A Population Pharmacokinetic Analysis to Study the Effect of Extracorporeal Membrane Oxygenation on Cefepime Disposition in Children

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Objectives: Limited data exist on the effects of extracorporeal membrane oxygenation on pharmacokinetics of cefepime in critically ill pediatric patients. The objective was to describe cefepime disposition in children treated with extracorporeal membrane oxygenation using population pharmacokinetic modeling.

Design: Multicenter, prospective observational study.

Setting: The pediatric and cardiac ICUs of six sites of the Collaborative Pediatric Critical Care Research Network.

Patients: Seventeen critically ill children (30 d to < 2 yr old) on extracorporeal membrane oxygenation who received cefepime as standard of care between January 4, 2014, and August 24, 2015, were enrolled.

Interventions: None.

Measurements and Main Results: A pharmacokinetic model was developed to evaluate cefepime disposition differences due to extracorporeal membrane oxygenation. A two-compartment model with linear elimination, weight effects on clearance, intercompartmental clearance (Q), central volume of distribution (V1), and peripheral volume of distribution (V2) adequately described the data. The typical value of clearance in this study was 7.1 mL/min (1.9 mL/min/kg$^{0.75}$) for a patient weighing 5.8 kg. This value decreased by approximately 40% with the addition of renal replacement therapy. The typical value for V1 was 1,170 mL. In the setting of blood transfusions, V1 increased by over two-fold but was reduced with increasing age of the extracorporeal membrane oxygenation circuit oxygenator.

Conclusions: Cefepime clearance was reduced in pediatric patients treated with extracorporeal membrane oxygenation compared with previously reported values in children not receiving extracorporeal membrane oxygenation. The model demonstrated that the age of the extracorporeal membrane oxygenation circuit oxygenator is inversely correlated to V1. For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_minimum inhibitory concentration of 16 mg/L, an appropriate target for the treatment of pseudomonal infections, for greater than 70% of the dosing interval. Pediatric patients on extracorporeal membrane oxygenation might benefit from the addition of therapeutic drug monitoring of cefepime to assure appropriate dosing. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: cefepime; extracorporeal membrane oxygenation; pediatrics; population pharmacokinetics

Extracorporeal membrane oxygenation (ECMO) can provide patients with severe cardiopulmonary failure partial or complete respiratory or cardiac support for days to weeks. This is accomplished by draining blood from the body into an extracorporeal circuit and pumping it across a membrane lung that oxygenates the blood and eliminates carbon dioxide (1). There are two types of ECMO circuits: 1) venovenous ECMO provides support for the lungs whereas 2) venoarterial ECMO provides support for both the heart and lungs. The ECMO system introduces variables that increase drug variability, which are inherent to the circuit itself, as well as the systemic inflammation that results from the use of the circuit. Sequestration of drugs in the circuit, increased volume of distribution (Vd), and decreased clearance are the major pharmacokinetic changes associated with ECMO (2, 3). Neonatal and adult studies have reported significant alterations in antibiotic, sedative, and analgesic disposition (4, 5). The amount of drug sequestration is influenced by many factors including the age of the circuit components, the circuit priming volume as well as the type of pump, oxygenator, and tubing (6–9). Patient factors such as systemic inflammation, hemodilution, bleeding, transfusion requirement, organ dysfunction, and renal replacement therapy (RRT) add to the challenges of appropriate drug administration during ECMO (10, 11). In addition, individual hospitals and ICUs use different techniques when building their respective ECMO circuits. The extent to which these factors can alter the variability in drug disposition has not been quantified to date and remains poorly characterized.

Cefepime, a fourth-generation cephalosporin, is a bactericidal agent that has broad spectrum of activity against both gram-positive and gram-negative bacteria, including activity against pseudomonas, making it a commonly used antibiotic in this population for suspected or known gram-negative infections (12). The pharmacodynamic relationship historically thought to be predictive of cefepime efficacy is the percentage of time of the dosing interval that the free drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting organism (*fT*_MIC) (13). Numerous in vivo animal studies with various cephalosporins have suggested that a *fT*_MIC target of 50–70% is required to achieve maximal reductions in the numbers of colony forming units of gram-negative bacteria (14). However, the data available from evaluations of cephalosporin pharmacodynamic have been less decisive and are discordant with the findings of in vivo animal studies. Published reports of studies examining cefepime pharmacodynamic in patients with gram-negative infections found the ratio of the minimum cefepime concentration to the MIC (C_{min}/MIC) to be the parameter best associated with a microbiological response, whereas another study defined the ratio of the area under the concentration-time curve to the MIC (AUC/MIC) to be the most predictive (15–17). Furthermore, when the *fT*_MIC for total drug was evaluated, investigators found that targets of 90–100% were required for predictable microbiological success (15, 17). These studies demonstrated that cefepime concentrations as high as 4–6.6 × MIC are required for bactericidal activity (17, 18), but these higher concentrations have also been associated with neurotoxicity (19). Overall, there is still no consensus on optimal dosing, but rather it is generally accepted to target a *fT*_MIC of 70–90% according to the suspected pathogen.

