Population Pharmacokinetic Modeling of Total and Free Ceftriaxone in Critically Ill Children and Young Adults and Monte Carlo Simulations Support Twice Daily Dosing for Target Attainment

Girdwood, Sonya Tang; Dong, Min; Tang, Peter; Stoneman, Erin; Jones, Rhonda; Yunger, Toni; Ostermeier, Austin; Curry, Calise; Forton, Melissa; Hail, Traci

Published in:
Antimicrobial Agents and Chemotherapy

DOI:
10.1128/AAC.01427-21

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Population Pharmacokinetic Modeling of Total and Free Ceftriaxone in Critically Ill Children and Young Adults and Monte Carlo Simulations Support Twice Daily Dosing for Target Attainment

Sonya Tang Girdwood,[a,b,c] Min Dong,[b,c] Peter Tang,[c,d] Erin Stoneman,[e] Rhonda Jones,[e] Toni Yunger,[e] Austin Ostermeier,[a,c*] Calise Curry,[a] Melissa Forton,[a] Traci Hail,[a] Randi Mullaney,[a] Patrick Lahni,[e] Nieko Punt,[f,g] Jennifer Kaplan,[c,e] Alexander A. Vinks[b,c]

[a]Division of Hospital Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[b]Division of Clinical Pharmacology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[c]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
[d]Division of Pathology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[e]Division of Critical Care Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[f]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[g]Medimatics, Maastricht, the Netherlands

ABSTRACT Critical illness, including sepsis, causes significant pathophysiologic changes that alter the pharmacokinetics (PK) of antibiotics. Ceftriaxone is one of the most prescribed antibiotics in patients admitted to the pediatric intensive care unit (PICU). We sought to develop population PK models of both total ceftriaxone and free ceftriaxone in children admitted to a single-center PICU using a scavenged opportunistic sampling approach. We tested if the presence of sepsis and phase of illness (before or after 48 h of antibiotic treatment) altered ceftriaxone PK parameters. We performed Monte Carlo simulations to evaluate whether dosing regimens commonly used in PICUs in the United States (50 mg/kg of body weight every 12 h versus 24 h) resulted in adequate antimicrobial coverage. We found that a two-compartment model best described both total and free ceftriaxone concentrations. For free concentrations, the population clearance value is 6.54 L/h/70 kg, central volume is 25.4 L/70 kg, and peripheral volume is 19.6 L/70 kg. For both models, we found that allometric weight scaling, postmenstrual age, creatinine clearance, and daily highest temperature had significant effects on clearance. The presence of sepsis or phase of illness did not have a significant effect on clearance or volume of distribution. Monte Carlo simulations demonstrated that to achieve free concentrations above 1 μg/ml for 100% of the dosing intervals, a dosing regimen of 50 mg/kg every 12 h is recommended for most patients. A continuous infusion could be considered if the target is to maintain free concentrations four times above the MICs (4 μg/ml).

KEYWORDS beta-lactams, ceftriaxone, critically ill, pharmacokinetics, pharmacodynamics

Pediatric sepsis is the result of a life-threatening infection that can lead to organ failure and has in-hospital mortality rates as high as 25% (1, 2). Beta-lactam antibiotics are the mainstay of treatment for sepsis. Timely administration of appropriate antibiotics and adequate fluid resuscitation are critical for survival (1, 2). Despite the crucial role of beta-lactam antibiotics in treating sepsis, there is limited evidence to guide their dosing in critically ill pediatric patients, as current dosing regimens of beta-lactam antibiotics are based on pharmacokinetic (PK) studies in noncritically ill patients. This

Address correspondence to Sonya Tang Girdwood, sonya.tanggirdwood@cchmc.org.

*Present address: Austin Ostermeier, Division of Hospitalist Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA.

Received 27 July 2021
Returned for modification 16 August 2021
Accepted 6 October 2021
Accepted manuscript posted online 11 October 2021
Published 18 January 2022

knowledge gap is important to address since critical illness can alter the PK of drugs, including antibiotics.

Sepsis causes significant pathophysiologic changes in the body that vary over the course of illness. These physiologic changes affect drug distribution, metabolism, and clearance (i.e., pharmacokinetics). The effectiveness (i.e., pharmacodynamics [PD]) of beta-lactams is determined by the time that the concentration of the free, non-protein-bound drug is above the bacterial MIC during a dosing interval ($fT_{>MIC}$). Thus, altering PK can affect the ability to attain the PD target.

The effect sepsis has on the PK of drugs may depend on the phase of sepsis (early versus late). During the early phase of sepsis, capillary leakage and aggressive fluid administration result in an increase in the volume of distribution (*V*), leading to low antibiotic concentrations in the blood. Additionally, augmented renal clearance resulting in increased drug elimination through the urine can further lower blood concentrations (3). During the late phase of sepsis, worsening end-organ dysfunction (e.g., kidney and liver failure) affects drug metabolism by the liver and drug elimination through the kidney, altering antibiotic clearance. Alternatively, as sepsis resolves blood vessel integrity is restored, fluid administration is limited, and renal function and clearance may normalize. During this time, patients may be at increased risk of harm from antibiotic exposure-induced drug toxicity.

Beta-lactam antibiotic PK can be significantly altered due to disease and also affected by the maturation of renal and hepatic clearance mechanisms in young children (i.e., maturation effect). However, therapeutic drug monitoring (TDM) and precision dosing to ensure appropriate concentrations are attained are not routinely performed. Model-based precision dosing, where patient factors and real-time concentration measurements are used to individualize dosing regimens to attain PD targets, may help to reduce toxic effects and avoid potential adverse outcomes from both high and low exposures (4). However, implementation of model-based precision dosing requires robust population PK models that describe the variability of beta-lactam antibiotics across patients and in different phases of critical illness.

Ceftriaxone is a third-generation cephalosporin that provides broad-spectrum Gram-positive and Gram-negative coverage and is often used as first-line therapy for critically ill children with sepsis. Dosing of ceftriaxone in the United States ranges from 50 mg/kg of body weight every 12 h (q12h) to 50 mg/kg every 24 h (q24h) and varies between intensive care units of different institutions. Ceftriaxone population PK studies in critically ill adults (5) and PK studies in noncritically ill children have existed for years (6–8). Only recently has a population PK model been published of ceftriaxone in critically ill children, which primarily used total concentrations with a protein binding factor and confirmed that a 100-mg/kg daily dose was adequate (9). We sought to develop population PK models of both total ceftriaxone concentrations and free ceftriaxone concentrations in critically ill children admitted to the pediatric intensive care unit (PICU) using a scavenged opportunistic sampling approach. We tested if the presence of sepsis altered ceftriaxone PK parameters among children who were critically ill and whether PK parameters varied by phase of illness (early versus late), as we hypothesized that clearance and volume of distribution would be higher in early phases of illness. We also performed Monte Carlo simulations to evaluate whether dosing regimens commonly used in PICUs in the United States (50 mg/kg q12h and 50 mg/kg q24h) resulted in adequate antimicrobial coverage.

RESULTS

Patient population and hospitalization characteristics. We initially enrolled 195 patients who were admitted to the PICU, given at least one dose of ceftriaxone, and from whom we obtained residual blood or plasma from at least one clinical sample that contained ceftriaxone. From these 195 patients, we obtained 734 samples with total ceftriaxone concentrations. We removed six samples that were obtained during ceftriaxone infusion (within 30 min of administration start time) and one sample whose total concentration at the end of a dosing interval was 800 μg/ml, approximately 10

times higher than the average concentration obtained during similar time points. Thus, a total of 7 samples (0.95%) were removed. For this analysis, we excluded 10 patients who were identified as being on extracorporeal membrane oxygenation (ECMO) and/or continuous renal replacement therapy (CRRT) given the variable effects of these extracorporeal support devices on clearance and volume of distribution. We also excluded one patient who received an intramuscular dose of ceftriaxone. The remaining 184 patients contributed 636 samples with total ceftriaxone concentrations. For sepsis patients, we collected a median of 3 samples (range, 1 to 19) per patient over a median of 4 days. For nonsepsis patients, we collected a median of 1.5 samples (range 1 to 13) per patient over a median of 3 days. Of these 636 samples, there was enough plasma remaining in 581 samples (91%) from 180 patients to measure free concentrations.

