (approximately 8) were collected at the same nominal times as for the eight interdosing blood samples described above.

Determination of CMS and colistin concentrations in plasma. CMS and colistin concentrations in plasma were quantified by previously reported high-performance liquid chromatographic methods (21–22). Plasma CMS and colistin concentrations were quantified within 4 months of collection to avoid *in vitro* conversion of CMS to colistin (11). The accuracies of the plasma colistin assay at the low, medium, and high quality control concentrations were 106%, 100%, and 103% of target concentrations, respectively, with corresponding precision (CV) of 6.27%, 7.85%, and 6.48%. The respective values for the low, medium, and high quality control concentrations for CMS were accuracies of 103%, 99%, and 98% with precision of 11.8%, 6.65%, and 6.46%. The limits of quantification were 0.10 mg/liter for colistin and 0.30 mg/liter for CMS.

Pharmacometric methods. A nonlinear mixed-effects modeling tool, S-ADAPT (Monte Carlo parametric expectation maximization [MCPEM]), was used to analyze the plasma concentration-versus-time data for both CMS and formed colistin (3, 8). One-, two-, and three-compartment models were explored for the plasma concentration-time profiles for CMS and colistin, with linear or nonlinear (saturable) elimination. The model was built in a piecewise manner; first the model for CMS was developed, after which colistin data were included and the model characterizing colistin disposition was built. These models were first fit to the data for patients not on renal replacement. Subsequently, the "best-fit" model was fit to the data for patients on HD and CRRT by including an extracorporeal clearance which played a role in the plasma disposition of CMS and colistin. Attempts to comodel the plasma and dialysate data in patients on renal replacement were not successful. The comodeled fits were inferior for some patients (compared with those from modeling of plasma data only), probably due to the proportion of dialysate concentrations that were below the limit of quantification. Subsequently, the extracorporeal clearances of CMS and colistin were modeled based upon plasma concentration data only. Additional modifications to this model were evaluated. These modifications included the presence or absence of transit compartments to characterize a decrease in plasma concentrations of CMS and the slow rise in plasma concentrations of colistin for subjects with renal failure. As a final step, the models for subjects on renal replacement and those not on renal replacement were combined and comodeled to allow for maximal benefit of population PK. Residual error models evaluated were proportional or additive plus proportional. The interindividual variability was assumed to be log-normally distributed. Plasma concentrations below the limit of quantification were handled by the Beal M3 method (5).

Covariate model building was performed using forward selection and backward deletion. Candidate covariates that were evaluated for their possible effect on CMS and colistin disposition included the following: body size (actual and ideal weight, body surface area [BSA], body mass index [BMI]), gender, age, creatinine clearance (CrCL), and APACHE II score on clearance; and body size (actual and ideal weight, BSA, BMI) on volume of distribution. Calculation of CrCL was done by use of the Jelliffe equation (18) for patients with unstable renal function. Model evaluation was performed via nonparametric bootstrap techniques using 500 randomly sampled data sets. Each new data set contained the same proportion of patients on HD or on CRRT as the original data set. After building the population PK model for CMS and colistin, we applied it to the development of suggestions for both loading and maintenance doses of CMS designed to achieve a desired target plasma colistin concentration. First, each individual's fitted PK parameter estimates from the final population PK model were used to compute that subject's ideal loading and maintenance doses to achieve a user-specified target plasma colistin concentration. Any and all covariates for CMS and colistin PK which were also significantly related to the ideal dose were incorporated into the dosing algorithms. Further detail is provided in Results.

RESULTS

Patient characteristics. A total of 105 patients studied to date (recruited between February 2009 and July 2010) were included in this study, of whom 12 were receiving HD and 4 were on CRRT (3 on continuous veno-venous hemodialysis

TABLE 1. Patient characteristics

Characteristic	Value
Median (range)	
Age (yr)	71 (19–92)
Wt (kg)	59.1 (30.0–106.4)
Height (cm)	162.0 (140.0–184.5)
APACHE II score	21 (4–38)
Serum creatinine (mg/dl)	1.2 (0.2–10.3)
Creatinine clearance (ml/min/1.73 m^2)	28.7 (0–169)
No. (%) of patients	
Sex	
Male	68 (64.8)
Female	37 (35.2)
With comorbidity	
Diabetes	24 (22.9)
Malignancy	22 (21.0)
Immunosuppression	13 (12.4)
Hepatic failure	10 (9.5)
With infection treated with CMS	
Bacteremia	11 (10.5)
Pneumonia	94 (89.5)
With source of bacteremia	
Pneumonia	1 (9.1)
Intra-abdominal	5 (45.5)
Urinary tract infection	2 (18.2)
Unknown	3 (27.3)
With renal replacement therapy	
Hemodialysis	12 (11.4)
Continuous renal replacement	4 (3.8)

[CVVHD] and 1 on continuous veno-venous hemofiltration [CVVH]). Patient characteristics are summarized in Table 1. The HD patients had dialysate flow rates ranging from 500 to 600 ml/min, blood flow rates ranging from 200 to 350 ml/min, membrane surface areas ranging from 1.5 to 1.9 m^2, and membrane type SF190E, Rex 18, or SF150; the frequency of HD ranged from daily to twice weekly, and session duration was 3 h 15 min to 4 h 15 min (median, 4 h). All 3 CVVHD patients had dialysate flow rates of 42 ml/min, blood flow rates of 150 ml/min, membrane surface area of 0.9 m^2, and membrane type ANG9HF. The median daily dose of colistin base activity across the 105 patients was 200 mg (range, 75 to 410 mg).