Data regarding the impact of ECMO on cefepime disposition is warranted given the need for therapeutic concentrations to ensure efficacy while also minimizing toxicity. Unlike antibiotics such as many aminoglycosides and vancomycin, cefepime dosing is not guided by therapeutic drug monitoring. As such, concentrations achieved with standard dosing are not routinely assessed. Achievement of target concentrations may not occur, especially in clinical scenarios such as ECMO where drug disposition may be impacted. The aim of this study was therefore to provide preliminary data on cefepime disposition in pediatric patients receiving ECMO therapy, specifically with regards to site-dependent differences in management.

MATERIALS AND METHODS

This multicenter observational pharmacokinetic study was conducted at hospitals in the Collaborative Pediatric Critical Care Research Network (CPCCRN). The project was approved by each institution's Institutional Review Board and the Data Coordinating Center at the University of Utah, and informed consent was obtained from parents/guardians before any study procedure commenced. Patients receiving ECMO therapy were screened daily for eligibility. Inclusion criteria included patients greater than or equal to 30 days old to less than 2 years old,

receiving ECMO therapy and IV cefepime for the treatment of known or suspected gram-negative infections based on the decision of the clinical care team. Exclusion criteria included treatment with ongoing massive blood product transfusion for hemorrhage, RRT, therapeutic plasma exchange, or previous enrollment in this study. A later protocol revision allowed subjects receiving RRT to be enrolled due to its frequent utilization during ECMO, enabling and assessment of its impact on cefepime pharmacokinetic and improved the study generalizability. Once eligibility criteria were met, the parent(s) or legal guardian(s) were approached for consent.

Cefepime could have been prescribed every 6, 8, 12, 18, or 24 hours. For each subject, target pharmacokinetic samples (n = 10) were collected based on the dosing interval for one or two cefepime doses separated in time by at least 24 hours. Separating the two cefepime doses by at least 24 hours instead of consecutive doses allowed evaluation of cefepime disposition due to any potential impact of circuit age within each subject. Hypothetically, older circuits are exposed to more medications, and potential drug-binding sites may became saturated. A maximum of 20 mL (1 mL per sample) could be collected from lumens not used to administer cefepime. After collection, samples were transferred to labeled lithium heparinized tubes and placed immediately on ice.

Plasma Sample Analysis

Plasma was separated from blood by centrifuging samples at 2,500 rpm for 10 minutes and then stored at –80°C. The cefepime concentrations in plasma samples were determined using a validated high-performance liquid chromatography and tandem mass spectrometry assay. Samples were processed on ice due to the limited stability of cefepime in plasma at room temperature (20). Plasma samples (50 µL) were mixed with 200 µL internal standard solution (250 ng/mL cefepime-d3 in acetonitrile), vortexed, and centrifuged at 4,000 rpm for 20 minutes. Next, 150 µL of the supernatant was transferred to a clean 96-well plate, and 10 µL was injected for analysis. Chromatographic separation was achieved using a Kinetex pentafluorophenyl (PFP) column (4.6 × 50 mm, 2.6 µm 100 A; Phenomenex, Torrance, CA), with mobile phase A consisting of 5 mM ammonium acetate in water (pH 5.0) and mobile phase B consisting of 5 mM ammonium acetate in 90/10 acetonitrile/water. Cefepime and cefepime-d3 were detected using an API4000 mass spectrometer (AB Sciex, Redwood City, CA). The lower limit of quantitation for the cefepime plasma assay was 5 ng/mL with an assay range of 5–10,000 ng/mL. The intraday precision based on the SD of replicates of quality control samples ranged from 2.9% to 4.8% with accuracy ranging from 91% to 107%. The interday precision based on the SD of replicates of quality control samples based on 3-day validation ranged from 4.7% to 9.2% with accuracy ranging from 98% to 108%. Cefepime was stable in human plasma under assay and storage conditions. Since the Kinetex PFP column was no longer available, the assay was validated with Kinetex F5 column (4.6 × 50 mm, 2.6 µm 100 A; Phenomenex, Torrance, CA) for further analysis of plasma and ultrafiltrate samples.