Demographics and hospitalization characteristics of the 184 patients are shown in Table 1. The median age was 4.2 years with a range of 1 month to 30 years, with 12 of the patients over the age of 19 (6.5%). More than 60% of the cohort had a comorbid condition, defined as a condition requiring subspecialty care or medication for treatment. In our cohort, 122 patients (66%) met sepsis definition (i.e., meeting 2 systemic inflammatory response syndrome [SIRS] criteria and receiving at least 7 days of antibiotics). Septic patients, compared to nonseptic patients, had a longer PICU length of stay (LOS) (median, 3.5 days [interquartile range, or IQR, 2 to 7] versus 3.0 [IQR, 1.3 to 6] days, respectively; $P = 0.048$) and hospital LOS (median, 9.0 days [IQR, 5.3 to 17] versus 5.0 days [3 to 10], respectively; $P = 0.007$). Surprisingly, patients with sepsis had more ventilator-free days (2 days [IQR, 1 to 3]) than nonseptic patients (1 day [IQR, 0 to 2], $P < 0.001$). As expected, those with sepsis were on ceftriaxone for more days than those without sepsis (4.0 days [IQR, 3 to 7] versus 3.0 days [IQR, 2 to 3], respectively, $P < 0.001$). There was no difference in percent protein binding of ceftriaxone between patients with sepsis and without sepsis (76% [IQR, 67 to 83%] versus 78% [IQR, 67 to 83%], $P = 0.61$).

We specifically evaluated volume of fluid boluses and cumulative fluid balance in our entire cohort to determine if fluid administration affected volume of distribution. Patients had more total volume of fluid boluses in the first 2 days than on study days 3 to 7 (26 ml/kg [IQR, 9.5 to 50.7 ml/kg] versus 0 ml/kg [IQR, 0 to 0 ml/kg], $P < 0.001$) (Fig. 1A). However, percent cumulative fluid balance was higher on study day 5 than study day 2 (8.1% [IQR, 3.1 to 15.0%] versus 5.7% [IQR, 2.2 to 9.3%], $P < 0.001$) (Fig. 1B).

Population pharmacokinetic models for total and free concentrations. Results of univariate testing of the covariates on the base models, which included allometric scaling of weight, are shown in Table 2. For the model of total concentrations, maturation effect, pediatric risk of mortality III (PRISMIII), pediatric index of mortality 3 (PIM3), daily highest temperature, daily lowest temperature, daily blood pH, daily highest lactate, creatinine clearance (a reflection of the calculated glomerular filtration rate [GFR]), C-reactive protein (CRP), and albumin each caused the objective function value (OFV) to drop by >3.84 ($P < 0.05$) when tested on total ceftriaxone clearance in the forward inclusion step. Early versus late sampling times (based on if samples were obtained from the patient before or after 48 h of antibiotic treatment), PRISMIII, daily blood pH, daily highest lactate, and cumulative fluid balance were identified to have a significant effect on central volume, as demonstrated by an OFV drop of more than 3.84 during forward selection. When including all the significant covariates in the full model, prior to backward elimination, we opted to use only daily highest temperature instead of lowest temperature, since higher temperatures increase ceftriaxone clearance, reducing the probability of target attainment (PTA). During backward elimination, those covariates that did not cause an increase in OFV by at least 6.63 ($P < 0.01$) were eliminated. The remaining covariates on clearance were albumin, daily highest temperature, daily blood pH, maturation effect, and creatinine clearance, a reflection of the calculated GFR. For central volume, daily blood pH remained a significant covariate. Since the residual standard error (RSE) for daily blood pH on central volume was high (58%),

TABLE 1 Demographics and hospitalization characteristics of patients included in population PK modeling[a]

Parameter	Overall (*N* = 184)	Nonsepsis (*N* = 62)	Sepsis (*N* = 122), 74% culture negative	*P* value (nonsepsis versus sepsis)
Age (yr)				0.21
Median (IQR)	4.2 (1.3, 11.8)	2.8 (1.1, 11.3)	4.8 (1.5, 11.8)	
Sex, no. (%)				0.38
Female	90 (48.9)	27 (43.5)	63 (51.6)	
Male	94 (51.1)	35 (56.5)	59 (48.4)	
wt (kilograms)				0.50
Median (IQR)	15.2 (10.4, 39.4)	13.5 (9.4, 36.2)	16.1 (10.7, 42.2)	
Race, no. (%)				0.53
White	131 (71.2)	41 (66.1)	90 (73.8)	
Black	36 (19.6)	15 (24.2)	21 (17.2)	
Hispanic	9 (4.9)	3 (4.8)	6 (4.9)	
Asian	3 (1.6)	2 (3.2)	1 (0.8)	
Native American or American Indian	0 (0)	0 (0)	0 (0)	
Hawaiian or Pacific Islander	0 (0)	0 (0)	0 (0)	
Other	0 (0)	0 (0)	0 (0)	
Unknown	5 (2.7)	1 (1.6)	4 (3.3)	
Presence of comorbid conditions, no. (%)				0.21
No	70 (38.0)	28 (45.2)	42 (34.4)	
Yes	114 (62.0)	34 (54.8)	80 (65.6)	
PICU length of stay (days)				0.048
Median (IQR)	3.0 (2.0, 7.0)	3.0 (1.3, 6.0)	3.5 (2.0, 7.0)	
Hospital length of stay				
Median (IQR) (days)	8.0 (4.0, 14.5)	5.0 (3.0, 10.0)	9.0 (5.3, 17.0)	0.007
Missing, no. (%)	1 (0.5)	1 (1.6)	0 (0)	
Vasopressor-free days				0.13
Median (IQR)	3.0 (2.0, 6.0)	3.0 (1.0, 5.0)	3.0 (2.0, 6.8)	
Ventilator-free days (days in hospital off ventilator)				<0.001
Median (IQR)	2.0 (1.0, 3.0)	1.0 (0.0, 2.0)	2.0 (1.0, 3.0)	
28-day outcome, no. (%)				0.41
Alive	178 (96.7)	59 (95.2)	119 (97.5)	
Deceased	6 (3.3)	3 (4.8)	3 (2.5)	
Complicated course (specific for sepsis)?				
No			115 (94.3)	
Yes			7 (5.7)	
Days on ceftriaxone				<0.001
Median (IQR)	3.0 (3.0, 6.0)	3.0 (2.0, 3.0)	4.0 (3.0, 7.0)	
PRISMIII score				0.71
Median (IQR)	3.0 (0.0, 6.0)	3.0 (0.0, 6.0)	3.0 (0, 5.8)	
PIM2 score				0.14
Median (IQR)	−4.6 (−5.0, −3.4)	−4.5 (−4.9, −3.3)	−4.6 (−5.9, −3.5)	
PIM3 score				0.36
Median (IQR)	−4.8 (−5.8, −3.9)	−4.7 (−5.7, −4.2)	−4.9 (−5.8, −3.7)	

[a]Comorbid condition defined as a condition requiring subspecialty care or medication for treatment. Complicated course for patients with sepsis defined as two organ failures on day 7 of hospital course or mortality by day 28.

we removed it from the model. When we individually eliminated each of the remaining covariates from the reduced model, we found that elimination of albumin effect on clearance increased the OFV by only 6.261 ($P > 0.01$); thus, it was removed from the model. The final total ceftriaxone model contains the covariates of daily highest temperature, daily blood pH, maturation effect, and creatinine clearance as a reflection of the calculated GFR on total ceftriaxone clearance (see Table 3). The final population estimates are body clearance (CL) of 1.66 L/h/70 kg, intercompartment clearance (*Q*) of