Plasma concentrations of CMS and colistin. A total of 851 plasma samples were available for each of CMS and colistin; no samples were excluded from the modeling analyses. Plasma concentration-time profiles of CMS and formed colistin for all patients are presented in Fig. 1. For each patient, the profile for formed colistin was much flatter than that for CMS, consistent with the active antibacterial having a longer terminal half-life than the prodrug. There was substantial interpatient variability in the plasma concentrations of both CMS and colistin achieved from the empirically selected CMS dosage regimens. The area under the plasma concentration-versus-time curve over a day ($AUC_{0–24}$) for formed colistin ranged from 11.5 to 225 mg · h/liter. Division of each $AUC_{0–24}$ value by 24 h generates the average steady-state plasma concentration ($C_{ss,avg}$) of colistin for each patient; the range of the colistin $C_{ss,avg}$ across all patients was 0.48 to 9.38 mg/liter (median, 2.36 mg/liter). There was a strong inverse trend between the colistin $C_{ss,avg}$ and the CrCL (Fig. 2); the corresponding relationship between the physician-selected daily dose of CBA and CrCL is shown in the same figure.

Population PK analysis. The disposition of CMS and formed colistin was best described by a linear model comprising two and one compartments, respectively. Equations 1 to 3 below represent the differential equations for the disposition of CMS and colistin. CMSc is the mass of CMS in the central compartment, CMSp is the mass of CMS in the peripheral compartment, and "colistin" in equation 3 is the mass of colistin in the single compartment for colistin. $V1$ and $V2$ represent the central and peripheral volumes for CMS, and $V3$ represents the volume of distribution for colistin. $R(1)$ represents the infusion rate of CMS, and CLD1 represents the distributional clearance between the central and peripheral compartments for CMS. CLT_{CMS} and CLT_C refer to the total intrinsic clearance for CMS and colistin. CLT_{CMS} was modeled as the sum of renal clearance and a nonrenal clearance ($CLNR_{CMS}$), with a portion of the latter

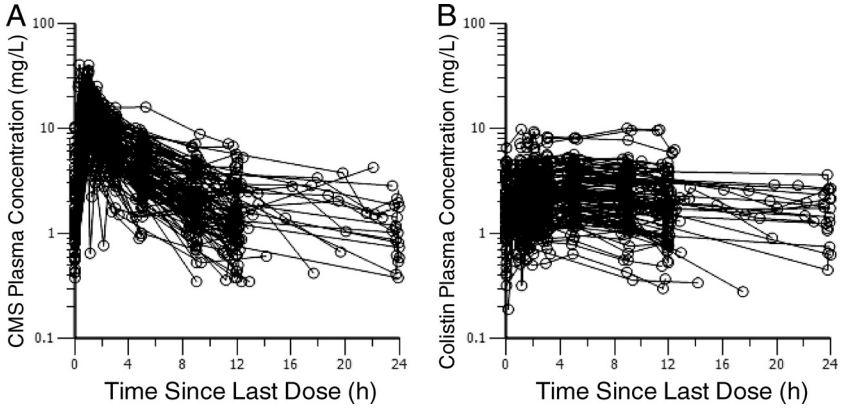

FIG. 1. Steady-state plasma concentration-time profiles of the prodrug CMS (A) or formed colistin (B) in 105 critically ill patients (89 not on renal replacement, 12 on intermittent HD, and 4 on CRRT). The physician-selected daily doses of colistin base activity (CBA) ranged from 75 to 410 mg/day; the dosage intervals ranged from 8 to 24 h, and hence the interdosing blood sampling interval spanned the same range.

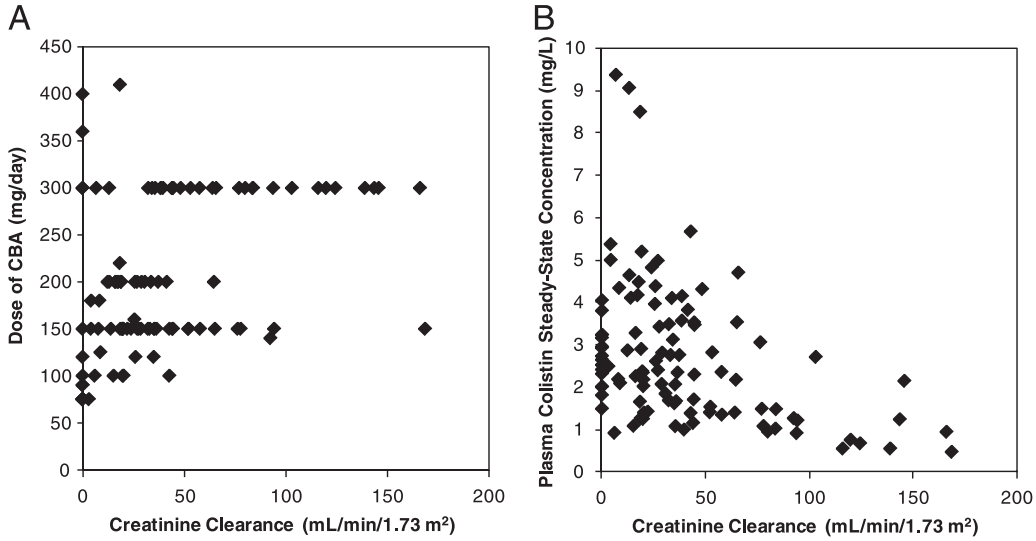

FIG. 2. Relationship of physician-selected daily dose of colistin base activity (CBA) (A) and the resultant average steady-state plasma colistin concentration (B) with creatinine clearance in 105 critically ill patients.

forming colistin. Colistin clearance and volume of distribution ($V3$) are thus conditioned on the unknown fraction (fm) of the nonrenal clearance of CMS that actually forms colistin (this fm is not the fraction of the total administered dose of CMS converted to colistin). For patients on hemodialysis, HD clearance for CMS ($CLHD_{CMS}$) and colistin ($CLHD_C$) also played a role in the disposition of CMS and colistin. These clearance values were estimated during dialysis and set to zero when dialysis was turned off. Similarly, for patients on CRRT, $CLRRT_{CMS}$ and $CLRRT_C$ played a role in the disposition of CMS and colistin.