Plasma Protein Binding Assessment

A previous study demonstrated concentration independent plasma protein binding of 21% (fraction unbound = 0.79 ± 0.09) for cefepime based on ultrafiltrate-dialysate samples from patients (21). Since cefepime is not stable in plasma at 37°C, the equilibrium dialysis method could not be used (20). We therefore evaluated an ultrafiltration method that had been successfully used for other cephalosporin antibiotics (22, 23). The cefepime plasma assay was cross-validated for the analysis of ultrafiltrate samples to measure total plasma and ultrafiltrate concentrations in a single assay. Twenty representative plasma samples were processed by ultrafiltration of 170 µL of plasma with a Spin-X ultrafiltrate membrane (10,000 molecular weight cutoff; Corning Inc, Lowell, MA) at 4°C for 30 minutes to measure unbound cefepime. However, the measured concentrations of cefepime in ultrafiltrate samples were higher (112%) than the concentrations in the corresponding plasma samples. To further evaluate the limitation of the ultrafiltration method to measure cefepime free fraction, cefepime plasma standards (100 µg/mL) were subjected to ultrafiltration. The concentration measured in an ultrafiltrate sample was 102 µg/mL, and the residual plasma was 36.6 µg/mL. It was determined that during ultrafiltration, cefepime concentration in the upper reservoir decreased and cefepime concentration in the ultrafiltrate increased compared with the starting plasma concentration. This is likely due to the dissociation of bound cefepime and equilibration during ultrafiltration (24). Therefore, the ultrafiltration method could not be used for accurately measuring plasma protein binding of cefepime, and the free fraction could not be determined. As a result, the free fraction was assumed to be 80% of the total based on previous reports and which has been successfully implemented (21).

Pharmacokinetic Analysis

Initial concentration-time plots were constructed using linear interpolation between two measured concentrations to produce an approximated concentration value every 5 minutes. This concentration-time profile was used to calculate the percent of the dosing interval that was above a target MIC. This was performed for both the total and free concentrations. A target MIC of 16 mg/L was used based on published evidence that this represents the MIC90 of cefepime against pseudomonas (25).

Cefepime disposition was estimated using a population pharmacokinetic analysis (NONMEM software, Version 7.2; ICON, Gaithersburg, MD). All models were run with the first-order conditional estimation with interaction. Goodness-of-fit diagnostics and graphical displays were generated in R (www.r-project.org). The goodness of fit from each run was assessed by examining the following criteria: visual evaluation of diagnostic plots, parameter precision, successful minimization, changes in Akaike Information Criteria (AIC) which is based on the minimum objective function value (OFV), and the size of interindividual and residual variabilities for the specified model.

Various compartmental disposition models were investigated. Unexplained random variability of parameters between

individuals was described using an exponential variance model. Additive, proportional, and combined (additive and proportional) residual error models were considered during the model building process. The effect of weight on clearance, intercompartmental clearance (Q), central (V1), and peripheral (V2) volumes of distribution were investigated by allometric scaling: $TVP = \theta_{TVP} \times (WT_i/WT_{ref})^{\theta allometric}$ where TVP is the typical value of the parameter, θ_{TVP} is the population value for the typical subject, WT is the weight of each subject *i* and a reference weight which was set at the median weight for the cohort, 5.8 kg. The impact of size is represented by $\theta_{allometric}$, which is a power parameter and is fixed at 0.75 for clearance and Q and 1 for volumes (26).

Covariates were prespecified and included in the model based on prior knowledge, clinical interest, and physiologic plausibility of their potential effects. The following hypotheses were evaluated via estimation of covariate effects: 1) blood transfusions (BTs) may increase circulating volume and therefore may increase V1; 2) tube coating (TC) would decrease V1 since many ECMO circuits are constructed of tubing that is coated to prevent binding of circulating drugs to the circuit tubing; 3) oxygenator age may impact V1 as newer oxygenators may have less of the surface area bound by circulating drugs whereas older oxygenators may have saturated their surface areas; and 4) renal dysfunction would result in a decrease in systemic clearance since cefepime is primarily renally cleared. Serum creatinine (SCr) values were evaluated as surrogates for renal dysfunction. Additionally, if RRT was used, cefepime clearance could be increased if drug was filtered off during RRT, or alternatively decreased if drug not filtered and accumulates with renal dysfunction. Dichotomous covariates (BT, TC, and RRT) were evaluated as multiplicative covariate models specified as $TVP = \theta_{TVP} \times (\theta_{COV})^{COVyes/no}$ where θ_{TVP} is the population parameter estimate and θ_{cov} is the effect of the covariate. In the event that the covariate was not present (equal to 0), $(\theta_{COV})^{COVyes/no}$ is equal to 1 and there is no effect of that covariate on the parameter. Continuous covariates (SCr and oxygenator age in days) were evaluated using power models where $TVP = \theta_{TVP} \times (\text{covariate value})^{\theta covariate}$ where the covariate value is the value at the time the pharmacokinetic samples were obtained and $\theta_{covariate}$ is the effect of that covariate on the parameter of interest. In order to assess impact of potentially correlated covariates on parameter estimates and model stability, univariate exclusion of covariates was conducted.