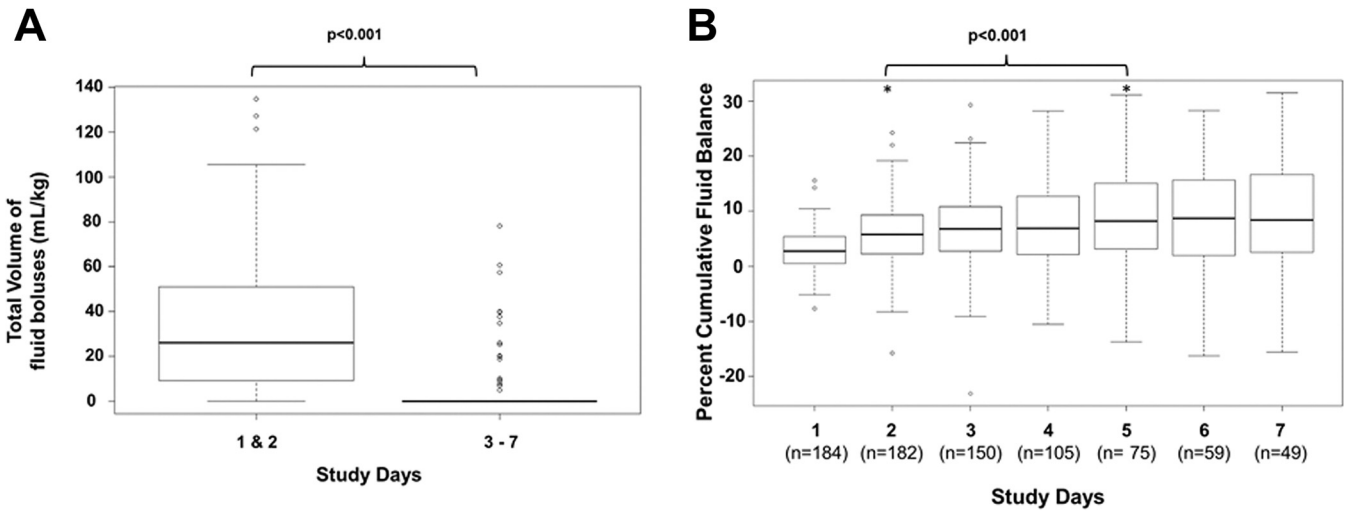

FIG 1 (A) Total volume of fluid administered as boluses on study days 1 and 2 versus study days 3 to 7. (B) Cumulative percent fluid balance in patients still on ceftriaxone therapy on each study day. Negative percent fluid balance indicates there was higher cumulative fluid output than intake until that study day. *n*, number of patients from which percent fluid balance was calculated. For each box plot, the dark horizontal line is the median, the upper border of the box is the 75th percentile, and the lower border of the box is the 25th percentile. Circles represent individual outlier observations.

3.52 L/h/70 kg, central volume (V_1) of 9.56 L/70 kg, and peripheral volume (V_2) of 7.48 L/70 kg for total ceftriaxone. Between-subject variability was 24.8% for CL and 42.4% for V_1.

For the population PK model of free concentrations, maturation effect, PRISMIII, PIM2, PIM3, creatinine clearance (a reflection of the calculated GFR), and daily highest temperature had significant effect (OFV drop of at least 3.84) when univariately tested on clearance (Table 2). Only daily highest lactate significantly improved the model when tested on central volume. Following backward elimination, the final free ceftriaxone model contained the covariates of daily highest temperature, PRISMIII, maturation effect, and creatinine clearance, a reflection of the calculated GFR, on free ceftriaxone clearance. The final population estimates were CL of 6.54 L/h/70 kg, Q of 4.26 L/h/70 kg, V_1 of 25.4 L/70 kg, and V_2 of 19.6 L/70 kg for free ceftriaxone. Between-subject variability was 33.3% for CL and 56.5% for V_1.

Model evaluation. Goodness-of-fit plots were generated to evaluate the relationship between the observed concentrations and predicted concentrations (Fig. 2A and B, top). Both models performed reasonably well, with slight deviations from the line of identity at higher concentrations. Conditional weighted residuals were also plotted against predicted concentration and time (Fig. 2A and B, bottom). Values were equally distributed around the line of zero. The pcVPC plots (Fig. 3A and B) show the 5th, 50th, and 95th percentiles of the prediction-corrected concentrations and suggest a good model fit for the observed total and free ceftriaxone concentrations. Bootstrap validation was performed and demonstrated stability and reproducibility of the models (Table 3).

Monte Carlo simulation. Using Monte Carlo simulation, we evaluated the probability of four dosing regimens to attain two different pharmacodynamic targets, 100% $fT_{>MIC}$ and 100% $fT_{>4\times MIC}$ (free concentrations above the MIC or 4×MIC, respectively, for 100% of dosing intervals), in patients with or without fever (defined as ≥38.5°C), while stratifying by age and creatinine clearance, as a reflection of the calculated GFR (Table 4, Fig. 4; see also Table S1 and Fig. S1 to S5 in the supplemental material). We also identified the MICs below which there would be ≥90% probability that concentrations would remain above the MIC for the entire dosing interval for each of the four evaluated dosing regimens (Tables S2 and S3). Based on an optimal PTA of 90% or above, we found that patients who are febrile, which commonly occurs in critically ill patients with sepsis, are at risk of not meeting either pharmacodynamic target when utilizing a 50-mg/kg q24h regimen, regardless of creatinine clearance, a reflection of

TABLE 2 Impact of covariates in total and free models on CL and central volume[a]

Parameter and covariate	Change in OFV for:	
	Total concn	Free concn
Univariate analysis (forward addition)		
CL		
Maturation effect	−35.43*	−32.59*
Presence of sepsis	−0.027	−0.196
Early versus late concn	−2.297	−0.257
PRISMIII	−17.034*	−19.405*
PIM2	−3.22	−4.957*
PIM3	−5.843*	−5.905*
Daily highest temp (dichotomized)	−4.982*	−14.023*
Daily lowest temp (dichotomized)	−11.108*	−2.176
Daily blood pH (dichotomized)	−23.06*	−0.68
Daily highest lactate	−8.137*	−2.377
Creatinine clearance	−51.678*	−36.478*
CRP	−4.719*	−0.337
Albumin	−4.342*	−3.568
Procalcitonin	−1.028	−1.289
Cumulative fluid balance		−0.001
V_1		
Presence of sepsis	−0.228	+0.737
Early versus late concn	−4.923*	−0.606
PRISMIII	−8.629*	−2.166
PIM2	−2.316	−0.791
PIM3	−3.543	−2.029
Daily highest temp (dichotomized)	−3.01	−0.667
Daily lowest temp (dichotomized)	−0.336	−0.427
Daily blood pH	−7.57*	−0.117
Daily highest lactate	−7.814*	−4.158*
CRP	−0.1	−1.744
Albumin	−1.403	−0.805
Cumulative fluid balance	−4.893*	−0.451
Vol of fluid bolus		−0.327
Creatinine clearance		−0.567
Procalcitonin		−0.019
Multivariate analysis (backward elimination)		
CL		
Daily highest temp	+15.768**	+26.868**
Daily blood pH	+16.518**	+9.553**
Maturation effect	+29.798**	+28.287**
Creatinine clearance	+53.018**	+42.689**

[a]Base models for comparison for univariate testing already included weight as covariate (allometric scaling with exponent of 0.75 for clearances and linear scaling for volumes). An asterisk indicates that in univariate testing the covariate was significant ($\Delta OFV \leq -3.84$, $P < 0.05$) and included in full model prior to backward elimination. Two asterisks indicate that when covariate was eliminated from final model, it was statistically significant ($\Delta OFV \geq 6.63$, $P < 0.01$). Medians and ranges of covariates are the following: PMA for maturation effect, 260 weeks; 39.68 to 1,601.56 weeks; PRISMIII, 3; 0-42; PIM2, −4.56; −7.33–2.87; PIM3, −4.78; −7.68–4.75; daily highest temperature, 37.6°C; 33.1 to 42°C, dichotomized to less than and greater than or equal to 38.5°C; daily lowest temperature, 36.3°C; 27.6 to 39.1°C, dichotomized to greater than and less than or equal to 36°C; daily blood pH, 7.36; 6.63 to 7.55, dichotomized to greater than and less than or equal to 7.2; daily highest lactate, 1.3; 0.3 to 19.3; creatinine clearance (calculated by bedside Schwartz equation for children, CKD-EPI for adults), 149.5 ml/min/1.73m^2; 12.24 to 563.18 ml/min/1.73m^2; CRP, 13.3 mg/dl; 0.4 to 31 mg/dl; albumin, 2.8 gm/dl; 0.9 to 6.1 gm/dl; procalcitonin, 1.65 mg/dl; 0.1 to 591.08 mg/dl.

the calculated GFR. A daily 100-mg/kg regimen improves probabilities of target attainment, but they still fall below 90% in febrile patients between ages 1 and 5 across all creatinine clearance brackets, even for the lower stringent target. However, dosing every 12 h achieves the less stringent pharmacodynamic target (100% $fT_{>MIC}$) across all creatinine clearance brackets, except for 6- to 12-month-old infants with augmented renal clearance (PTA, 89%). To achieve the most stringent target of concentrations above 4×MIC for 100% of the dosing interval, continuous infusions of 50 mg/kg over

TABLE 3 Final population pharmacokinetic models for total ceftriaxone concentrations and free ceftriaxone concentrations[a]