$$\frac{dCMSc}{dt} = R(1) - CLD1 \times \left(\frac{CMSc}{V1} - \frac{CMSp}{V2}\right) - (CLT_{CMS} + CLHD_{CMS} + CLRRT_{CMS}) \times \frac{CMSc}{V1} \quad (1)$$

$$\frac{dCMSp}{dt} = CLD1 \times \left(\frac{CMSc}{V1} - \frac{CMSp}{V2}\right) \quad (2)$$

$$\frac{dColistin}{dt} = CLNR_{CMS} \times \frac{CMSc}{V1} - (CLT_C + CLHD_C + CLRRT_C) \times \frac{Colistin}{V3} \quad (3)$$

In order to inform the model and constrain clearance due to CRRT to be smaller than clearance due to dialysis in HD patients, clearances of CMS and colistin due to CRRT were modeled as a fraction (FRRT) of the respective clearances due to dialysis in HD patients. The equations below define the clearances due to CRRT.

$$CLRRT_{CMS} = CLHD_{CMS} \times FRRT \quad (4)$$

$$CLRRT_C = CLHD_C \times FRRT \quad (5)$$

A thorough PK covariate analysis was performed for candidate covariates (both as fixed and random effects where appropriate). Total CMS clearance (CLT_{CMS}) was modeled as a function of CrCL and two random effects, CLR_{SLOPE} and $CLNR_{CMS}$, using equation 6 below.

$$CLT_{CMS} = CrCL \times CLR_{SLOPE} + CLNR_{CMS} \quad (6)$$

The central compartment volume for CMS ($V1$) was modeled as a function of weight (fixed effect) and centered using a value approximating the median weight, 60.0 kg, using equation 7 below. $V1_{POP}$ is a standard "population" volume of distribution value (liters/60 kg) for the central volume of CMS, which was allowed to vary as a function of body weight.

$$V1 = V1_{pop} \times \left(\frac{WTKG}{60.0}\right) \quad (7)$$

The apparent colistin clearance (CLT_C/fm) was modeled as a sum of two fixed effects, a renally dependent component ($CLRC_{SL\_POP}$) and a nonrenally dependent component ($CLNR_{C\_POP}$), using equation 8 below.

$$CLT_C = CrCL \times CLRC_{SL\_POP} + CLNR_{C\_POP} \quad (8)$$

The derived terminal half-lives for CMS and colistin in patients not on CRRT were also dependent on CrCL: for 20 patients with CrCL of <10 ml/min/1.73 m^2, the median half-life (10th to 90th percentile) for CMS was 11 (6.3 to 43) h and that for colistin was 13 (7.0 to 18) h; for 62 patients with CrCL of 11 to 69 ml/min/1.73 m^2, the half-life for CMS was 5.6 (3.2 to 14) h and that for colistin was 13 (8.2 to 19) h; for 19 patients with CrCL of >70 ml/min/1.73 m^2, the half-life for CMS was 4.6 (1.9 to 9.1) h and that for colistin was 9.1 (6.3 to 12) h.

All model-fitted parameters were estimated with good to excellent precision (standard errors between 3.1 and 44%), with core parameters having moderate interindividual variability (23 to 70%) (Table 2). Representative individual fits are presented in Fig. 3. The overall goodness-of-fit plots (observed

TABLE 2. Population PK model-fitted parameters[a]

Category	Parameter (units)	Model-fitted result				Bootstrap result[c]		
		No. of subjects	Estimate	% SE	% IIV	Median	10th percentile	90th percentile
CMS	*V*1 (liters)	105	11.5		32	102	93.9	113
	*V*2 (liters)	105	18.7	9.0	79	99.4	85.6	124
	CLD1 (liters/h)	105	7.98	12	84	97.0	77.8	117
Random effects	CLR_{SLOPE} (liters/h/CrCL)	89	0.0613	8.8	70	99.5	88.1	113
	$CLNR_{CMS}$ (liters/h)	105	1.90	5.6	36	101	93.6	111
Colistin	*V*3/fm (liters)	105	45.1	6.1	48	102	90.1	116
	CLT_C/fm (liters/h)	105	2.72		23	100	92.0	110
Fixed effects	$CLRC_{SL\_POP}$/fm (liters/h/CrCL)	89	0.0147	28		102	68.0	142
	$CLNR_C$/fm (liters/h)	105	2.19	5.8		99.1	92.7	107
	$V1_{POP}$ (liters/60 kg)	105	11.9	5.1		103	94.1	113
Renal replacement[b]	$CLHD_{CMS}$ (liters/h)	16	5.69	44	96			
	$CLHD_C$ (liters/h)	16	3.40	3.1	15			
	$CLRRT_{CMS}$ (liters/h)	4	3.85	12	24			
	$CLRRT_C$ (liters/h)	4	2.06	18	37			
Error variance	SD_{SLOPE_CMS}	105	0.183	4.8		98.3	87.4	111
	SD_{SLOPE_C}	105	0.099	4.1		99.0	85.8	114
	$SD_{INTERCEPT}$	105	Fixed at LOQ	Fixed at LOQ	Fixed at LOQ			

[a] Estimates refer to the geometric mean of the estimates in the population. This may refer to the entire 105 subjects, 89 subjects not on any renal replacement, 16 subjects on some form of renal replacement, or 4 subjects on CRRT and is specified by the "No. of subjects" column. % SE refers to the standard error or the precision of the estimates, while % IIV refers to the interindividual variability in the population. LOQ refers to the limit of quantification.

[b] For the two RRT groups, the geometric mean, % SE, and % IIV are based on summary statistics of the *post hoc* estimates in the indicated population.