RESULTS

Seventeen infants from six participating CPCCRN sites were treated with cefepime and enrolled in the trial between January 4, 2014, and August 24, 2015. Indications for cefepime administration include suspicion/rule-out sepsis ($n = 3$), prophylaxis for surgery or ECMO ($n = 9$), active infection ($n = 3$), acute respiratory failure in a burn patient ($n = 1$), and unknown ($n = 1$). Cohort demographics including ECMO specific characteristics are listed in **Table 1**. One subject was treated with venovenous ECMO while the others were all treated with venoarterial. Details of the sampling schedule employed for the subjects are in **Table 2**. The number of samples, number of cefepime doses per subject (one or two), study covariates, including BT, TC, oxygenator age, and RRT are presented in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A814). Eleven subjects received a BT during a sampling period (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A815). Fourteen subjects were treated with coated ECMO circuits, and two subjects were treated with RRT. Oxygenator age during pharmacokinetic sampling ranged from 1 to 6 days. Limited pharmacokinetic sampling occurred in Subject 4 (two of 10 planned samples), and Subject 11 (six of 10). Furthermore, cefepime concentrations were not detectable in Subject 6. The reason for this could not be determined. Subject 9 demonstrated low concentrations and upon review of the medical record and discussions with the investigative team, it was identified that throughout the sampling period there were multiple issues with fluctuating ECMO flows and hemodynamics, which was caused by a clot obstructing the entire atrial cannula. The ECMO circuit was changed 90 minutes after the final sample was obtained.

Determination of percent of time above MIC is presented in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/PCC/A814). Subjects 4, 6, 9, and 11 were not included in this analysis. For total cefepime, 16 of the 19 doses (84%) demonstrated a *fT*_MIC of 16 mg/L for greater than 70% of the dosing interval. For free cefepime (based on 20% protein binding), 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L for greater than 70% of the dosing interval (again excluding Subjects 4, 6, 9, and 11).

Concentration-time curves per subject are provided in **Figure 1**. For the population pharmacokinetic model, subject 6 was excluded from analysis because of no detectable cefepime concentrations. The base pharmacokinetic model was developed using 196 samples from 16 subjects based on clinically-driven dosing decisions. A total of 22 doses were evaluated. Six of the 16 subjects underwent pharmacokinetic sampling for two doses separated in time by at least 24 hours while the remaining 10 subjects were sampled for only one dose.

A two-compartment model with linear elimination, with weight allometrically scaled on clearance, Q, V1, and V2 resulted in improved goodness-of-fit based on all criteria, relative to a one-compartment model. Progression of model development and the quantitative effects of each covariate on pharmacokinetic parameters are described in **Supplemental Table 3** (Supplemental Digital Content 3, http://links.lww.com/PCC/A816) which includes the assessment of BT, TC, RRT effects, SCr and then the addition of oxygenator age on cefepime pharmacokinetic parameters. Initially, the effect of BT, TC, creatinine, oxygenator age, and RRT were independently evaluated. Next, covariates were added to the model in combinations to determine if there was collinearity between the covariates, indicated by a change in the covariate effect when alone in the model as compared with a model that contained additional covariates. The covariates were deemed to not be collinear. The covariate effect of TC on V1 was

TABLE 1. Demographics, Dose, Dosing Interval, and Extracorporeal Membrane Oxygenation Information For Each Subject Enrolled in the Study

Subject Identification Number	Site[a]	Primary Diagnosis	Dose (mg/kg)	Dosing Interval (hr)	Weight (kg)	Age (mo)	Gender	Ethnicity	Extracorporeal Membrane Oxygenation Mode	Pump Type
1	1	Congenital CV	50	q12	4.0	1.4	Male	Not Hispanic/Latino	Venoarterial	Roller
2	1	Congenital CV	50	q12	4.3	5.3	Male	Not Hispanic/Latino	Venoarterial	Roller
3	2	Respiratory failure	50	q8	6.3	7.6	Female	Not Hispanic/Latino	Venoarterial	Centrifugal
4	3	Congenital CV	50	q12	5.0	2.1	Male	Hispanic/Latino	Venoarterial	Centrifugal
5	4	Congenital CV	50	q12	6.9	8.0	Female	Not Hispanic/Latino	Venoarterial	Roller
6	4	Cardiac arrest	50	q12	3.3	2.9	Female	Not Hispanic/Latino	Venoarterial	Roller
7	4	Congenital CV	50	q12	9.7	22.2	Male	Not Hispanic/Latino	Venoarterial	Roller
8	4	Congenital CV	50	q12	7.3	8.0	Male	Not Hispanic/Latino	Venoarterial	Roller
9	4	Cardiac arrest	50	q12	3.8	2.4	Male	Not Hispanic/Latino	Venoarterial	Roller
10	4	Acquired CV	50	q12	8.0	3.3	Female	Not Hispanic/Latino	Venoarterial	Roller
11	2	Congenital CV	50	q12	5.3	4.1	Female	Not Hispanic/Latino	Venoarterial	Centrifugal
12	5	Congenital CV	50	q12	4.8	5.2	Male	Not Hispanic/Latino	Venoarterial	Centrifugal
13	5	Congenital CV	50	q8	7.5	6.3	Male	Hispanic/Latino	Venoarterial	Centrifugal
14	2	Congenital CV	50	q8	5.5	8.0	Male	Not Hispanic/Latino	Venoarterial	Centrifugal
15	1	Burn[b]	50	q12	10.0	12.3	Female	Not Hispanic/Latino	Venoarterial	Roller
16	6	Congenital CV	50	q12	3.3	1.3	Female	Not Hispanic/Latino	Venovenous	Centrifugal
17	5	Congenital CV	50	q24	4.2	3.8	Female	Unknown	Venoarterial	Centrifugal

