

Population Pharmacokinetics and Outcomes of Critically Ill Pediatric Patients Treated with Intravenous Colistin at Higher Than Recommended Doses

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ABSTRACT Limited pharmacokinetic (PK) data suggest that currently recommended pediatric dosages of colistimethate sodium (CMS) by the Food and Drug Administration and European Medicines Agency may lead to suboptimal exposure, resulting in plasma colistin concentrations that are frequently <2 mg/liter. We conducted a population PK study in 17 critically ill patients 3 months to 13.75 years (median, 3.3 years) old who received CMS for infections caused by carbapenem-resistant Gram-negative bacteria. CMS was dosed at 200,000 IU/kg/day (6.6 mg colistin base activity [CBA]/kg/day; 6 patients), 300,000 IU/kg/day (9.9 mg CBA/kg/day; 10 patients), and 350,000 IU/kg/day (11.6 mg CBA/kg/day; 1 patient). Plasma colistin concentrations were determined using ultraperformance liquid chromatography combined with electrospray ionization-tandem mass spectrometry. Colistin PK was described by a one-compartment disposition model, including creatinine clearance, body weight, and the presence or absence of systemic inflammatory response syndrome (SIRS) as covariates ($P < 0.05$ for each). The average colistin plasma steady-state concentration ($C_{ss,avg}$) ranged from 1.11 to 8.47 mg/liter (median, 2.92 mg/liter). Ten patients had $C_{ss,avg}$ of ≥ 2 mg/liter. The presence of SIRS was associated with decreased apparent clearance of colistin (47.8% of that without SIRS). The relationship between the number of milligrams of CBA per day needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ and creatinine clearance (in milliliters per minute) was described by linear regression with different slopes for patients with and without SIRS. Nephrotoxicity, probably unrelated to colistin, was observed in one patient. In conclusion, administration of CMS at the above doses improved exposure and was well tolerated. Apparent clearance of colistin was influenced by creatinine clearance and the presence or absence of SIRS.

KEYWORDS colistin, population pharmacokinetics, children, creatinine clearance, systemic inflammatory response syndrome

The emergence of nosocomial infections caused by multidrug-resistant Gram-negative bacteria, observed worldwide for both adult and pediatric patients, has led to the resurgence of use of colistin. Also called polymyxin E, colistin was introduced in clinical practice in the 1950s but was soon replaced by newer antibiotics due to nephro- and neurotoxicity. It is currently active against many carbapenem-resistant

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isolates of *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Susceptibility MIC breakpoints for *A. baumannii*, *P. aeruginosa*, and the *Enterobacterales* are ≤ 2 mg/liter (CLSI, EUCAST). Colistin is administered parenterally in its inactive prodrug form, colistimethate sodium (CMS), which is subsequently converted to its active metabolite, colistin. Early pharmacokinetic (PK) studies of CMS in humans were based on microbiologic assays for determination of colistin concentrations in biological fluids and therefore overestimated colistin concentrations because of continuous, *ex vivo* conversion of CMS to colistin during the incubation period (1). Over the last decade, PK studies in adults using reliable high-performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods for quantification of colistin concentrations have led to proposed dosage recommendations for these patients (2–9). These studies have revealed significant interpatient variability in plasma concentrations among adult critically ill patients; population PK analysis also identified creatinine clearance (CrCL) as an important covariate for the clearance of CMS and the apparent clearance of colistin (3, 7, 8).

The U.S. Food and Drug Administration (FDA)- and the European Medicines Agency (EMA)-recommended doses of CMS for children with normal renal function are currently 75,000 to 150,000 IU/kg/day (equivalent to ~ 2.5 to 5 mg of colistin base activity [CBA]/kg/day) in 2 to 4 divided doses (10, 11). There have been only a few PK studies of CMS in pediatric patients using modern, valid assays for determination of colistin concentrations, with each study consisting of single or small series of patients (12–15). Results reported from another study involving 7 pediatric patients suggested dose-normalized plasma colistin concentrations substantially higher than those previously reported (16). That report prompted correspondence questioning the results (17); subsequently, the authors of the original report indicated that the conditions used in the LC-MS/MS assay to quantify colistin in the plasma of the 7 pediatric patients resulted in artificially high plasma colistin concentrations in samples containing CMS (18). A recently published PK study of 20 patients included children aged ≥ 2 years; traditional noncompartmental PK analysis was conducted, and covariates of the apparent clearance of colistin were not identified (19). Results of several of these studies suggest that administering CMS at doses currently recommended by the FDA or EMA for pediatric patients frequently results in plasma colistin concentrations of < 2 mg/liter (12–15, 19), which is the breakpoint for susceptibility of nosocomial Gram-negative pathogens to colistin. Population PK covariate analysis in 5 patients with a median age of 1.75 (range, 0.1 to 6.25) years also demonstrated that the clearances of CMS and colistin were related to CrCL (15).

In the present study, we aimed to investigate colistin PK in critically ill pediatric patients, aged 1 month to 14 years, who were treated with doses higher than those recommended by the FDA and EMA. We performed population PK analysis in order to investigate relationships between various demographic or clinical factors, such as CrCL or the presence of systemic inflammatory response syndrome (SIRS), with the apparent clearance of colistin. Based upon the population PK covariates identified, we investigated approaches to possibly develop a dosing algorithm for determination of CMS dose needed to achieve each 1 mg/liter of average steady-state plasma colistin concentration and evaluated generated equations using patient data from two previous studies (12, 15).