[c] Bootstrap results are expressed as a % of the model-fitted estimates.

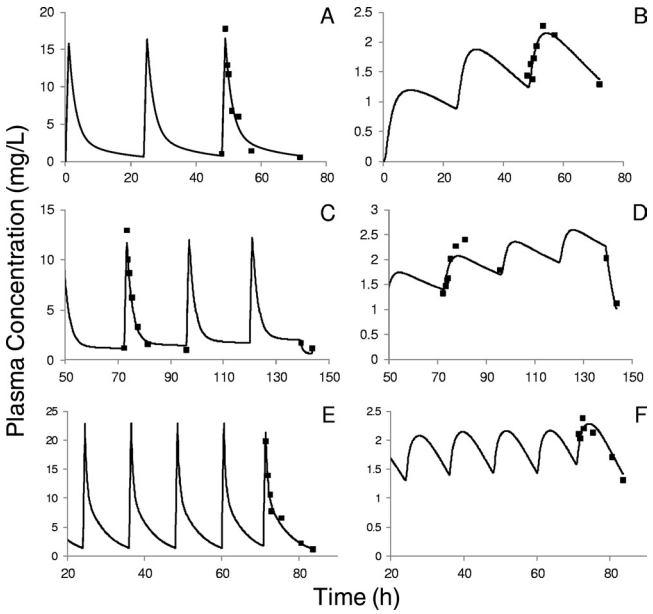

FIG. 3. Representative individual population PK model fits of CMS (A, C, and E) or formed colistin (B, D, and F) in critically ill patients. Panels A and B are representative of a subject not on renal replacement, C and D are representative of a subject on HD, and E and F are representative of a subject on CRRT.

versus fitted concentrations) for both CMS and colistin indicated that the individual fits were precise and unbiased, with r^2 values of >0.94 for both CMS and colistin (data not shown). The results of the bootstrap analysis (Table 2) agreed well with the final model estimates (for parameters not relating to renal replacement), with the median value from the bootstrap runs being within 1 to 3% of the final estimate, with a 10 to 90% confidence interval (CI) for all parameter means (except $CLRC_{SL\_POP}$/fm) no more than 22.3% below or 24.6% above the final model estimate. Similar precision was also noted for the variance (not shown) around the estimates, with the median value from the bootstrap being within 1 to 6% of the final model-fitted estimate with a 10 to 90% CI no more than 48.2% above or 48.5% below the fitted value.

Development of CMS dose suggestions for various categories of patients. The population PK models for patients not on renal replacement and those receiving HD or CRRT were then used to derive maintenance dosing suggestions for CMS in critically ill patients to achieve a desired "target" $C_{ss,avg}$ of colistin in plasma.

For those patients not on renal replacement (n = 89) together with those receiving HD (n = 12), each patient's "ideal" maintenance dose of CMS (expressed as CBA) was computed, based on their individual fitted PK parameter estimates from the population PK model and a chosen target plasma colistin $C_{ss,avg}$. The "ideal" maintenance dose of CBA required to achieve each 1.0 mg/liter of target colistin $C_{ss,avg}$ for each patient was then regressed against the corresponding CrCL, adjusted by differentially weighing the cost of being above

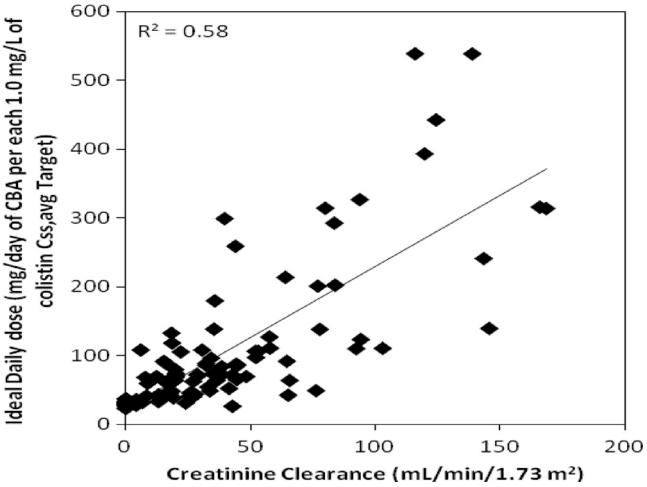

FIG. 4. Relationship between the "ideal" maintenance dose of CMS (expressed as mg per day of colistin base activity [CBA] per each 1.0 mg/liter of colistin $C_{ss,avg}$ target) and creatinine clearance in 101 critically ill patients (89 not on renal replacement and 12 on HD).

(increased likelihood of toxicity) and below (subtherapeutic concentrations, thus decreasing the likelihood of efficacy) the target (4). We accomplished this by minimizing a weighted least-squares cost function. For weighting, we defined a desirable window and made the judgment to consider missing the window "high" (with a risk of toxicity) as one-half the cost (weight) of missing it "low" (with a risk for treatment failure). The final weighted regression maximized the cases within the desired window and minimized the resulting cost function (balancing the risks of being below versus being above the window, favoring the latter by approximately 2:1). The resultant relationship (Fig. 4) forms the basis of a maintenance dosing algorithm for critically ill patients in the two above-mentioned categories (Table 3, equation 10). It should be noted that the "ideal" maintenance dose of CBA required to achieve each 1.0 mg/liter of colistin target $C_{ss,avg}$ for each of the 12 HD patients ranged from 23 to 41 mg CBA per day (median, 30 mg CBA per day). This median accords well with the daily maintenance dose of CBA calculated using equation 10 (Table 3) in a patient with a CrCL of zero.