	Total ceftriaxone concn[b]					Free ceftriaxone concn[c]				
			Bootstrap estimates (n = 1,000, 95% success)					Bootstrap estimates (n = 1,000, 77% success)		
Parameter	Estimate	RSE (%)	Median	2.5%	97.5%	Estimate	RSE (%)	Median	2.5%	97.5%
CL_{pop} (L/h/70 kg)	1.66	3.3	1.66	1.54	1.78	6.54	5.6	6.50	5.40	7.40
HILL	2.85	26	2.94	1.70	6.10	4.26	23.5	4.44	2.84	12.27
TM_{50} (wk)	39.9	10.7	40.5	31.4	47.9	45.4	9.8	45.1	35.1	53.2
Θ1 (PHDI)	0.794	8.7	0.90	0.642	0.932					
Θ1 (PRISMIIII)						−0.0142	30.7	−0.0141	−0.0249	−0.0046
Θ2 (CRCL)	0.347	15.6	0.344	0.224	0.444	0.357	17.9	0.349	0.213	0.477
Θ3 (HITEMPDI)	1.12	3	1.15	1.06	1.20	1.19	3.1	1.19	1.12	1.27
Q_{pop} (L/h/70 kg)	3.52	38.1	3.48	0.57	6.65	4.26	15.1	4.23	2.84	12.27
V_{1pop} (L/70 kg)	9.56	25.7	9.44	5.92	14.8	25.4	13.8	25.4	15.9	35.5
V_{2pop} (L/70 kg)	7.48	21	7.62	5.31	10.7	19.6	9	19.5	16.5	23.9
BSV										
CL, CV (shrinkage)	24.8 (17.9%)	15.2	24.3	20.5	28.6	33.3 (15.9%)	17.4	32.4	25.8	37.6
V_1, CV (shrinkage)	42.4 (49%)	33.8	40.8	19.8	62.9	56.5 (41.7%)	33.2	55.4	15.9	72.3
Q, CV (shrinkage)	Fixed to 20%	(84.4%)				Fixed to 20%	(81.5%)			
V_2, CV (shrinkage)	Fixed to 30%	(61.3%)				Fixed to 20%	(73.6%)			
Residual variability										
Proportional	0.0460	13.6	0.0448	0.0336	0.0590	0.0742	14	0.0740	0.0557	0.0948
Additive	Fixed to 0.0001					Fixed to 0.0001				

[a]RSE, residual standard error; CL, clearance; Q, intercompartmental clearance; V, volume; WT, weight; HILL, Hill coefficient for maturation effect; TM_{50}, age in weeks when clearance is half the adult value; PHDI, 0 when blood pH >7.2, 1 when blood pH ≤7.2; CRCL, creatinine clearance; HITEMPDI, 0 when highest temperature of the day is <38.5°C, 1 when ≥ 38.5°C; CV, coefficient of variation.

[b]$CL_i = CL_{pop} \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{PMA^{HILL}}{PMA^{HILL}+TM_{50}^{HILL}}\right) \times \theta 1^{PHDI} \times \left(\frac{CRCL}{149.5}\right)^{\theta 2} \times \theta 3^{HITEMPDI}$; $Q_i = Q_{pop} \times \left(\frac{WT}{70}\right)^{0.75}$; $V_{1i} = V_{1pop} \cdot \left(\frac{WT}{70}\right)^{1.0}$; $V_{2i} = V_{2pop} \times \left(\frac{WT}{70}\right)^{1.0}$.

[c]$CL_i = CL_{pop} \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{PMA^{HILL}}{PMA^{HILL}+TM_{50}^{HILL}}\right) \times e^{\theta 1 \times PRISM3} \times \left(\frac{CRCL}{149.5}\right)^{\theta 2} \times \theta 3^{HITEMPDI}$.

24 h are needed, especially in critically ill children with normal and augmented renal clearance.

Patients without fever have lower clearance of free ceftriaxone and, therefore, have higher PTAs than febrile patients, as expected (Table S1 and S3, Fig. S3 to S5). However, similar to febrile patients, patients without fever are still at risk of not meeting either pharmacodynamic target with a 50-mg/kg q24h dosing regimen. To achieve the less stringent target (100% $fT_{>MIC}$), a dosing regimen of 50 mg/kg q12h should be utilized in patients with normal or augmented renal clearance. For patients with acute kidney injury, the twice-daily 50-mg/kg dosing regimen or 100-mg/kg daily regimen is recommended for patients between the ages of 1 to 5 years; in the other age groups, once-daily dosing with 50 mg/kg is sufficient for attainment of the lower stringent target.

DISCUSSION

We describe the population pharmacokinetics of total and free ceftriaxone in critically ill children in the pediatric intensive care unit. To our knowledge, this is the largest study to date of ceftriaxone in critically ill children and the first study to develop a population PK model using only measured free concentrations, the active antimicrobial portion.

Our previous work has shown that there is high variability in plasma protein binding of other β-lactam antibiotics in the critically ill pediatric population (10), which is not unexpected given the high prevalence of hypoalbuminemia in critical illness (11). Since ceftriaxone is more highly bound to protein than many other β-lactam antibiotics, we sought to measure both total and free concentrations and develop separate

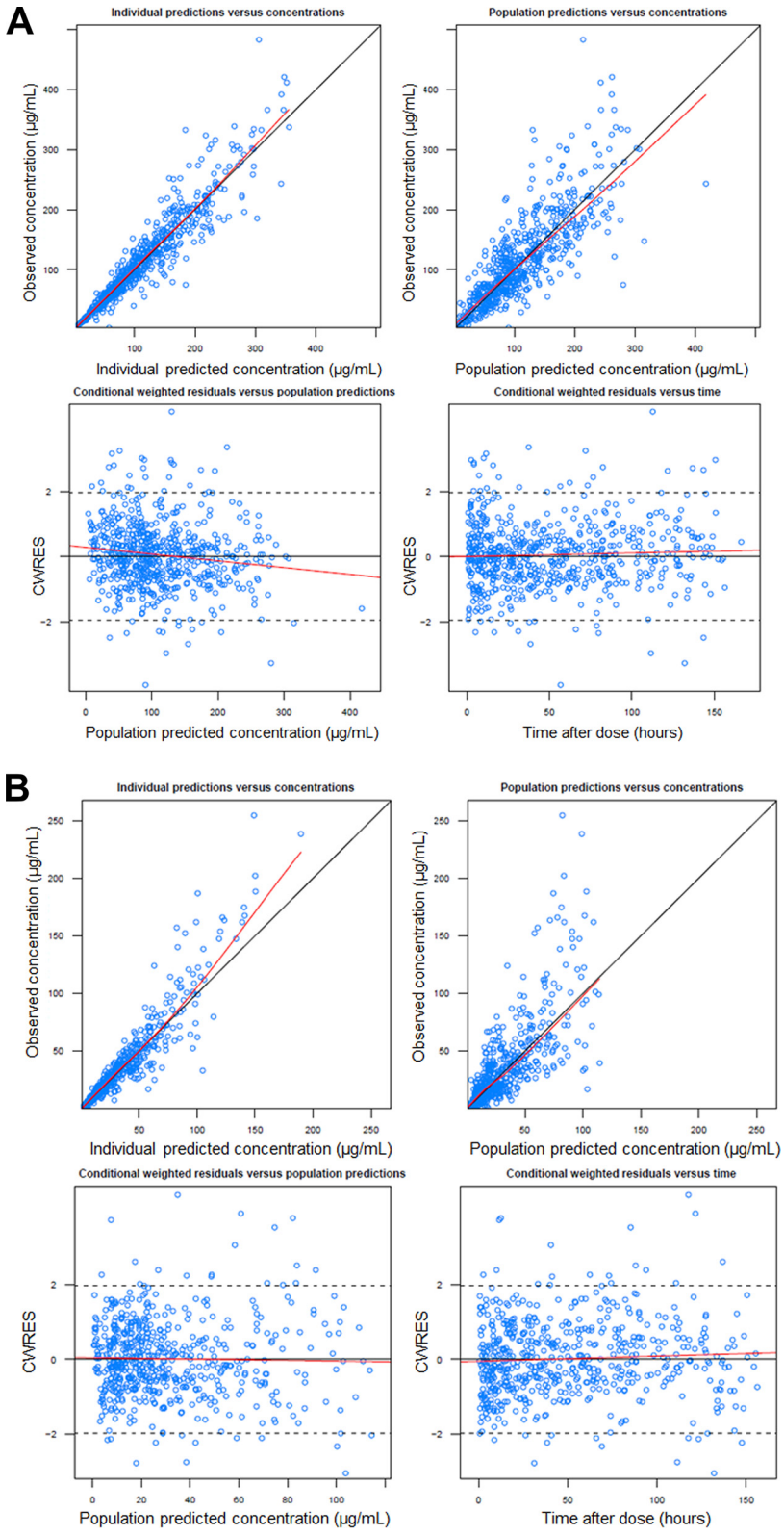

FIG 2 Goodness-of-fit plots for total ceftriaxone model (A) and free ceftriaxone model (B). Top left, individual predictions versus observed concentrations (μg/ml). Black line is the line of identity. Top right, population predictions versus observed concentrations (μg/ml). Black line is the line of identity. Bottom left, conditional weighted residuals (CWRES) versus population prediction concentrations. Bottom right, CWRES versus time, in hours, after first dose. Figure was generated by R with Pirana interface.