RESULTS

Patient characteristics. A total of 17 patients (6 female) were studied, aged from 3 months to 13.75 years (median age, 3.3 years). Fourteen of these patients were hospitalized in pediatric intensive care units (PICU) and 3 in neurosurgical and pediatric oncology units. Six patients (median age, 9.2 years) received CMS at 200,000 IU/kg/day (6.6 mg CBA/kg/day), 10 patients (median age, 2.8 years) were dosed at 300,000 IU/kg/day (9.9 mg CBA/kg/day), and one infant (5 months old) was dosed at 350,000 IU/kg/day (11.6 mg CBA/kg/day) (Table 1). SIRS data, pediatric risk of mortality (PRISM) score,

TABLE 1 Patients' demographic characteristics, CMS doses, and presence of SIRS^a

Patient	Sex	Age range	Wt (kg)	Estimated CrCL (ml/min/1.73 m ²) for dose		CMS dose [IU/kg/day (mg CBA/kg/day)]	SIRS presence at dose	
				1	5		1	5
1	F	2 yr to <4 yr	9.5	126.3	133.6	200,000 (6.6)	Yes	Yes
2	M	1 mo to <2 yr	13	111.3	106.1	300,000 (9.9)	Yes	Yes
3	M	2 yr to <4 yr	9	127.4	146.7	300,000 (9.9)	No	No
4	M	1 mo to <2 yr	5	72.5	74.6	300,000 (9.9)	No	No
5	M	1 mo to <2 yr	6.2	65.1	65.1	300,000 (9.9)	Yes	Yes
6	M	6 yr to <8 yr	22	113.9	115.9	300,000 (9.9)	NR	NR
7	M	1 mo to <2 yr	3.8	61.9	61.9	350,000 (11.6)	No	No
8	F	8 yr to <10 yr	34	176.8	NR	200,000 (6.6)	NR	NR
9	M	8 yr to <10 yr	27	138.0	146.3	300,000 (9.9)	NR	NR
10	F	1 mo to <2 yr	6.5	168.7	168.7	300,000 (9.9)	Yes	Yes
11	M	10 yr to <12 yr	40	131.2	175.0	200,000 (6.6)	Yes	Yes
12	F	8 yr to <10 yr	50	130.7	135.2	200,000 (6.6)	Yes	Yes
13	M	4 yr to <6 yr	18	113.2	127.9	300,000 (9.9)	Yes	No
14	F	12 yr to 14 yr	47	149.8	127.8	200,000 (6.6)	Yes	No
15	M	1 mo to <2 yr	5.8	85.9	NA	200,000 (6.6)	Yes	NA
16	M	12 yr to 14 yr	44	244.2	305.3	300,000 (9.9)	Yes	Yes
17	F	2 yr to <4 yr	15	172.3	172.3	300,000 (9.9)	Yes	Yes

^aCrCL, creatinine clearance; CMS, colistimethate sodium; CBA, colistin base activity; SIRS, systemic inflammatory response syndrome; F, female; M, male; NR, not recorded; NA, not applicable (patient did not receive the fifth dose).

and pediatric logistic organ dysfunction (PELOD) score were provided only for PICU patients. Most patients received CMS for sepsis or ventilator-associated pneumonia (VAP) caused by Gram-negative organisms, such as *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. Seven of these patients had documented bacteremia. In all cases, CMS was coadministered with other antimicrobials possibly active against Gram-negative bacteria. Duration of CMS treatment ranged between 10 and 28 days (Table 2).

Pharmacokinetic analysis. The population PK of formed colistin was described by a one-compartment disposition model (see Fig. S1A in the supplemental material). The final model included a first-order process that described the increase in formed colistin concentrations due to conversion of CMS to colistin and estimated a first-order formation rate constant. The apparent clearance and volume of distribution of formed colistin, including their interindividual variabilities, were also estimated. Interindividual variability of the formation rate constant was not estimable. Interoccasion variability in the apparent volume of distribution was incorporated in the model. Covariate effects that were included in the final model were total body weight and the presence or absence of SIRS on the apparent clearance of formed colistin, CrCL on the estimated relative fraction of CMS that was converted to formed colistin (20), and total body weight on the apparent volume of distribution of colistin. All covariates were included as time-varying covariates. Following inclusion of these covariate effects, no further biologically plausible effects of other potential covariates, such as height, age, sex, PRISM, or PELOD, were identified. The final model described the data well, as indicated by the diagnostic plots and model fits (Fig. S1B and C).

The population mean parameters were estimated with good precision by the final model (all standard errors [SE] were <30%) (Table 3). The apparent population mean clearance was 4.10 liters/h for a typical subject with 15 kg body weight and without SIRS. The presence of SIRS was correlated with a substantially decreased apparent clearance of colistin, which was 47.8% of that without SIRS. The relative fraction of CMS converted to colistin was inversely correlated with CrCL. A potential effect of the outlying concentrations that were omitted from the final modeling data set was evaluated. The final model was rerun with the two outlying concentrations from patient 7 included in the data set, which resulted in very similar population PK parameter estimates but increased the unexplained interindividual variability.