Our population PK modeling in the present study (Table 2) and previous findings (15, 28) indicate that both CMS and colistin are efficiently cleared by hemodialysis. In order to replace CMS and colistin lost due to hemodialysis and maintain a colistin $C_{ss,avg}$ on an HD day similar to that on a non-HD day, the fitted clearances due to HD for each of CMS and colistin were used to determine the magnitude of a CMS supplemental dose. A higher supplemental dose of CMS is required if it is administered during the last hour of the HD session compared with administration after the end of the HD session (Table 3). It was assumed that the HD session occurs toward the end of a CMS maintenance dosage interval. The "ideal" maintenance doses computed from the population PK model for 4 patients on CRRT (3 CVVHD and 1 CVVH) ranged from 112 to 260 (median, 192) mg CBA/day per 1.0 mg/liter colistin target $C_{ss,avg}$, leading to the suggested daily

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.
	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

[a] Expressed as mg of colistin base activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose. Example: To target a colistin $C_{ss,avg}$ of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m^2 would receive a loading dose of 275 mg CBA followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

[b] Colistin $C_{ss,avg}$ target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.

[c] Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA (see the text for more details).

[d] Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin $C_{ss,avg}$ target expressed in mg/L. Creatinine clearance (CrCL) expressed in ml/min/1.73 m^2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m^2. See text for caveat regarding use of the algorithm in patients with CrCL values > 70 ml/min/1.73 m^2 or when targeting a "high" colistin $C_{ss,avg}$, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

[e] Based upon use of equation 10 and setting CrCL to zero.

[f] Supplemental dose of CMS to achieve a similar colistin $C_{ss,avg}$ on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.

[g] Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.

maintenance dose of CBA listed in Table 3. The suggested dose intervals are dependent on CrCL; see Table 3.

The maintenance dosing suggestions for various categories of critically ill patients (Table 3) were then applied to all patients studied to date, using a colistin $C_{ss,avg}$ target of 2.5 mg/liter, corresponding to a steady-state colistin $AUC_{0–24}$ of 60 mg · h/liter; the colistin $C_{ss,avg}$ target of 2.5 mg/liter was very similar to the median $C_{ss,avg}$ of 2.36 mg/liter achieved in the 105 patients with the physician-selected maintenance doses of CMS, but the predicted variances were substantially lower. Among those not on any renal replacement plus those on HD, 3/101 (~3%) of patients are predicted to have achieved a colistin $C_{ss,avg}$ of 0.5 to 1 mg/liter, 86/101 (~85%) a colistin $C_{ss,avg}$ of 1.0 to 4.0 mg/liter, and 12/101 (~12%) a colistin $C_{ss,avg}$ of >4.0 mg/liter. Among those on HD, all 12 patients would have been predicted to achieve a colistin $C_{ss,avg}$ between 1.9 and 3.4 mg/liter. Patients on CRRT required a maintenance dose ~6-fold higher than that required by an HD patient on a nondialysis day. With a dose of 480 mg CBA per day, aiming to achieve a colistin $C_{ss,avg}$ of 2.5 mg/liter, all 4 CRRT patients would be predicted to achieve $C_{ss,avg}$ concentrations of colistin between 1.9 and 4.2 mg/liter.

The predicted steady-state colistin $AUC_{0–24}$ values, from the above algorithm-predicted maintenance doses applied back to all 105 patients, were then linked with PD models for 3 strains of *A. baumannii* (MICs of 0.5, 1.0, and 1.0 mg/liter) and 3 strains of *P. aeruginosa* (MICs of 0.5, 1.0, and 1.0 mg/liter) previously studied using neutropenic mouse thigh and lung infection models (12–13). In both murine models, the most predictive PK/PD index for antibacterial effect of colistin against both species was the ratio of $AUC_{0–24\ [unbound]}$ to MIC (12–13). At this time, the plasma binding of colistin in critically ill patients is not known, because the concomitant presence of variable concentrations of CMS in plasma samples and other factors pose significant technical difficulties. Thus, the parameter estimates (effect in the absence of drug [E_o], maximal drug effect [E_{max}], 50% effective concentration [EC_{50}], and Hill coefficient) for the inhibitory sigmoid dose-effect model linking the AUC_{0-24}/MIC ratio (i.e., for the total plasma colistin concentration) with the magnitude of effect in the murine models (unpublished data from references 12 and 13) were used in the current translational analysis. Assuming similar plasma unbound fractions in mice and humans, it was possible to use the human AUC_{0-24} values predicted using the maintenance dosing algorithm, the respective MICs, and parameter estimates from the murine models to predict the net logs of effect in the murine models. The results of such an analysis for *A. baumannii* in murine thigh infection are shown in Fig. 5; the graph contains AUC_{0-24}/MIC values for 105 critically ill patients × 3 strains: 315 data points representing predicted logs of effect relative to the respective baseline inocula. Results for similar analyses performed for the same strains of *A. baumannii* in a murine lung infection model (13) and for 3 strains of *P. aeruginosa* studied in neutropenic mice with infected thighs and lungs (12) are presented in Table 4. The number of cases corresponding to various predicted magnitudes of effect against each bacterial strain in each murine model is delineated.

The potential consequences of commencing maintenance therapy with CMS in the absence of a loading dose must be considered. Because of slow conversion of the administered prodrug, CMS, to the active antibacterial, colistin, and the long half-life of the latter, accumulation to plasma colistin concentrations likely to be effective takes some time in the absence of a loading dose (31). The slow accumulation of formed colistin in plasma was also evident in the population PK model fits in this study (Fig. 3). We used the fitted model to determine the appropriate mean loading dose of CMS to more rapidly achieve steady-state plasma concentrations of formed colistin. A Monte Carlo simulation (ADAPT 5) (9) was performed, simulating 9,999 randomly selected patients using parameters and distributions achieved in our study. Equation 9 (Table 3) represents the loading dose required to achieve a desired plasma colistin $C_{ss,avg}$ target; the loading dose should be calculated using the lower of ideal or actual body weight and would be administered on day one, followed by commencement 24 h later of the relevant maintenance dosage regimen (Table 3).