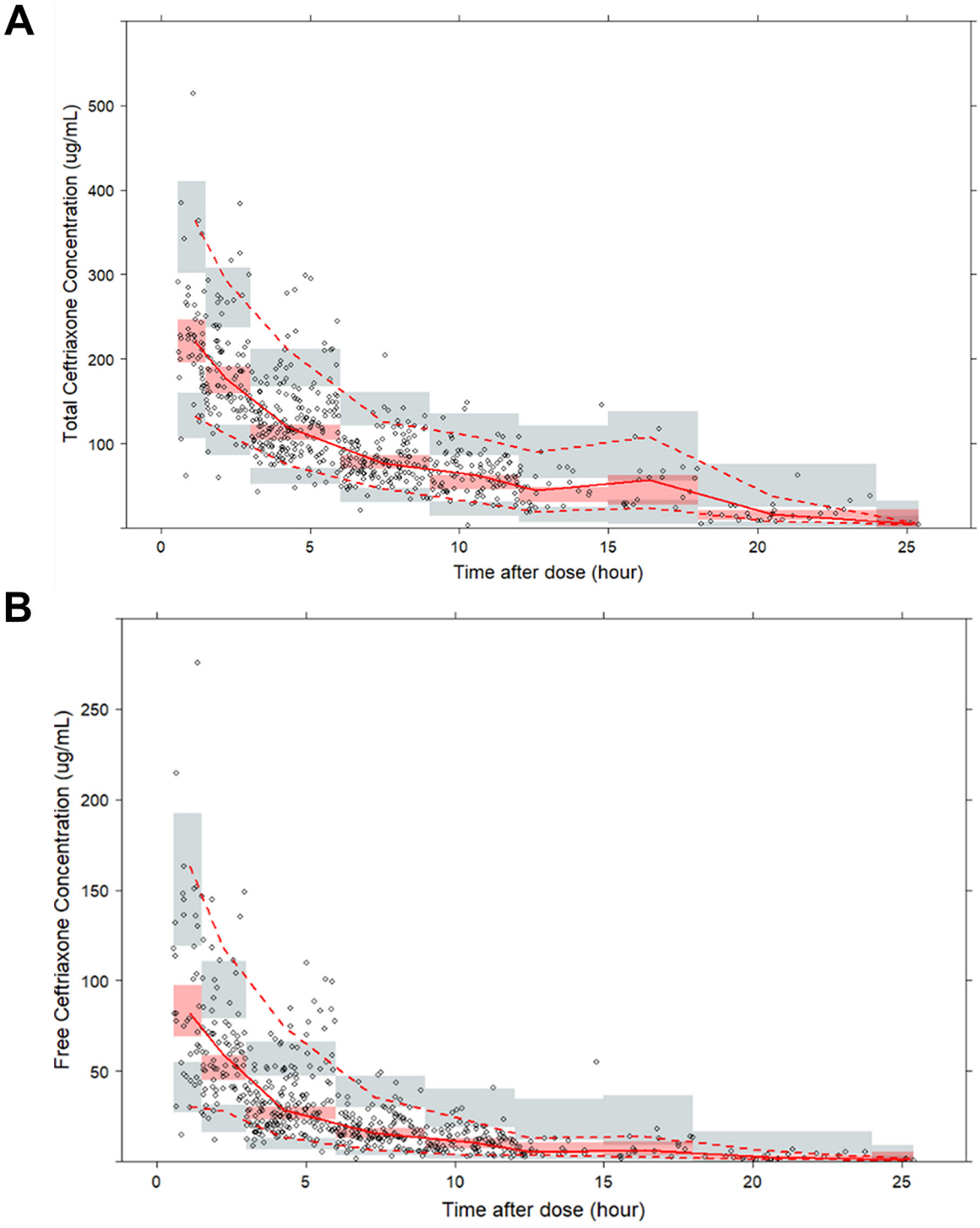

FIG 3 Prediction-corrected visual predictive check (pcVPC) plots of total ceftriaxone model (A) and free ceftriaxone model (B). Open circles, prediction-corrected observed plasma concentrations. Red solid line, median of prediction-corrected observed concentrations. Red dashed lines, 5th and 95th percentiles of the prediction-corrected observed concentrations. Shaded areas are the simulation-based 95% confidence interval around the 5th, 50th, and 95th, percentiles.

models to account for dynamic protein binding throughout illness course instead of assuming a fixed binding percentage or developing an integrated model that incorporated binding capacity and dissociation constants. Having these two separate models also allows for greater flexibility in their future use for model-informed precision dosing with Bayesian estimation (12), as institutions may only be able to measure total

TABLE 4 PTA in patients with fever based on Monte Carlo simulation[a]

	%PTA					
	Acute kidney injury		Normal creatinine clearance		Augmented renal clearance	
Age group and dosing regimen	100% $fT_{>MIC}$	100% $fT_{>4xMIC}$	100% $fT_{>MIC}$	100% $fT_{>4xMIC}$	100% $fT_{>MIC}$	100% $fT_{>4xMIC}$
1–3 mo						
50 mg/kg q12h	100	100	100	97	100	88*
50 mg/kg q24h	99	91	86*	50*	66*	23*
100 mg/kg q24h	100	97	94	71*	82*	46*
50 mg/kg continuous	100	100	100	100	100	100
3−6 mo						
50 mg/kg q12h	100	98	99	85*	96	65*
50 mg/kg q24h	93	66*	63*	20*	39*	6*
100 mg/kg q24h	97	82*	80*	41*	58*	21*
50 mg/kg continuous	100	100	100	100	100	100
6–12 mo						
50 mg/kg q12h	100	94	96	67*	89*	42*
50 mg/kg q24h	83*	43*	39*	7*	20*	3*
100 mg/kg q24h	91	65*	59*	20*	38*	8*
50 mg/kg continuous	100	100	100	100	100	100
1−2 yr						
50 mg/kg q12h	99	90	97	64*	92	47*
50 mg/kg q24h	73*	36*	38*	6*	23*	3*
100 mg/kg q24h	87*	56*	58*	19*	43*	10*
50 mg/kg continuous	100	100	100	100	100	100
2−5 yr						
50 mg/kg q12h	100	91	97	70*	94	53*
50 mg/kg q24h	77*	38*	44*	9*	30*	4*
100 mg/kg q24h	89*	61*	65*	25*	50*	14*
50 mg/kg continuous	100	100	100	100	100	100
5−12 yr						
50 mg/kg q12h (2,000 mg/dose max)	100	96	100	81*	98	70*
50 mg/kg q24h (2,000 mg/dose max)	87*	55*	62*	17*	48*	8*
100 mg/kg q24h (4,000 mg/dose max)	95	75*	80*	38*	70*	25*
50 mg/kg continuous (2,000 mg max)	100	100	100	100	100	100
12−18 yr						
50 mg/kg q12h (2,000 mg/dose max)	100	95	100	82*	98	68*
50 mg/kg q24h (2,000 mg/dose max)	91	55*	68*	18*	53*	9*
100 mg/kg q24h (4,000 mg/dose max)	97	78*	87*	42*	77*	27*
50 mg/kg continuous (2,000 mg max)	100	100	100	100	100	100

[a]The scenarios shown are when the patients have acute kidney injury, normal creatinine clearance, or augmented renal clearance and have a temperature of ≥38.5°C. Two different pharmacodynamic targets were evaluated: free concentrations above 1 μg/ml (CLSI breakpoint for *Enterobacteriaceae* and *S. pneumoniae*) for 100% of the dosing interval (100% $fT_{>MIC}$) and free concentrations above 4 μg/ml for 100% of the dosing interval (100% $fT_{>4xMIC}$). Asterisks indicate PTA of <90%, the optimal PTA.

concentrations but not free, unbound concentrations. The PK parameters of CL, V_1, and V_2 in the model of free concentrations are 2.5- to 4-fold higher than those of the model of the total concentrations. This finding is consistent with the reported ceftriaxone protein binding of 60 to 95% (5 to 40% free fraction, which would be expected to change parameters 2.5- to 20-fold), which is known to be dependent on total ceftriaxone concentrations (13).