TABLE 2 Type of infection, Gram-negative organism implicated, coadministered antimicrobial agents, outcome, and renal toxicity^a

Patient	Type of infection	Treatment duration (days)	Organism implicated	Site of isolation	Coadministered antimicrobial agents	Outcome	Renal toxicity
1	VAP	28	<i>P. aeruginosa</i>	BA	TZP, CLR	Death	No
2	Fever unresponsive to broad-spectrum ABx, colonization with CR, <i>P. aeruginosa</i>	10	<i>P. aeruginosa</i>	Throat swab	MEM, AMK, TEC	Cure	No
3	Possible VAP, colonization with <i>P. aeruginosa</i> and <i>A. baumannii</i>	20	<i>P. aeruginosa</i> , <i>A. baumannii</i>	BA	CIP, TGC	Cure	No
4	VAP	20	<i>P. aeruginosa</i>	BAL fluid	FEP, TEC	Cure	No
5	Sepsis	19	<i>A. baumannii</i>	Blood	MEM, AMK, LZD	Cure	No
6	Bacteremia	10	<i>K. pneumoniae</i>	Blood	MEM, GEN, SXT	Cure	No
7	VAP	20	<i>A. baumannii</i>	BA	MEM, AMK	Clinical improvement	No
8	VAP	10	<i>A. baumannii</i>	BA	MEM, TEC	Cure	No
9	Bacteremia	10	<i>A. baumannii</i>	Blood	MEM, GEN, TZP	Cure	No
10	Septic shock, VAP	15	<i>Stenotrophomonas maltophilia</i>	BAL fluid	MEM	Death	No
11	Septic shock	17	<i>P. aeruginosa</i>	Blood	MEM, VAN, RIF, CIP, AZM	Clinical improvement	No
12	VAP, bacteremia	10	<i>A. baumannii</i>	Blood, BA	TGC, TEC, AMK, TZP	Cure	No
13	Sepsis	23	<i>K. pneumoniae</i>	Blood	MEM, GEN, TEC, TGC, FOF, SXT	Death	Yes
14	Surgical trauma infection	20	<i>A. baumannii</i>	Trauma site, BAL fluid	MEM, LZD, TGC	Cure	No
15	VAP	28	<i>A. baumannii</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	BAL fluid	GEN, TGC	Cure	No
16	Septic shock	20	<i>P. aeruginosa</i>	Blood	MEM, GEN, TZP, SXT	Clinical improvement	No
17	Sepsis	17	<i>S. maltophilia</i>	Blood	CIP, TEC	Cure	No

^aABx, antibiotics; AMK, amikacin; BA, bronchial aspirate; BAL, bronchoalveolar lavage; CIP, ciprofloxacin; CLR, clarithromycin; CR, carbapenem-resistant; FEP, cefepime; FOF, fosfomicin; GEN, gentamicin; LZD, linezolid; MEM, meropenem; RIF, rifampin; SXT, trimethoprim-sulfamethoxazole; TEC, teicoplanin; TGC, tigecycline; TZP, piperacillin-tazobactam; VAN, vancomycin; VAP, ventilator-associated pneumonia.

In the current study, the clinician-selected daily dose of CMS ranged from 200,000 to 350,000 IU/kg/day (6.6 to 11.6 mg CBA/kg/day), and the resulting average steady-state plasma colistin concentration ($C_{ss,avg}$) derived from the population PK analysis ranged from 1.11 to 8.47 mg/liter, with a median of 2.92 mg/liter. Ten of the 17 patients achieved a plasma colistin $C_{ss,avg}$ of ≥ 2 mg/liter, five of whom had a concentration of ≥ 4 mg/liter. The median (range) plasma colistin $C_{ss,avg}$ expected to be achieved if the 17 patients had been administered the lower (2.5 mg/kg/day) or upper (5 mg/kg/day) limit of the FDA- and EMA-approved doses were 0.75 (0.29 to 3.21) mg/liter and 1.50 (0.58 to 6.42) mg/liter, respectively; i.e., at each dose, there was an expected 11-fold range of concentrations.

A number of graphical approaches were explored in an attempt to identify a possible path to formulation of dosing guidelines to target a desired plasma colistin concentration. From knowledge of the plasma colistin $C_{ss,avg}$ achieved from the administered daily dose of CBA in each patient, it was possible to calculate the daily dose of CBA needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$. These daily doses of CBA are presented in Fig. 1 as a function of the covariates of the apparent clearance of colistin identified in the population PK analysis, namely, CrCL, the presence or absence of SIRS, and total body weight. In Fig. 1A, the relationship between the number of milligrams per day of CBA needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ and CrCL (in milliliters per minute) was described by linear regression both for patients with SIRS and for those without SIRS; the slope of the relationship for patients with SIRS (slope = 0.823; $R^2 = 0.81$) was 47% of that for patients without SIRS (slope = 1.748; $R^2 = 0.74$). In contrast, there was no relationship between the body weight-normalized

TABLE 3 Population PK parameter estimates, interindividual and interoccasion variability, and precision of estimates

Parameter (unit) ^a	Population estimate	% CV (% shrinkage)		% SE
		Interindividual	Interoccasion	
Apparent clearance (liters/h/15 kg ^{0.75}) in absence of SIRS	4.10	53 (4.1)		20
Apparent vol of distribution (liters/15 kg)	20.7	40 (37)	62 (dose 1, 41; dose 5, 8.1)	21
Formation rate constant (h ⁻¹)	1.50			17
RFM _{slope} [(48 ml/min) ⁻¹]	0.146			12
Fraction of clearance in the presence of SIRS	0.478			26
Terminal half-life of colistin (h)	4.96 ^b			
SD _{slope} (%)	20			
SD _{intercept} (mg/liter)	0.300			

^aApparent clearance and volume of distribution for a creatinine clearance of 0 ml/min; RFM, relative fraction of CMS converted to colistin {1 - [RFM_{slope} × creatinine clearance/(48 ml/min)]} (14); RFM_{slope}, slope of RFM change by creatinine clearance; SD_{slope}, proportional residual error; SD_{intercept}, additive residual error (ε shrinkage was 12.6%).