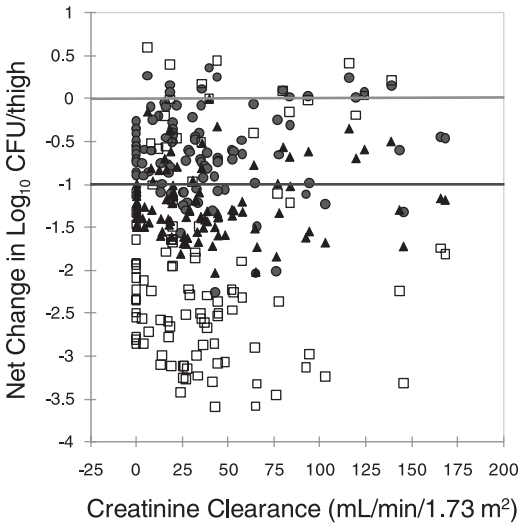

FIG. 5. Pharmacodynamic activity predicted by applying the $AUC_{0–24}$ values (from the algorithm-predicted maintenance doses targeting a colistin $C_{ss,avg}$ of 2.5 mg/liter) for each of the 105 critically ill patients together with the PD parameters from 3 isolates of *A. baumannii* in a murine thigh infection model (unpublished PD parameter estimates referenced to total plasma colistin concentration from reference 13). The predicted logs of effect are relative to the respective baseline inocula and are plotted as a function of creatinine clearance in the critically ill patients. The symbols represent the following strains: ●, 248-01-C.248 (MIC = 1.0 mg/liter); ▲, ATCC 19606 (MIC = 1.0 mg/liter); and □, N-16870.213 (MIC = 0.5 mg/liter).

DISCUSSION

Data supporting dosing recommendations for CMS from prospective studies continue to be scarce. Although some data describing the PK of CMS and formed colistin in critically ill patients are available (29, 31), the studies included only 14 and 18 patients, respectively, and all 32 patients had creatinine clearance values greater than 40 ml/min; none of the patients was in receipt of renal replacement therapy. Thus, the patient populations were not representative of the full range of critically ill patients who may require intravenous administration of CMS for treatment of a Gram-negative infection. Neither of

TABLE 4. Pharmacodynamic activity predicted by applying $AUC_{0\text{-}24}$ values[a] for each of 105 critically ill patients together with PD parameters from 3 isolates of *A. baumannii* and 3 isolates of *P. aeruginosa* in murine thigh and lung infection models[b]

Study (reference)	Strain	MIC (mg/liter)	% of cases corresponding to predicted magnitude of effect[c]			
			< stasis	Stasis to 1 log kill	1 log kill to 2 log kill	>2 log kill
P. aeruginosa murine thigh infection (12)	19056	0.5	13.3	22.9	41.0	22.9
	PAO1	1	78.1	17.1	1.9	2.9
	ATCC 27853	1	95.2	1.9	0.0	2.9
P. aeruginosa murine lung infection (12)	19056	0.5	1.0	17.1	53.3	28.6
	PAO1	1	36.2	52.4	8.6	2.9
	ATCC 27853	1	24.8	62.9	9.5	2.9
A. baumannii murine thigh infection (13)	248-01-C.248	1	12.4	68.6	16.2	2.9
	N-16870.213	0.5	7.6	11.4	22.9	58.1
	ATCC 19606	1	0.0	21.9	75.2	2.9
A. baumannii murine lung infection (13)	248-01-C.248	1	18.1	62.9	16.2	2.9
	N-16870.213	0.5	1.0	80.0	19.0	0.0
	ATCC 19606	1	0.0	17.1	80.0	2.9

[a] $AUC_{0\text{-}24}$ values are from algorithm-predicted maintenance doses targeting a colistin $C_{ss,avg}$ of 2.5 mg/liter.
[b] Unpublished PD parameter estimates referenced to the total plasma colistin concentration from references 12 and 13.
[c] Percentage of cases (105 patients) corresponding to various predicted effects relative to the respective baseline inocula.

these previous studies (29, 31) provided maintenance dosing suggestions for CMS in critically ill patients. The current study describes the disposition of the prodrug, CMS, and formed colistin in 105 critically ill patients, including 12 on intermittent hemodialysis and 4 on continuous renal replacement therapy. Of the 105 patients, 69 had CrCL of less than 40 ml/min/1.73 m^2. Based upon population PK analysis and a thorough search for covariates in the disposition of CMS and formed colistin, we have been able to develop dosing suggestions for various categories of critically ill patients.

Across the two previous PK studies of critically ill patients (29, 31), 30 patients received a CMS dose of 9 million units (MU) per day, while the remaining two patients received 6 and 4 MU per day; this corresponds to a range of CBA doses of about 120 to 270 mg/day, although clearly the majority of patients received the highest dose. In the present study, there was about a 5.5-fold range in the physician-selected daily dose of CMS (75 to 410 mg CBA) across the patients, with a clear trend for lower doses to be prescribed for patients with low CrCL (Fig. 2A). There was an ~20-fold range in the $AUC_{0\text{–}24}$ and corresponding $C_{ss,avg}$ values for formed colistin (Fig. 2B; see also Fig. 1B). Close examination of the data in both panels of Fig. 2 is instructive. First, it reveals the important role of renal function as a determinant of the plasma concentrations of the active antibacterial, formed colistin; as discussed below, CrCL was an important covariate in the population PK model developed in this study. Second, it is evident that in patients with moderate to good renal function, administration of a daily dose of CBA at the upper limit of the current product-recommended dose range (300 mg CBA per day) (2) was not able to generate plasma colistin concentrations that would be expected to be reliably efficacious.