Our initial hypothesis was that ceftriaxone clearance and volume of distribution would be significantly different in the first 48 h of treatment (early phase of critical illness) compared to later phases of critical illness. While univariate testing showed that early versus late phase of illness did have a significant effect on central volume of distribution for total ceftriaxone concentrations (effect on peripheral volume was not tested), it was not statistically significant in multivariate analysis. One reason for this is that while the amount of fluid administered as boluses is greater in the first 2 days of critical illness, cumulative fluid balance is higher in the later days of critical illness (Fig. 1), and these two factors may counteract one another.

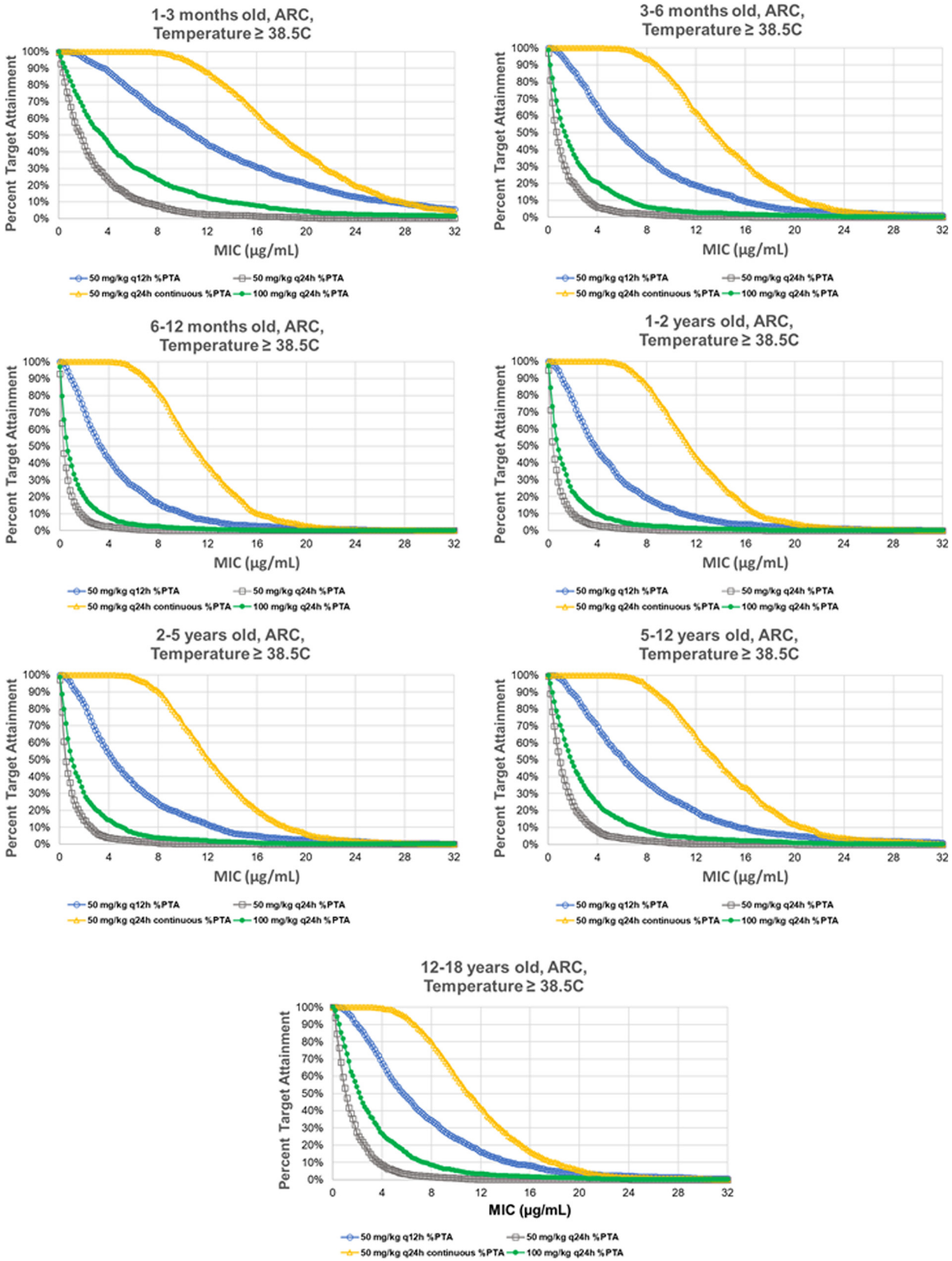

FIG 4 Probability of target attainment obtained from Monte Carlo simulations for a target defined as 100% $fT_{>MIC}$ for patients with a fever (temperature ≥ 38.5°C) and augmented renal clearance (ARC) (2 to 6 standard deviations above the median clearance for age). Blue circles, 50 mg/kg every 12 h regimen. Gray squares, 50 mg/kg every 24 h regimen. Orange triangles, 50 mg/kg given continuously every 24 h. Green filled circles, 100 mg/kg every 24 h.

We also found that the presence of sepsis did not significantly affect ceftriaxone clearance or volume of distribution. Many of the patients who were categorized as nonsepsis initially met systemic inflammatory response syndrome (SIRS) criteria and likely had pathophysiologic changes that would affect ceftriaxone disposition similar to those with sepsis. It is often around 48 h after admission that clinicians decide to continue patients on a full course of antibiotics to treat a bacterial infection or discontinue treatment. Thus, even patients without sepsis have clinical characteristics in the early phase of illness similar to those of septic patients.

Similar to previously published PK models of ceftriaxone in critically ill adults and children (5, 9), we found that a two-compartment model best fit our data. We do find differences in our population PK parameters compared to the other models. Compared to the Garot et al. adult model (5), our clearance for total ceftriaxone is 1.66 L/h/70 kg, while the clearance in the adult model was 0.88 L/h/76 kg, with 76 kg being the median weight for the adult population. The difference in ceftriaxone clearance may be due to higher creatinine clearances, reflections of calculated GFR, in our population, since nearly a quarter of the population in the adult model required renal replacement therapy. Our central volumes (V_1) and peripheral volumes (V_2) for total ceftriaxone are comparable (9.56 L/70 kg and 7.81 L/76 kg versus 7.48 L/76 kg and 7.35 L/76 kg). Compared with the critically ill pediatric model (9), we demonstrate lower clearance for total ceftriaxone (1.66 L/h/70 kg versus 2.08 L/h/70 kg) despite our population's median creatinine clearance, a reflection of the calculated GFR, being much higher than that reported in the Hartman et al. model (149.5 ml/min/1.73 m^2 [calculated primarily with the bedside Schwartz equation] versus 85.22 ml/min/1.73m^2 [calculated by modified Schwartz equation]). A reason for the difference is that the Hartman et al. pediatric model estimated parameters to describe protein binding, combining total and free concentrations for modeling. Our population clearance value for total ceftriaxone is similar to that found in hospitalized patients with community-acquired pneumonia who had a mean age close to that of our population (1.42 L/h/70 kg) (14). Our slightly higher clearance value compared to the pneumonia study may be a result of critical illness leading to augmented renal clearance and lower albumin concentrations, which can also increase drug clearance. Our central volume for total ceftriaxone is smaller than that reported by Hartman et al. (9.56 L/70 kg versus 22 L/70 kg) but again may be due to their combining total and free concentrations. The central volume in Hartman et al.'s model is more similar to that in our model of free concentrations (25.4 L/70 kg).

Covariate analysis showed that weight has a significant effect on all four parameters (CL, Q, V_1, and V_2), with allometric scaling for clearance and intercompartmental clearance in our models. The previously published critically ill pediatric model also showed an effect of weight on body clearance with allometric scaling and on central volume with linear scaling but not with intercompartment clearance or peripheral volume (9). Similar to the previously published ceftriaxone models in critically ill adults and children by Garot et al. and Hartman et al. (5, 9), respectively, we found that creatinine clearance, a reflection of calculated GFR, significantly affected ceftriaxone clearance. This is not surprising, given that up to 67% of ceftriaxone is excreted unchanged in the urine (15). Interestingly, our population's median creatinine clearance was much higher than the median creatinine clearance in the Hartman et al. model. This difference may be a reflection of a lower median age (2.53 years versus 4.2 years), and nearly half of the patients were under the age of 2 years in Hartman et al.'s model.