^bMedian of the individual estimates calculated based on the apparent clearance and apparent volume of distribution (10th to 90th percentile 2.57 to 10.80 h).

daily dose needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ and CrCL for patients either with SIRS ($R^2 = 0.12$) or without SIRS ($R^2 = 0.001$) (Fig. 1B); there was a 6.95-fold range of daily doses for patients with SIRS (0.78 to 5.42 mg/kg/day) and a 3.52-fold range for patients without SIRS (2.44 to 8.59 mg/kg/day).

The corresponding plots of the daily dose of CBA to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ versus CrCL normalized to body surface area (i.e., milliliters per minute per 1.73 m²) are presented in Fig. S2. The relationships in Fig. S2A had lower coefficients of determination (R^2) and very large intercepts on the x axis relative to the corresponding relationships for CrCL expressed in milliliters per minute (Fig. 1). Although patient age was not identified as a covariate in the population PK analysis, that variable was investigated for possible relationships with the daily dose of CBA for each 1 mg/liter plasma colistin $C_{ss,avg}$ (Fig. S3). The R^2 values for the relationships

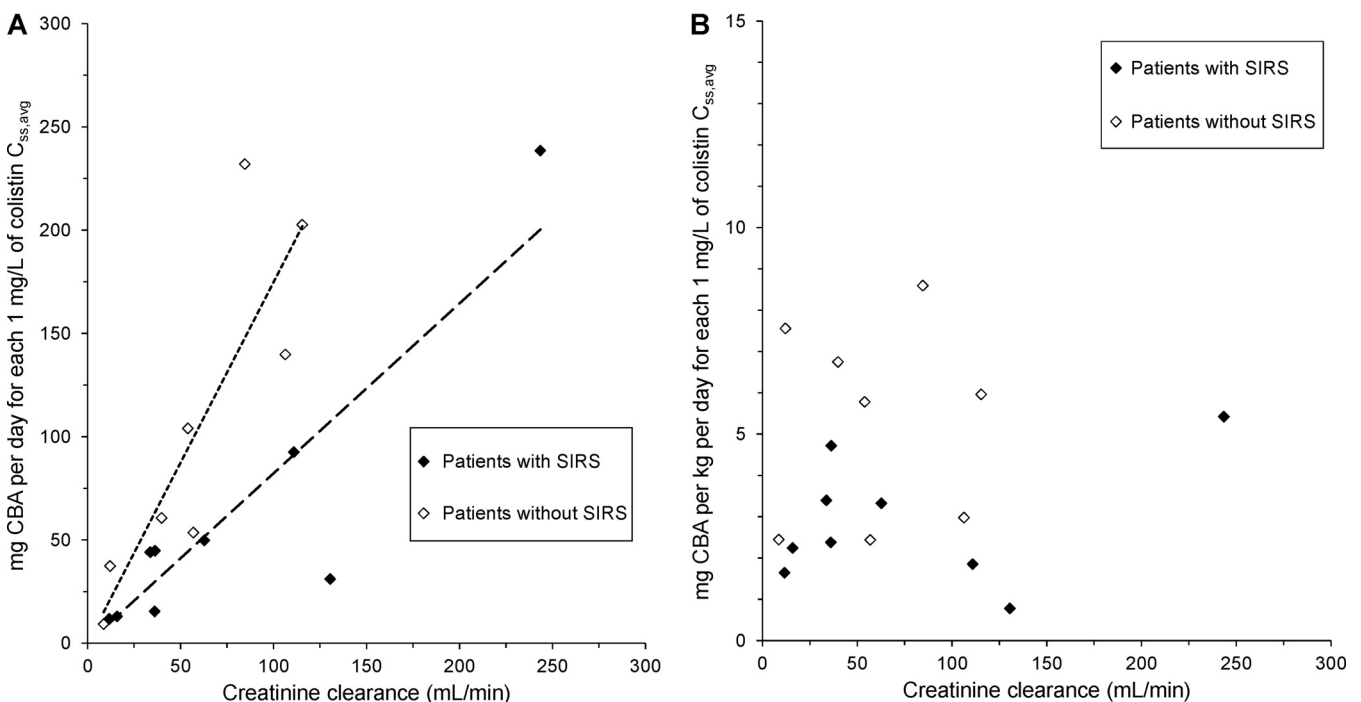


FIG 1 Relationships between the daily dose of colistin base activity (CBA), expressed as milligrams per day (A) and as milligrams per kilogram per day (B), needed for each 1 mg/liter of the average steady-state plasma concentration of colistin ($C_{ss,avg}$) and creatinine clearance (in milliliters per minute). In panel A, data for patients with SIRS (filled symbols; $R^2 = 0.81$) and without SIRS (empty symbols; $R^2 = 0.74$) were regressed separately.

presented in Fig. S3A were low relative to the relationships for patients with and without SIRS presented in Fig. 1A; the relationships in Fig. S3A almost certainly arose because there were strong relationships ($R^2 = 0.87$ and 0.85 , respectively) (Fig. S4) between the physiological variable, CrCL, and the demographic variable, age.