Our final (best-fit) population PK model was linear, with two compartments for CMS and one compartment for colistin. This structural model was similar to that used by Plachouras et al. (31) to describe the disposition of CMS and formed colistin in 18 critically ill patients; in the study by Markou et al. (29), plasma concentrations of formed colistin only were quantified in 14 patients and the resultant concentration-time profiles were subjected to noncompartmental analysis. In the current population PK analysis, the volume of the central compartment for CMS was modeled as a function of weight and, as discussed in more detail below, the clearances for CMS and colistin were modeled as functions of CrCL. The volume of distribution and clearance of formed colistin were conditioned on fm, which in the current analysis represents the unknown fraction of the nonrenal clearance of CMS resulting in formation of colistin. In the study by Plachouras et al. (31), the reported clearance and volume of distribution for colistin were conditioned on a different fm, the fraction of the total CMS dose that was converted to colistin. The results from the current and previous study agree well when we adjust the fm in our study to mirror the one used by Plachouras et al. (31); under these circumstances, in patients with CrCL values of at least 40 ml/min/1.73 m^2, the geometric mean apparent clearance of colistin in our study was 10.8 liters/h with an intersubject variability of 76.5%, compared to 9.09 liters/h with an intersubject variability of 59% in the earlier study (31).

Renal function, expressed as CrCL, was an important covariate for the clearance of both CMS and colistin in our population PK model. In renally healthy individuals, the prodrug, CMS, is predominantly cleared by renal excretion, with only a relatively small fraction of a dose converted to the active antibacterial, colistin (23, 26); thus, total clearance of CMS is expected to decline with CrCL. At first thought it may seem surprising that CrCL was an important covariate for the clearance of formed colistin, because following direct administration of colistin in animal studies, it is cleared predominantly by nonrenal mechanisms, with only a very small fraction of the administered dose recovered in urine in unchanged form (24, 26). The explanation for CrCL being a covariate for the apparent clearance of formed colistin in this study lies in the somewhat unusual overall disposition of CMS and formed colistin. As mentioned above, only a small fraction of an ad-

ministered dose of CMS is converted to colistin (23); since CMS is cleared predominantly by renal excretion, as CrCL declines a progressively larger fraction of a dose of CMS will be converted to colistin, although we cannot discount the possibility of an associative decrease in the actual clearance of colistin as renal function declines. The practical consequence of this rather complex interplay of dispositional processes for administered CMS and formed colistin and the impact of renal function thereon are clearly evident in Fig. 2. Not surprisingly, CrCL was the major PK factor involved in the CMS maintenance dosing algorithm for generation of a target plasma concentration of formed colistin (Table 3, equation 10). Neither of the previous PK studies of critically ill patients found CrCL to be a covariate for the clearance of formed colistin (29, 31); similarly, CrCL was not a covariate for the clearance of administered CMS (31). It is very likely that the inability to detect relationships between renal function and clearances of CMS and colistin in the previous studies was the result of the small sample sizes (14 and 18 patients) and the relatively narrow range of CrCL values (>40 ml/min) for the enrolled patients (29, 31). We also found body size to be a relevant covariate affecting the volume of the central compartment for CMS; as a consequence, suggested CMS loading doses are a function of body weight (Table 3). We did not, however, find any significant trends in clearance of either CMS or colistin against body size, and thus we were not able to propose a weight-based maintenance dosing algorithm for CMS.

Since the physician-selected CMS maintenance doses in this study provided a substantive variance in $AUC_{0\text{-}24}$ (and corresponding $C_{ss,avg}$) for colistin (Fig. 1), we developed a dosing algorithm incorporating renal function to estimate the suggested CMS maintenance dose (expressed as mg CBA per day) required to reach a target $C_{ss,avg}$ for colistin (Table 3, equation 10). CrCL as a covariate explained ~60% of the variability in the "ideal" maintenance dose of CBA required to achieve a given target $C_{ss,avg}$ for colistin (Fig. 4). Further improving on this precision would require identification of additional PK covariates and/or development of an adaptive feedback control algorithm for colistin (individual optimization based on PK/PD/TD principles). The maintenance dosing algorithm performed satisfactorily when it was applied to patients not on any renal replacement and those on HD, using a colistin $C_{ss,avg}$ target of 2.5 mg/liter, corresponding to a steady-state colistin $AUC_{0\text{-}24}$ of 60 mg · h/liter. Similarly, the suggested CMS maintenance dose for patients on CRRT (Table 3) performed well when applied to the 4 patients in this category.

It is noteworthy that the CMS maintenance dose required to achieve each 1.0 mg/liter of the colistin $C_{ss,avg}$ target in patients on CRRT (192 mg CBA per day) (Table 3) is very similar to that required in a patient with a CrCL of ~100 ml/min/1.73 m^2 (Table 3, equation 10). This may seem surprising given that colistin is predominantly nonrenally cleared in individuals with normal kidney function (26). The explanation most likely relates to the mechanisms involved in the renal handling of colistin in the presence of intact kidney function in comparison with the extracorporeal clearance mechanisms in operation in CRRT. The renal handling of colistin involves very extensive tubular reabsorption; this serves to retain in the body a very large fraction of the filtered load of colistin, and it contributes to an extremely low fraction excreted unchanged in urine (24, 26). In contrast, following clearance by diffusion and/or convection in a CRRT cartridge, there is no carrier-mediated mechanism to return colistin from dialysate to blood perfusing the cartridge.