CV = cardiovascular disorder, q = every.

[a]Collaborative Pediatric Critical Care Research Network site assignment.

[b]Subject 15 sustained burns over 73% of their body surface area.

estimated at 10.9 when alone in the model, and reduced to 1.6 with other covariates. However, the value of 10.9 was imprecise with a 95% CI of –11.6 to 33.4, and therefore we did not deem this change to represent collinearity with other covariates. The addition of RRT and creatinine as a covariate on clearance, and BT, TC, and oxygenator age on V1 resulted in a 30 point reduction in both OFV and AIC, without a successful covariance step. The removal of the intersubject variability term on Q (which was estimated to be very small) resulted in an additional 15-point reduction in both measures and successful execution of the covariance step. CIs for covariate effects demonstrated poor precision with 95% CI crossing the null value except for the estimate of BT on V1 and RRT on clearance in the final model.

Final estimates for population model typical values, covariate effects, and variability parameters, along with the asymptotic normal 95% CIs, are shown in **Table 3**. A proportional error model was used to describe the random residual variability. Creatinine demonstrated a narrow range of only 0.1–0.9 mg/dL. Despite this narrow range, SCr values were included in the model to account for renal function in this population. Observed versus population and individual predicted concentrations for the full covariate pharmacokinetic model are presented in **Figure 2**.

TABLE 2. Sampling Schedule for Cefepime During the Study Provides the Time (Minutes) After the Dose That Samples Were Collected From Each Subject Based Upon the Dosing Interval of Cefepime

Dosing Schedule	Minutes After Dose											Total No. of Samples
	15	30	60	90	120	180	240	300	480	600	720	
Every 8 hr	✓	✓	✓	✓	✓	✓	✓	✓	✓			10
Every 12 hr	✓	✓	✓		✓	✓		✓	✓	✓	✓	10