The equations for the regression lines in Fig. 1A for patients with and without SIRS were used to estimate for each patient the dose of CMS, expressed as milligrams of CBA per day, needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$. Those doses were then applied back to the patients to estimate the plasma colistin $C_{ss,avg}$ predicted to be achieved had those doses been administered. For the 8 patients without SIRS, the median (range) plasma colistin $C_{ss,avg}$ predicted was 1.07 (0.56 to 1.86) mg/liter, a 3.3-fold range; for the 9 patients with SIRS, the corresponding values were 0.99 (0.63 to 3.44) mg/liter, a 5.5-fold range. Across all 17 patients, the median predicted $C_{ss,avg}$ was 1.00 mg/liter with a 6.1-fold range when the respective regression equations for patients with and without SIRS were applied. When the same equations were applied to the 5 cases reported by Antachopoulos et al. (12) and the 5 patients reported by Ooi et al. (15), the predicted plasma colistin $C_{ss,avg}$ were 0.67 (0.21 to 1.02) mg/liter and 0.69 (0.25 to 1.07) mg/liter, respectively. When the respective regression equations for patients with and without SIRS were applied to all patients across the present and those two previous studies (i.e., 27 cases) the median (range) predicted $C_{ss,avg}$ was 0.91 (0.21 to 3.44) mg/liter, a >16-fold range. In Fig. 1B, the median body weight-normalized daily doses of CMS needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ for patients with and without SIRS were 2.38 and 5.87 mg/kg/day, respectively. When those doses were applied back to each of the 17 patients in the current study to estimate the plasma colistin $C_{ss,avg}$ predicted to be achieved had those doses been administered, the median (range) plasma colistin $C_{ss,avg}$ predicted for the 8 patients without SIRS was 1.00 (0.68 to 2.41) mg/liter, a 3.5-fold range; for the 9 patients with SIRS the corresponding values were 1.00 (0.44 to 3.05) mg/liter, a 7.0-fold range. When the median doses (in milligrams per kilogram per day) for patients with and without SIRS (Fig. 1B) were applied to the 5 cases reported by Antachopoulos et al. (12) and the 5 patients reported by Ooi et al. (15), the predicted plasma colistin $C_{ss,avg}$ were 0.88 (0.28 to 1.19) mg/liter and 0.30 (0.15 to 2.04) mg/liter, respectively. When the respective median body weight-normalized daily doses of CMS needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ for patients with and without SIRS were applied to all patients across the present and those two previous studies (i.e., 27 cases), the median (range) predicted $C_{ss,avg}$ was 0.98 (0.15 to 3.05) mg/liter, a >20-fold range.

Patient outcome and adverse events. In 14 of 17 patients a favorable outcome was observed, with cure or clinical improvement. Death occurred in 3 patients. Renal toxicity was observed in only one patient treated with 300,000 IU/kg/day (9.9 mg CBA/kg/day), who had rapidly progressing Burkitt lymphoma and was also receiving gentamicin and teicoplanin (patient 13 [Pt13]) (Tables 1 and 2). Three patients (Pt7, Pt11, and Pt14) (Tables 1 and 2) had moderate and transient increase of transaminases during the second week of treatment with CMS (maximum alanine aminotransferase values, 105, 132, and 113 U/liter, respectively, which for Pt7 and Pt14 normalized while they were still on CMS treatment). One patient (Pt12) developed urticarial rash on the last (10th) day of treatment. Finally, Pt11 developed seizures on the last (17th) day of treatment, which recurred 1 and 2 weeks after the discontinuation of CMS administration.

DISCUSSION

In the present study, we investigated colistin PK in critically ill hospitalized pediatric patients across a wide range of ages. The patients received CMS at doses higher than currently recommended by the FDA and EMA for treatment of severe infections caused by multidrug-resistant Gram-negative bacteria. These doses (200,000, 300,000, and 350,000 IU/kg/day, or 6.6, 9.9, 11.6 mg CBA/kg/day, respectively) were employed by the treating physicians based on published data suggesting suboptimal exposure for pediatric patients treated with lower doses (12–15). We performed population PK

analysis in order to identify factors affecting colistin apparent clearance and possibly develop a dosing algorithm. As there are no studies on the use of such high CMS doses in children, we closely monitored our patients for clinical and laboratory signs of toxicity.

The population PK analysis was based on concentrations of colistin, as unfortunately plasma concentrations of the inactive prodrug, CMS, were not available. The modeling approach was as described by Lee et al. (20), which involved a parameter (the relative fraction of CMS converted to colistin) to reflect the influence of renal function on the fraction converted, and hence on the apparent clearance of formed colistin. A one-compartment structural model satisfactorily described the PK of colistin formed *in vivo* after the administration of CMS, in keeping with previous studies in pediatric patients (14, 15) and healthy and sick adults (2, 3, 5, 7, 20, 21).

A number of potential covariates were examined in the population PK modeling. While the relatively small number of 17 subjects in the study may have resulted in a risk of selection bias, it should be noted that eta shrinkage was small and that this is to date the largest population PK study of colistin in pediatric patients. Total body weight was found to be a covariate of the apparent volume of distribution of formed colistin, in agreement with a small-population PK study in pediatric patients reported previously (15). Since the apparent clearance of colistin is the PK parameter that influences the daily dose of CMS required to achieve a desired target plasma colistin $C_{ss,avg}$, an important finding was that the apparent clearance was influenced by CrCL and the presence or absence of SIRS.