Unlike other published models, we showed additional covariate effects. When the highest daily temperature is at or above 38.5°C, there was a nearly 20% increase in clearance of free drug. As body temperature increases, we expect that blood flow to the kidneys increases due to tachycardia and vasodilation, with increased clearance of drug and lower probability of target attainment (PTA). We also noted an effect of pH on the clearance of total ceftriaxone and the PRISMIII mortality score, of which pH is a component, on free ceftriaxone clearance. We dichotomized the effect of pH and

found that when the daily blood pH is below 7.2, the clearance of total ceftriaxone decreases by over 20%. Blood pH may be low from lactic acid production due to vasoconstriction and decreased blood flow to the kidneys and/or liver, thereby affecting excretion and metabolism. PRISMIII is a mortality score calculated 4 h after PICU admission from multiple physiologic variables, including vital signs and lab values, reflecting kidney and liver function (16); the higher the score, the higher the mortality risk. We found that increasing PRISMIII scores were associated with a decrease in free ceftriaxone clearance, likely due to kidney and liver dysfunction, as reflected in the score. Albumin was identified as a significant covariate for total concentrations, but when eliminated from the final total model, the OFV increase was less than 6.63 ($P > 0.01$). It may be that the effect of albumin is masked by another covariate, such as temperature or blood pH, that was selected first due to greater effects.

Renal clearance and hepatic metabolism mature over the first 2 years of life. Population pharmacokinetic analysis of ceftriaxone in noncritically ill infants has previously shown an effect of age, scaled to an exponent of 0.21, on ceftriaxone clearance (17). We initially tested age on ceftriaxone clearance and found a significant effect but sought to characterize the maturation effect using the Hill equation and postmenstrual age (PMA) instead of using age only, as recommended by Anderson and Holford (18, 19). We found maturation of organ function had a significant effect on both total and free ceftriaxone clearance, with the change in OFV nearly as large as that when including creatinine clearance. Our models show that the mechanisms contributing to ceftriaxone clearance (e.g., renal clearance and biliary excretion) reach 50% of full maturation between PMA of 39.9 and 45.4 weeks (i.e., at birth or shortly thereafter) with a Hill coefficient between 2.85 and 4.26. Our findings for ceftriaxone show that maturation of ceftriaxone clearance precedes that of GFR maturation (age at which half of the adult clearance function is achieved [TM_{50}], 47.6 weeks; Hill coefficient of 3.4) and clearance of other drugs, including acetaminophen-paracetamol and morphine (18, 19).

At our institution, ceftriaxone is dosed at 50 mg/kg q12h for most critically ill patients, while other institutions frequently dose ceftriaxone at 50 mg/kg q24h for critically ill pediatric patients unless meningitis is suspected (personal communication). Our results suggest that a 50-mg/kg q24h approach puts critically ill pediatric patients at risk of not meeting pharmacodynamic targets, especially those patients with fevers and augmented renal clearance. Our simulation results are similar to those found in the Hartman et al. study, which showed that a 50-mg/kg q12h dosing regimen is preferred for MICs greater than 1, especially when creatinine clearance is greater than 80 ml/min/1.73 m^2 (9), which is true of most patients with normal or augmented renal clearance. Further studies are needed to evaluate the relationship between target attainment and clinical outcomes.

Our study is not without limitations. The between-subject variability for Q and V_2 were fixed to 20 or 30%, and the shrinkage for both these parameters in both models was high (61 to 84%). This finding is expected given the nature of sparse opportunistic sampling and having less data per individual subject. Therefore, we specifically did not test covariates on Q and V_2 given the sparse sampling approach and that we obtained concentrations from the blood (central compartment) only. Except for weight, no other covariates were found to significantly affect V_1 despite testing several variables, including volume of boluses and cumulative fluid balance. Thus, the between-subject variability remains quite large (42.4 to 56.5%), similar to what was seen in critically ill adults (5) and lower than that seen in a younger critically ill pediatric population (9). We also dichotomized certain variables based on clinically relevant thresholds, even though there is likely a continuous effect. We dichotomized pH due to the tight range typically observed even in critical illness and chose to dichotomize the daily highest temperature based on the presence or absence of fever, as defined by 38.5°C.

Conclusions. We successfully developed population PK models of total ceftriaxone and free ceftriaxone using an opportunistic sampling approach in critically ill children. Phase of illness (early versus late) did not influence any of the parameters. However,

weight, creatinine clearance (a reflection of calculated GFR), daily highest temperature, and maturation effect had effects on both total and free ceftriaxone clearance. In addition, blood pH and risk of mortality score were found to be significant covariates of total ceftriaxone clearance and free ceftriaxone clearance, respectively. These models can allow for individualized dosing of ceftriaxone using patient characteristics, including weight, age, renal function, and temperature. Monte Carlo simulations with our free ceftriaxone model showed that using a 50-mg/kg q24h approach in critically ill children did not achieve the target of free concentrations above the MIC for 100% of the dosing interval. Thus, we recommend a 50-mg/kg q12h approach in critically ill children and to consider a continuous infusion in patients with augmented renal clearance.

MATERIALS AND METHODS

Study design and ethics. A prospective, observational β-lactam study was conducted in the pediatric ICU (PICU) of Cincinnati Children's Hospital Medical Center (CCHMC) between October 2018 and March 2020. The parent β-lactam antibiotic study included patients who were administered at least one dose of ceftriaxone, cefepime, meropenem, or piperacillin-tazobactam. For this ceftriaxone study, patients of all ages (newborn to 30 years) admitted to the PICU and who received at least one dose of ceftriaxone were eligible for the study. Only those patients who did not have residual blood samples for ceftriaxone concentration measurement were excluded from the study. The study was approved by the CCHMC Institutional Review Board, which granted a waiver of consent.

Drug dosing and administration. Ceftriaxone initiation and dosing regimen were determined by the clinical team for each patient. In the CCHMC PICU, ceftriaxone is most commonly prescribed as 50 mg/kg/dose (maximum, 2,000 mg) every 12 h and typically administered over 30 min.

Opportunistic sampling. Blood samples were obtained using scavenged opportunistic sampling as described previously (10, 20). Briefly, all patients in the PICU who were administered at least one dose of ceftriaxone were screened to determine if the clinical team had ordered laboratory tests (e.g., complete blood counts and metabolic panels) after a ceftriaxone dose was given. Blood samples were requested within 7 days of blood draws from the clinical laboratory, which stores the residual sample at 4°C after test completion. We conducted stability studies, as described previously (10), and showed that total ceftriaxone did not degrade more than 15% over a period of 7 days at 4°C (see Table S4 in the supplemental material). Samples that were obtained within 30 min of the start of ceftriaxone administration or more than 30 h after a dose were excluded. Samples were collected daily while patients were on ceftriaxone, up to seven study days. Study day 1 was considered the first day the patient was in the PICU and administered a β-lactam antibiotic dose (typically ceftriaxone but may have been cefepime, piperacillin-tazobactam, or meropenem for patients whose antimicrobial regimen was narrowed to ceftriaxone as part of the parent beta-lactam study). Time zero was defined as the time the first β-lactam dose was given on study day 1. Early samples were considered those that were drawn within the first 48 h of antibiotic treatment. Late samples were those drawn after the first 48 h of antibiotic treatment. We chose 48 h as the threshold as it is the typical time frame when clinicians determine if a patient warrants a full antibiotic course. After obtaining residual blood or plasma from the clinical laboratory, samples were centrifuged (2,060 $\times$ *g*, 10 to 20°C, 10 min; Eppendorf 5417R) and the supernatant was removed and stored at −80°C until ceftriaxone concentrations were measured (average time of storage at −80°C, 6 months; range, 2 to 10 months). The time samples were out of the 4°C refrigerator before storage in the freezer was usually no more than 1 h.

Total and free ceftriaxone assays. Sample preparation for total ceftriaxone concentrations in plasma was achieved using protein precipitation and ultracentrifugation procedures. To a 100-μl aliquot of plasma sample, 100 μl of internal standard and 300 μl of methanol were added. After vortex mixing, the sample was centrifuged at 10,000 $\times$ *g* for 10 min at 4°C. After centrifugation, the liquid phase was distributed to an autosampler vial. A 10-μl aliquot of the sample was injected into the high-performance liquid chromatography (HPLC) system.