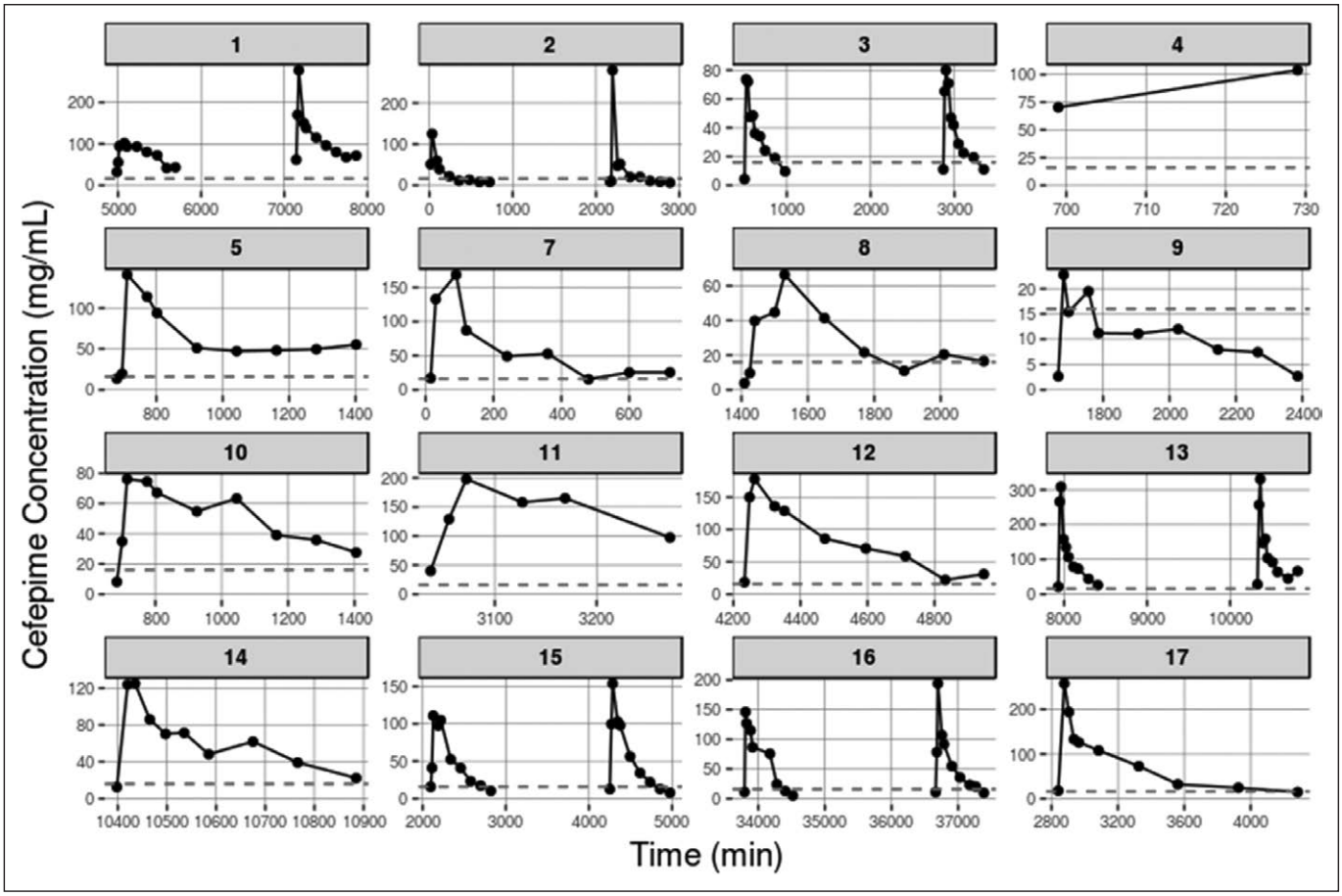

Figure 1. Concentration-time plots for total concentrations. *Dashed line* represents minimum inhibitory concentration for pseudomonas of 16 mg/L (25). Time 0 denotes the time that the subject first received cefepime. Plasma concentrations represent when the dose that was measured for the study was administered in reference to the first administered dose (time [*x*-axis] = 0).

DISCUSSION

In infants receiving ECMO, the pharmacokinetic model estimated a typical value of allometrically scaled clearance of 7.1 mL/min/5.8 kg (1.9 mL/min/kg$^{0.75}$) for a subject not treated with RRT, BT, or TC. Cefepime pharmacokinetic parameters can be estimated using the model structure (shown in the legend of Table 3). The model suggests that clearance is reduced in the presence of RRT. In addition, our model suggests that V1 is increased in the setting of BTs and TC, whereas V1 is decreased with increasing oxygenator age. However, the covariate effects of TC and oxygenator age were not precise or statistically significant, but are presented to demonstrate that they may be important covariates in cefepime disposition if evaluated in a larger cohort. Each institution used similar ECMO components (tubing and oxygenators). Variability in ECMO management (BTs, coating, and RRT) were accounted for during model development by the interindividual and residual variabilities (Table 3), representing interinstitutional variability.

Linear interpolation between observed concentrations allowed for the determination of the percent of the dosing interval above the target MIC. Specifically, linear interpolation only assumes linearity between two observed concentrations but does not assume linearity across the whole profile of each subject, therefore does not affect clearance predictions produced by the population pharmacokinetic model. Five of the 19 doses evaluated achieved a *fT*_MIC of 16 mg/L of 70% for free concentrations. The target of 70% itself may not be sufficient, with some studies stating that the *fT*_MIC should be closer to 90% (15, 17). This represents failures in target attainment in 26% of the doses. These failures occurred in both doses for Subject 2 and the single dose in Subject 8. The doses used for analysis in these subjects were the first and fourth cefepime dose for Subject 2 and the third cefepime dose for Subject 8. This may suggest that standard dosing early in the treatment course, prior to achievement of steady state, may result in concentrations that do not achieve the target, and warrants the consideration of a loading dose. However, Subjects 5, 7, 15, and 17 also had early doses evaluated, and these doses achieved the target *fT*_MIC of 16 mg/L of 70% for both total and free concentrations.