Creatinine clearance has been reported as a covariate of the apparent clearance of formed colistin in both pediatric and adult patients (3, 7, 8, 15, 20). The apparent clearance of formed colistin is strongly influenced by renal function because the latter modulates the proportion of each dose of the extensively renally cleared prodrug (CMS) that is available for conversion to colistin; as renal function declines, the fraction of a CMS dose converted to colistin increases, thereby decreasing the apparent clearance of formed colistin (3, 5, 7, 22). SIRS (or sepsis) has been reported to influence the PK of some antibiotics (23) but not, thus far, of colistin. The dysregulated inflammatory and other responses associated with SIRS (or sepsis) can lead to a wide range of pathophysiological changes in the functioning of numerous organs, including the heart, lungs, liver, and kidneys (24). In the case of the kidneys, outcomes can range from augmented renal clearance (ARC) relatively early in the pathogenesis to renal impairment and acute kidney injury (AKI) if sepsis is not controlled (23, 25–29). ARC (creatinine clearance > 130 ml/min/1.73 m²) was observed in 9 of the 17 patients in this study and has been reported to be common in pediatric patients (25, 30, 31). The impact of ARC and/or renal impairment in pediatric patients on the PK of antibiotics in general (32, 33), and colistin in particular (14, 15), has been reported.

The duration of SIRS has been observed to modulate the PK of vancomycin, a renally cleared drug; vancomycin clearance in patients with a SIRS duration of <2 days was higher than that for patients with a SIRS duration of ≥ 6 days (34). The impact of SIRS on PK is not restricted to drugs that are primarily excreted in urine. A population PK study of pantoprazole, a proton pump inhibitor that is extensively metabolized, in pediatric patients reported that the presence of SIRS was associated with a significantly lower clearance of the drug, a finding considered to be the result of SIRS-related inflammatory processes impairing cytochrome P450 enzymes (35). In the current study, the apparent clearance of colistin at a given CrCL in patients with SIRS was only $\sim 47\%$ (based on both the population PK modeling and the relative slopes in Fig. 1A) of that in patients without SIRS. This may have been partly due to an effect on the nonrenal excretory clearance of formed colistin, although metabolic and other elimination pathways for colistin have not been elucidated.

We sought to investigate possible ways to select a daily dose of CMS for an individual pediatric patient. First, we predicted the plasma colistin $C_{ss,avg}$ expected if each patient in the study had received the lower- and upper-limit doses approved by the

FDA and EMA for pediatric patients, 2.5 and 5 mg CBA/kg/day, respectively. That analysis revealed that only 1 and 7, respectively, of the 17 patients were expected to achieve a plasma colistin $C_{ss,avg}$ of ≥ 2 mg/liter, a proposed initial target concentration intended to cover isolates with an MIC at the clinical breakpoint (2 mg/liter) (6, 7, 9). At the higher of the two doses, 6 patients would be likely to achieve a $C_{ss,avg}$ of < 1 mg/liter. The observation in the current study of an inability to reliably achieve a plasma colistin $C_{ss,avg}$ of ≥ 2 mg/liter with FDA- and EMA-approved doses adds to the same finding from two studies involving a total of 6 pediatric patients (14, 15). This observation should be considered in the context of a recently reported study based on prescribing information from 2 international data collection networks spanning 6 World Health Organization regions. That study found that 63.8% of children and 58.8% of neonates were prescribed intravenous doses of colistin below the lowest FDA and EMA recommendation (2.5 mg CBA/kg/day) (36). It is likely that many, perhaps most, of those pediatric patients would have had plasma colistin $C_{ss,avg}$ substantially lower than the suggested target of 2 mg/liter (6, 7, 9).

Of the various graphical approaches explored as possible means to develop a dosing algorithm for pediatric patients, the most promising were the relationships, for patients with and without SIRS, between the number of milligrams of CBA per day needed to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ and CrCL in milliliters per minute (Fig. 1A), the same as the relationship employed to develop dosing suggestions for individual adult critically ill patients (7, 9). When the algorithm-derived doses were applied back to each of the 17 patients in the current study, the median predicted $C_{ss,avg}$ was ~ 1 mg/liter, but wide interpatient variability was observed, similar to that reported previously in adult patients (7). When the derived doses were applied to patients reported in previous studies (12, 15), the median predicted $C_{ss,avg}$ values were only ~ 0.7 mg/liter and the maxima were only slightly greater than 1 mg/liter. Variability within and across the three studies in the predicted plasma colistin $C_{ss,avg}$ is very likely the result of batch-to-batch variability in the multicomponent composition of CMS products, which influences the fraction of each dose of the prodrug that is converted to colistin, this fraction being a key determinant of the apparent clearance of colistin (3, 7, 8, 37, 38).

While it would be beneficial to have data from a larger number of pediatric patients, the current analyses suggest that it is not likely to be a satisfactory way to select individualized doses for pediatric patients. The findings highlight the importance of (i) closely monitoring each patient for clinical and microbiological signs of improvement or deterioration in infection status, (ii) careful observation to detect any deterioration in renal function or evidence of other adverse effects, and (iii) undertaking therapeutic drug monitoring whenever possible to fine-tune CMS dosing based on measurement of plasma colistin concentrations (9, 37).