This and other (15, 28) studies have also shown that CMS and colistin are efficiently cleared during intermittent HD; the magnitudes of extracorporeal clearances of CMS and colistin in this study are in accord with those reported elsewhere (15, 28). Even when a dialysis session occurs toward the end of a CMS dosage interval, a substantial amount of CMS and colistin would be cleared, necessitating a supplemental dose of CMS to maintain a colistin $C_{ss,avg}$ similar to that occurring on a nondialysis day; a larger supplemental dose would be required if administered during dialysis compared with dosage after the session (Table 3). Because of the large fluctuations in plasma CMS concentrations during a dosage interval (Fig. 1), a much larger amount of CMS would be cleared if dialysis occurs early in a dosage interval. For this reason, it is suggested that dialysis is best conducted toward the end of a CMS dosage interval.

It is important to provide caveats about the loading and maintenance dose suggestions for CMS in Table 3. When computing the absolute loading dose of CBA from the result of applying equation 9 (Table 3), the lower of either the actual or ideal body weight should be used. In addition, there is little experience with using (single daily) doses of CMS greater than the current upper limit in the product information (300 mg CBA), and the potential impact of large loading doses of CMS on renal function is not known. Thus, at this time we suggest caution in the use of a loading dose greater than 300 mg CBA. In relation to suggested maintenance doses, the algorithm (Table 3, equation 10) predicts the need for increasingly high CMS maintenance doses as CrCL increases, and dependent upon the desired colistin $C_{ss,avg}$, this may generate suggested CMS daily doses above the upper limit (300 mg CBA per day) in the current product labeling (2). For example, if targeting a colistin $C_{ss,avg}$ of 2.5 mg/liter, a patient with a CrCL of 70 ml/min/1.73 m^2 would require 337.5 mg CBA per day. In such patients (i.e., with moderate to good renal function), it is theoretically possible to use daily doses of CMS higher than 300 mg CBA per day to generate a desired target colistin $C_{ss,avg}$ similar to those occurring with lower maintenance doses of CMS in patients with poorer kidney function (Fig. 2). However, increasing the daily dose of CBA beyond the current upper limit daily dose in patients with relatively good renal function comes at the expense of presenting a larger mass of CMS to the kidneys, with the potential for intrarenal conversion to colistin (23), which may increase the possibility of nephrotoxicity. This is not an insignificant risk given the rate of nephrotoxicity even with the currently recommended CMS dosage regimen. In the present study, of the 89 patients not on renal replacement, all but two had been prescribed a CMS maintenance dose of 300 mg CBA per day or less, and 43/89 (48%) had a rise in serum creatinine of >50%, of which, for 27/43 (63%), levels remained elevated at the end of the study; these findings are similar to those reported for other studies (10, 16). Thus, care is needed in the use of the maintenance dosing algorithm for patients with moderate to good renal function and/or when it is desired to target a relatively high colistin $C_{ss,avg}$ target, circumstances where the algorithm-suggested daily dose of CBA may be sub-

stantially greater than 300 mg/day. At this time, we do not recommend use of the algorithm for patients with CrCL of >70 ml/min/1.73 m^2 unless it is appropriate to target a low $C_{ss,avg}$ of colistin.

The PK data for critically ill patients obtained in the current study were integrated with PD data for *A. baumannii* and *P. aeruginosa* in murine thigh and lung infection models (12–13). In undertaking these translational analyses, because of the absence of information on plasma binding of colistin in critically ill patients, we utilized PD parameter estimates for total (i.e., unbound plus bound) colistin in plasma in the murine models and linked them with the colistin $C_{ss,avg}$ (i.e., total plasma concentration) expected to be achieved in the individual critically ill patients from algorithm-predicted maintenance doses targeting a colistin $C_{ss,avg}$ of 2.5 mg/liter. This approach assumes that the "average" unbound fraction in infected mice is similar to that in infected humans. We chose a colistin $C_{ss,avg}$ of 2.5 mg/liter (corresponding to a target AUC_{0-24} of 60 mg · h/liter) for two reasons: first, it was similar to the median $C_{ss,avg}$ of 2.36 mg/liter in the 105 patients with the physician-selected maintenance doses of CMS; second, against 3 strains each of *A. baumannii* and *P. aeruginosa* in murine thigh and lung infection models, a ratio of AUC_{0-24} to MIC of 60 was generally associated with an effect somewhere between stasis and 1-log kill, with the exception of *P. aeruginosa* in thigh infection, where a smaller effect was observed (unpublished data from references 12 and 13 for data based on the total plasma colistin concentration). From the results of these analyses, it appears that the above maintenance doses (and resultant colistin $C_{ss,avg}$) would not be reliably effective against isolates with MICs greater than 0.5 mg/liter (Fig. 5 and Table 4). It is our opinion that in order to achieve dosage regimens with a high probability of safety and efficacy, it appears that colistin might best be used as part of a highly active combination. This is especially likely to be the case for patients with moderate to good renal function, for whom, as discussed above, it is not possible to achieve colistin $C_{ss,avg}$ values that are likely to be reliably effective without administration of maintenance doses of CMS which may increase the risk of nephrotoxicity.

In conclusion, this is the first study to report the results of population PK modeling for more than 100 critically ill patients with a diverse range of renal functions, including those requiring intermittent hemodialysis or continuous renal replacement therapy. Our modeling revealed that creatinine clearance was an important covariate in the clearance of both CMS and formed colistin. As a result, we have developed the first scientifically based dosing suggestions for CMS to generate a desired target steady-state plasma concentration of formed colistin in various categories of critically ill patients. Our current results suggest that because of the inability to achieve adequate plasma concentrations of formed colistin with CMS monotherapy, CMS/colistin might best be used as part of a highly active combination, especially when treating an infection caused by an organism with an MIC of >0.5 mg/liter in a patient with a creatinine clearance of >70 ml/min/1.73 m^2. The loading and maintenance dosing suggestions reported herein should be regarded as interim; they will be refined as we complete recruitment to a total of 238 critically ill patients and also model the pharmacodynamic and toxicodynamic endpoints.

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