Cefepime pharmacokinetic has been evaluated in pediatric patients who were not receiving ECMO following single and multiple 50 mg/kg doses on every 8-hour and every 12-hour schedules (27). The mean (± SD) age of the patients was 3.6 years (± 3.3 yr) and ranged from 2.1 months to 11.2 years. Following a single IV dose, total body clearance averaged 3.3 mL/min/kg (± 1.0 mL/min/kg) (28). In another study of

TABLE 3. Parameter Estimates From the Final Cefepime Population Pharmacokinetic Model

Parameter	Point Estimate	Relative SE%
Fixed		
Clearance (mL/min) for a 5.8 kg individual	7.1	24.3
V1 (mL/5.8 kg)	1,170	46.3
Q (mL/min/5.8 kg)	12.5	19.8
V2 (mL/5.8 kg)	1,130	26.8
Renal replacement therapy clearance	0.60	25.6
Serum creatinine clearance	−0.22[a]	78.7
Blood transfusion OXYDAY V1	2.86	25.0
Tube coating V1	1.37[a]	56.9
OXYDAY V1	−0.29	66.0
Interindividual variability, %		
Clearance	54.5	51.5
V1	73.8	38.4
V2	47.3	86.2
Residual variability, %		
Proportional	30.4	17.9

OXYDAY = age of the oxygenator of the extracorporeal membrane oxygenation unit represented in days.

[a]Indicates 95% CI crosses null value.

Parameter estimates are for a typical individual of 5.8 kg, with no renal replacement therapy (RRT), no blood transfusion, uncoated tubing, and 0 oxygenator days.

Interindividual and residual variability are presented as percent coefficient of variation calculated by the square root of the variance × 100.

Clearance (mL/min) = 7.05 × (weight of the subject [WT]/5.8)$^{0.75}$ × 0.60 (if receiving RRT) × (serum creatinine)$^{-0.22}$.

In setting of no blood transfusions: V1 (mL) = 1,170 × (WT/5.58) × 1.37 (if tubing is coated) × (oxygenator day)$^{-0.29}$.

In setting of a blood transfusion: V1 (mL) = 1,170 × (WT/5.58) × 1.37 (if tubing is coated) × (oxygenator day)$^{-0.29}$ × 2.86.

Q = 12.5 × (WT/5.8)$^{0.75}$.

V2 = 1,130 × (WT/5.8).

neonates, infants and children who received cefepime without ECMO, clearance was determined to be 2.59 mL/min/kg for children greater than 30 days. These clearance values are higher than estimated in the ECMO population in the current study (1.9 mL/min/kg$^{0.75}$)(29), suggesting that clearance is reduced while on ECMO. However, the steady-state Vd of 0.37 ± 0.07 L/kg (29) in the previously reported study is slightly smaller than the total Vd (V1 + V2) determined in this ECMO study (0.4 L/kg). This larger Vd may contribute to the failure in achieving target concentrations, especially in the presence of BTs and TC where the total volume can increase substantially (1.0 L/kg). Even with an older oxygenator (~ 6 d as in this study) reduction in volume, the Vd is still larger (0.7 L/kg) than the previously reported value. Overall, the Vd of cefepime with the use of ECMO can increase almost 2.5-fold compared with the volume without the use of ECMO, thereby reducing the overall amount of cefepime available to be cleared.

Cefepime has been associated with a greater risk of mortality than other β-lactams in patients treated for severe sepsis. Cefepime's pharmacokinetic and efficacy were examined in a prospective noninterventional study of 21 consecutive ICU adult patients treated with cefepime for nosocomial pneumonia (30). Patients (median age, 55.1 yr; range, 21.8–81.2) received IV cefepime at 2*g* every 12 hours for creatinine clearance (CLCr) greater than or equal to 50 mL/min, and 2*g* every 24 hours or 36 hours for CLCr less than 50 mL/min. Seventeen first-doses and 11 steady states were measured. Plasma levels varied greatly between individuals, from two- to three-fold at peak-concentrations to up to 40-fold at trough concentrations. Twenty-one of 21 patients (100%) had cefepime concentrations above the MIC for the pathogens recovered in that study (MIC ≤ 4 mg/L), but only 45–65% of them had appropriate coverage for potential pathogens with cefepime MIC greater than or equal to 8 mg/L. Furthermore, two of 21 patients (10%) with renal impairment (CLCr < 30 mL/min) demonstrated accumulation of cefepime (trough concentrations of 20–30 mg/L) in spite of dosage adjustment. Both had symptoms compatible with nonconvulsive epilepsy that were not attributed to cefepime-toxicity until plasma levels were disclosed to the caretakers and symptoms resolved promptly after cefepime was discontinued. The authors confirmed the suspected risks of hidden side effects and inappropriate pharmacokinetic/pharmacodynamic parameters (for pathogens with upper-limit MICs) in a population of ICU adult patients. In yet another study, high cefepime plasma concentrations were associated with neurologic toxicity in febrile neutropenic patients with mild renal dysfunction (19). Given these reports and observations, an approach to dosing that includes a philosophy of "just give more" places patients at risk of toxicities. Unfortunately, cefepime and additional β-lactam antibiotics do not have readily available therapeutic drug monitoring, leaving the prescriber to rely on best guesses in circumstances such as renal impairment and ECMO.