The clinical outcomes across the 17 patients were very good. Clinical cure or improvement of infection occurred in 14 patients. A formal PK/pharmacodynamic (PD) analysis was not possible for three reasons. First, the total number of patients in the study was relatively small, and there were only three cases where death occurred during treatment (in those cases the plasma colistin $C_{ss,avg}$ were 1.40, 4.16, and 1.71 mg/liter). Second, all of the patients received one or more other antibiotics for treatment of their infection. Third, information on colistin susceptibility (MIC) for implicated organisms was mostly based on the Vitek2 automated system (bioMérieux, Marcy l'Étoile, France), which may yield high rates of erroneous susceptible results (39). Similarly, a formal PK/toxicodynamic (TD) analysis was not possible because there was only one patient who manifested renal toxicity, and that was considered to be due to Burkitt lymphoma, and the patient succumbed; the plasma colistin $C_{ss,avg}$ was 1.71 mg/liter. The renal findings were remarkable given that all patients received doses higher than the upper limit dose approved by the FDA and EMA; indeed, $\sim 65\%$ of patients received a dose approximately double that of the maximum label dose. Five of the patients achieved plasma colistin $C_{ss,avg}$ of ≥ 4 mg/liter, higher than the value (≥ 2 mg/

liter) associated with increased incidence and severity of AKI in adult patients (9, 40–42), and most of the patients received one or more other potentially nephrotoxic antibiotics. Recent reports and reviews have concluded that coadministration of colistin with other antibiotics was associated with a favorable outcome in the majority of pediatric patients and a relatively low rate of nephrotoxicity (43, 44). The results of the current and previous studies may serve to prompt the FDA and EMA to review the appropriateness of pediatric dosing guidelines in the product label.

In conclusion, intravenous administration of CMS at doses higher than those recommended by the FDA and EMA in critically ill pediatric patients was well tolerated and resulted in improved exposure, although wide interpatient variability was observed, similar to that previously reported for adult patients. Colistin PK was satisfactorily described by a one-compartment disposition model and its apparent clearance was influenced by creatinine clearance and the presence or absence of SIRS. The relationship between the dose of CBA (expressed in milligrams per day) required to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$ and creatinine clearance (expressed in milliliters per minute) was described by linear regression with different slopes for patients with and without SIRS. However, when the equation-derived doses were applied back to patients of the current and previous studies, considerable variability in the predicted plasma colistin $C_{ss,avg}$ was observed, precluding the development of a generalizable dosing algorithm for pediatric patients. When available, therapeutic drug monitoring is recommended to assist in dose titration to achieve a desired level of exposure.

MATERIALS AND METHODS

Patients and study design. This was a prospective, open-label PK study, enrolling patients from two pediatric intensive care units (PICU), a neurosurgical and a pediatric oncology unit, located at Hippokraton Hospital of Thessaloniki and University Hospital of Heraklion, Greece. The study was approved by the Ethics Committees of the two hospitals. Written informed consent was obtained from patients' parents or alternative legal representatives.

Patients eligible for the study were children 1 month to 14 years old, who were hospitalized from June 2014 to December 2017 and received CMS because of possible or documented infection by carbapenem-resistant Gram-negative bacteria. The decision to initiate or discontinue CMS was taken by the treating physicians, with no involvement of the study team. Criteria for exclusion were (i) administration of CMS through other routes (intraventricular, intrathecal, or via inhalation); (ii) cystic fibrosis; (iii) renal impairment, manifested as serum creatinine above the upper limit for age (>0.4 mg/dl, 0.7 mg/dl, and 1.0 mg/dl for infants, children, and adolescents, respectively); (iv) great difficulty in vascular access; and (v) parental refusal of consent.

CMS administration. CMS (Norma Hellas S.A., Athens, Greece) was administered at doses of 200,000 IU/kg/day (6.6 mg CBA/kg/day), 300,000 IU/kg/day (9.9 mg CBA/kg/day), or 350,000 IU/kg/day (11.6 mg CBA/kg/day), at 8-h intervals, infused intravenously over 20 min in 50 ml of normal saline. The decision on the dose of CMS to be administered was taken by the patients' treating physicians in consultation with the attending infectious diseases specialist. The above doses were chosen based on our previous study (12) as well as preliminary PK data. In general, a dose of 200,000 IU/kg/day (6.6 mg CBA/kg/day) was administered to younger patients (1 month to 8 years old) with possible infection and to older children (9 to 14 years old) with possible or documented infection of moderate severity. The dose of 300,000 IU/kg/day (9.9 mg CBA/kg/day) was administered to children 9 to 14 years old with severe infection and to those 1 month to 8 years old with probable or documented infection of any severity. The dose of 350,000 IU/kg/day (11.6 mg CBA/kg/day) was chosen as an exception for patients 1 month to 2 years old with very severe sepsis.

PK sampling. Blood samples (0.5 to 1 ml) were collected immediately before and at 30, 60, 90, 120, 240, and 360 min after the end of infusion of the first and fifth doses of CMS. The precise time of collection was documented for each sample. After immediate centrifugation of samples at 4°C, collected plasma was stored at –80°C until assayed to minimize potential *ex vivo* conversion of CMS to colistin (1, 45).