The small sample size of this study limits its ability to adequately estimate all the factors that impact cefepime disposition. The cohort did not demonstrate renal insufficiency based on creatinine values despite two subjects undergoing treatment with RRT. Early implementation of RRT may have prevented SCr to rise and the determination of renal insufficiency based on SCr. In addition, the cohort was compromised of predominately venoarterial ECMO patients, and therefore, differences between venoarterial and venovenous could not be determined. Finally, the reasons that one subject had no detectable plasma cefepime concentrations and for failure to attain target concentrations in Subjects 2 and could 8 could not be determined. The subjects enrolled in this study were sedated on ECMO, and potential neurologic side effects were therefore not evaluated. These neurologic side effects have been reported to occur in the setting of higher concentrations, which was not the case for the subjects enrolled in the study.

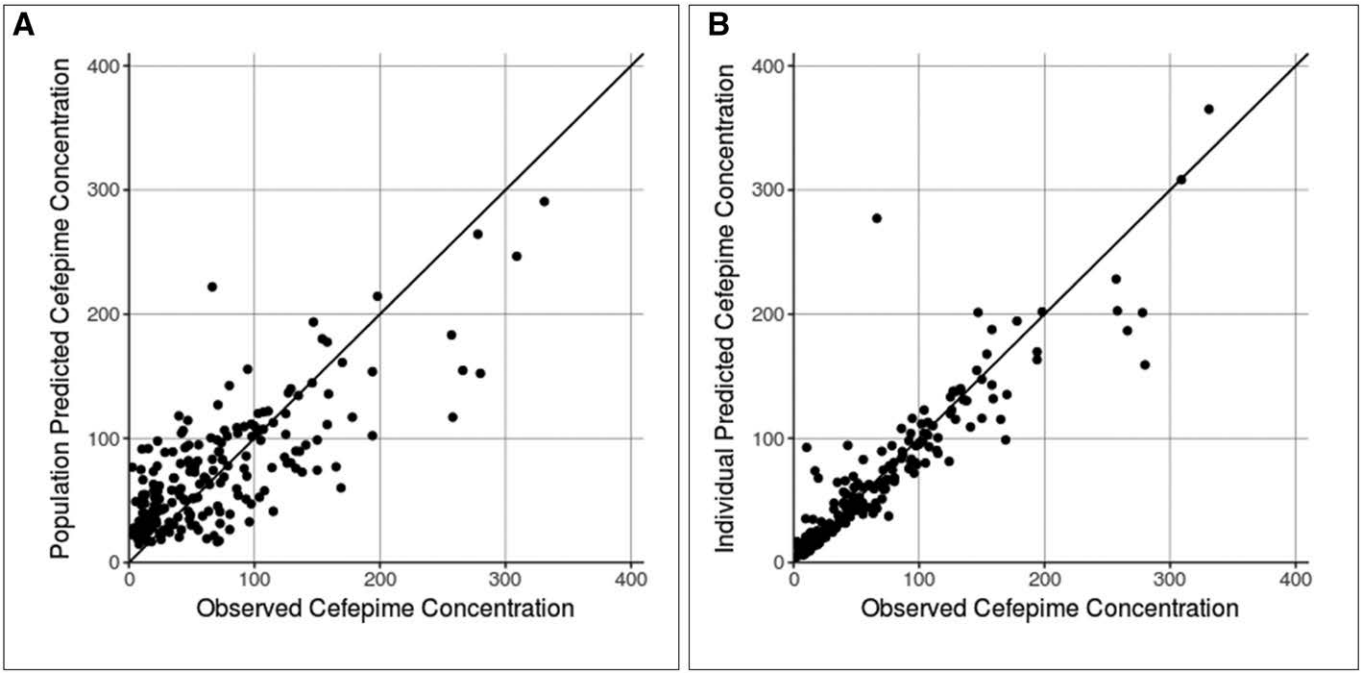

Figure 2. Observed concentration versus individual (**A**) and population (**B**) predicted plots.

In conclusion, the results suggest that cefepime clearance in infants receiving therapy with ECMO is reduced when compared with children who are not receiving ECMO, and the Vd is larger. Clearance may be reduced in the setting of RRT, and V1 may be increased during BTs and in circuits that are coated. V1 is decreased as the oxygenator ages, and this effect was precisely estimated. For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L for greater than 70% of the dosing interval, demonstrating inadequate dosing to treat pseudomonal infections. Although the current model provides insight into the effects of ECMO on the cefepime pharmacokinetic, larger studies should include subjects of all ages to identify the impact of covariates on drug disposition as a step toward precision dosing. Additionally, further studies are necessary to determine the exact *fT*_MIC percentage improves the clinical outcomes in this population. Alternatively, cefepime therapeutic monitoring should be considered in the clinical setting to improve the ability to achieve therapeutic targets and minimize the potential for toxicity.

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