Determination of colistin concentrations in plasma. Colistin concentrations in plasma were determined using ultraperformance liquid chromatography (UPLC) combined with electrospray ionization (ESI) tandem mass spectrometry (MS/MS) on a hybrid quadrupole time of flight (QTOF) instrument, as previously described (46). The method presented good fit (regression coefficient, ≥ 0.998) over the quantitation ranges of 0.02 to 3 and 0.03 to 4.5 mg/liter, with the lower limit of quantitation (LLOQ) being 0.02 and 0.03 mg/liter for colistin A and colistin B in human plasma, respectively. Samples for which the measured concentrations of colistin A or B exceeded the upper limit of the calibration curve (3 or 4.5 mg/liter, respectively) were diluted with blank drug-free plasma in order to bring the concentrations into the above-mentioned ranges. The intraday and interday precision of the method was 14.2% and 13.2%, respectively, while the relative error did not exceed 14.9%. The colistin plasma concentrations reported here are the sum of colistin A and colistin B concentrations for each patient and time point.

Patient data. Various parameters were recorded that could possibly be implicated in colistin PK, such as sex, age, body weight, height, body surface area, serum creatinine, calculated CrCL, the presence of SIRS, pediatric risk of mortality (PRISM) score, and pediatric logistic organ dysfunction (PELOD) score at the time of sampling. Serum creatinine levels were determined using the Jaffe method. CrCL was calculated using the Schwartz formula (estimated CrCL = $k \times \text{height}/\text{serum creatinine concentration}$, where $k = 0.45$ for infants, 0.55 for children and adolescent [>10 years old] girls, and 0.70 for adolescent boys, CrCL is measured in milliliters per minute per 1.73 m^2 , height is measured in centimeters, and serum creatinine concentration is measured in milligrams per deciliter) (47). The presence of SIRS was determined after assessment of patients' core temperature, heart rate, respiratory rate, and blood leukocyte count, using previously published age-specific criteria for pediatric patients (48). PRISM and PELOD scores were calculated as previously described (49, 50).

In addition, infection- or treatment-related data were recorded, such as type of infection for which CMS was administered, causative organism (if isolated), duration of CMS treatment, coadministered antibiotics and potentially nephrotoxic agents, and outcome. Patients had daily clinical assessment and laboratory workup (including full blood count, liver function tests, electrolytes, and renal function). Any clinical or laboratory adverse events that could be attributed to CMS treatment were recorded. Renal toxicity was identified as increase of serum creatinine above the upper limit for age.

Pharmacokinetic analysis. Population PK modeling of colistin in plasma was conducted using the first-order conditional estimation algorithm with interaction (FOCE+I) in NONMEM version 7.2 (ICON Development Solutions, Ellicott City, MD). After careful examination of the observed data, the only concentration-time point data not included were as follows: (i) 26 samples (22 of which were collected after the first dose) for which the concentration of colistin A was below the lower limit of quantification, as the PK analysis was based on the sum of concentrations of colistin A and colistin B as described previously (2–4, 7, 8); (ii) for patient 7, data for the 32- and 63-min samples after the fifth dose, as the concentrations (15.8 and 20.9 mg/liter, respectively) were implausibly high compared to the subsequent concentrations for this dose in the same subject and also relative to the concentrations at the corresponding time points after the first dose. All remaining colistin concentrations from all 17 subjects were modeled simultaneously.

Models with one and two disposition compartments for formed colistin were evaluated. The formation of colistin from CMS was described by a first-order process. The interindividual variability in the PK parameters was described by a log-normal distribution. Models with and without covariance were tested. Inclusion of interoccasion variability was evaluated to describe differences in the formed colistin concentrations between the first and fifth dose within a subject, which were not explained by the increase of formed colistin concentrations to steady state. The residual unexplained variability was incorporated through a combined proportional plus additive error model.

The possible effects of patient characteristics, including renal function (creatinine clearance) (47), total body weight, presence or absence of SIRS (48), height, age, sex, PRISM, and PELOD on the disposition of formed colistin were explored. The effect of body weight on the PK parameters was based on allometric scaling, using standard power coefficients of 0.75 for clearance and 1.0 for volume of distribution. Inclusion of covariates was based on graphical analysis, change in the objective function, the reduction in unexplained interindividual variability, and biological plausibility. Candidate models were evaluated based on plots of observed versus individual-fitted and observed versus population-fitted concentrations, conditional weighted residuals, the normalized prediction distribution error, and the log-likelihood ratio test for nested models.

The population PK analysis enabled determination for each patient of the average plasma steady-state concentration ($C_{ss,avg}$) of colistin achieved with the respective administered daily dose of CMS, expressed as CBA. This enabled the following analyses. First, the performance of the current FDA and EMA pediatric dosing guidelines (10, 11) was investigated as follows. Using direct proportionality, based on linear PK of colistin (3, 5, 7, 8, 21), the plasma colistin $C_{ss,avg}$ expected to be achieved had each patient received the upper- and lower-limit FDA- and EMA-recommended daily doses were calculated (6, 15). Second, to explore possible approaches to formulating new dosage guidelines, the daily dose of CBA required to achieve each 1 mg/liter of plasma colistin $C_{ss,avg}$, a surrogate of the apparent clearance of formed colistin, was also determined for each patient (3, 7). This enabled graphical approaches to investigate possible clinically useful relationships with patient characteristics (e.g., CrCL and other clinical characteristics) to develop a dosing algorithm. Promising approaches were further evaluated using patient data from previous studies by Antachopoulos et al. (12) and Ooi et al. (15). In the first of those studies peak and trough plasma colistin concentrations were reported (12); for the current analyses, the plasma colistin $C_{ss,avg}$ for each patient was determined as the logarithmic average of the peak and trough concentrations.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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