Sample preparation for free ceftriaxone concentrations in plasma was based on ultrafiltration, as described in the Centrifree user guide (Merck Millipore, Burlington, MA). A 0.4-ml aliquot of plasma was distributed over a Centrifree ultrafiltration device. The filled ultrafiltration device was subjected to centrifugation at 2,500 $\times$ *g* for 30 min at room temperature using a benchtop centrifuge (Clinifuge; Heraeus Instruments). After centrifugation, a 100-μl aliquot of filtrate was pipetted into an autosampler vial. To this vial, 100 μl internal standard was added. After mixing, a 10-μl aliquot of the sample was injected into the HPLC system.

Total and free ceftriaxone were quantified using an automated Hitachi Chromaster system (Tarrytown, NY) equipped with a Model 5110 quaternary pump, Model 5210 autosampler, Model 5310 column oven, and Model 5410 UV detector. The EZChrom Elite software was used for monitoring output signal and processing result. The analytical column was a 250-mm by 4.6-mm validated C_{18} column (PerkinElmer, Waltham, MA) with 5-μm spherical particles connected to a Security Guard (Phenomenex, Torrance, CA) equipped with a C_{18} cartridge (4-mm by 3-mm). MAGNA nylon filter (0.2 μm; 47-mm diameter) from GE Water & Process Technologies (Boston, MA) for the filtration of mobile phase.

In this report, we adapted a previously published assay (21) with minor modifications to determine ceftriaxone concentrations using ion-pairing HPLC with UV detection. The mobile phase consisted of an aqueous solution containing 50 mM dibasic sodium phosphate and 10 mM cetyltrimethylammonium

bromide (pH 6.9) with acetonitrile (63:37, vol/vol). The column temperature was set at 35°C and the flow rate at 1 ml/min. Ceftriaxone and chloramphenicol (used as an internal standard) were detected using a UV detector set at a wavelength of 274 nm. The limit of detection and the limit of quantitation for this assay were 0.3 μg/ml and 1 μg/ml, respectively. Linear assay range was established from 1 to 200 μg/ml. The coefficients of variation ranged from 3.2 to 5.6% for intraday precision and from 4.2 to 7.3% for interday precision. Concentrations of ceftriaxone examined were 10, 40, 80, and 160 μg/ml (n = 6 for each concentration fortified in plasma).

Clinical data collection. Clinical data related to the hospitalization were extracted by chart review for up to seven study days while the patient was on ceftriaxone. Data collected included but were not limited to demographics (age, sex, weight, height, body mass index, and comorbidities), antibiotic doses and administration times, sepsis-related data (length of antibiotic courses, cultures and organisms, and fluid administration), vital signs, concomitant medications, fluid intake and output, organ failure, ventilator and vasopressor use, clinical lab results, and mortality risk scores. We also collected outcome data, including length of stay in the PICU and hospital, and 28-day outcome. Mortality scores, including PRISMIII (16), PIM2 (22), and PIM3 (23), were also calculated using the relevant patient demographics, clinical status, vital signs, and laboratory values. To meet the definition of sepsis for our study, patients must have met at least two of the four systemic inflammatory response syndrome criteria (24) and received at least 7 days of antibiotics. Creatinine clearances, as a reflection of calculated GFRs, were calculated using the bedside Schwartz equation for patients under the age of 19 and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, as recommended by the National Institute of Diabetes and Digestive and Kidney Diseases (25, 26). All data were stored in a secure REDCap database (27).

Pharmacokinetic model development with covariate selection. For pharmacokinetic modeling, patients who received continuous renal replacement therapy or extracorporeal membrane oxygenation therapy were excluded from analysis. In addition, patients who received nonintravenous doses (i.e., intramuscular) were excluded. Separate models were developed for total ceftriaxone and free ceftriaxone concentrations. Population PK parameters were estimated using NONMEM, version 7.2 (Icon Development Solutions, Ellicott City, MD), and Pirana 2.9.9 (Certara, Princeton, NJ), with the first-order conditional estimation with the interaction (FOCE-I) subroutine. One- and two-compartment models were compared, and a two-compartment model was selected based on goodness-of-fit metrics. Weight was tested as a covariate on all four PK parameters (clearance [CL], central volume [V_1], intercompartmental clearance [Q], and peripheral volume [V_2]). CL and Q were scaled allometrically by weight [$(\text{weight}/70)^{0.75}$], while V_1 and V_2 were scaled linearly by weight [$(\text{weight}/70)^{1.0}$] for the base model before additional covariates were tested.

Potential clinical covariates were first selected for testing based on biological plausibility and then on plots of covariates and the interindividual variability of PK parameters (η). Covariates were only tested on CL and V_1. Most covariates were tested as a continuous variable normalized to the population median. Percent cumulative fluid balance was calculated by taking the difference between cumulative fluid intake and cumulative fluid output for each study day and dividing the difference by admission weight. After initial trials of covariate testing, the following covariates were tested as dichotomous variables: sepsis (present or not), sample collected before or after 48 h of antibiotic treatment (early versus late), daily lowest temperature (36°C threshold), daily highest temperature (38.5°C threshold), and blood pH (7.2 threshold). Maturation effect was evaluated using postmenstrual age (PMA), as described previously (18, 28, 29). PMA was calculated by the summation of age at PICU admission (in weeks) and gestational age (in weeks). For those whose gestational age was not documented or for patients over the age of 3 years, gestational age was assumed to be 40 weeks. Maturation effect was tested as a covariate with the equation $\frac{PMA^{Hill}}{PMA^{Hill}+TM_{50}^{Hill}}$, where Hill is the Hill coefficient and TM_{50} is the age (in weeks) at which half of the adult clearance function is achieved (18, 19).

The impact of covariates was screened by univariate analysis. Covariates that decreased the objective function by at least 3.84 ($P < 0.05$) were included in the full multivariate model. Backward elimination of each covariate from the multivariate model was then performed. Covariates that led to an increase in the objective function by 6.63 ($P < 0.01$) when eliminated were retained. For the total model, between-subject variability (BSV) for Q was fixed to 0.04 (ω^2) (ω = 20%), and BSV for V_2 was fixed to 0.09 (ω = 30%). For the free model, BSV for Q and V_2 were fixed to 0.04 (ω = 20%). The additive error (σ) for both models was fixed to 0.0001, as this assumption allowed for the greatest model stability when multiple error models were tested. The performance of the final population models was evaluated with goodness-of-fit plots and by using bootstrap analysis (n = 1,000) and prediction-corrected visual predictive check (pcVPC) (30).

Monte Carlo simulation analysis. Monte Carlo simulation analysis using MICLab version 2.72 (Medimatics, Maastricht, Netherlands) (31–34) was conducted using the final free population PK model, since the free portion is considered to represent the active antimicrobial component. The simulation data set was created using the CDC-NHANES demographic data (35) to simulate weights in the following age ranges: 1 to 3 months, 3 to 6 months, 6 to 12 months, 1 to 2 years, 2 to 5 years, 5 to 12 years, and 12 to 18 years. Ages were then converted to PMA by assuming a gestational age of 40 weeks (19). Within each age range, creatinine clearances (as a reflection of calculated glomerular filtration rates) were distributed between categories of acute kidney injury (AKI), normal creatinine clearance, and augmented renal clearance (ARC). We defined normal creatinine clearance as within two standard deviations of the median creatinine clearance in each age group (36, 37). ARC was defined as two standard deviations above the median creatinine clearance (38); we placed a maximum limit of six standard deviations above the median. AKI was defined as less than two standard deviations below the median. For each age range and creatinine clearance bracket, we also varied temperature dichotomously (≥38.5°C or less). We fixed

PRISMIII scores to 0, since the mortality risk score is not available at the time of admission, when antibiotics are usually prescribed when concerned for sepsis. We tested four different dosing regimens: 50 mg/kg every 12 h, 50 mg/kg every 24 h, 100 mg/kg every 24 h (4,000 mg/dose maximum), and 50-mg/kg continuous infusion, with a maximum of 2,000 mg per dose. In total, we performed 168 simulations with 1,000 patients in each simulated scenario. We used free concentration above MIC and 4×MIC for 100% of the dosing interval (100% $fT_{>MIC}$ and 100% $fT_{>4xMIC}$) as the pharmacodynamic targets for the critically ill population (39) to calculate the percent probability of target attainment (PTA). For the MIC, we used the Clinical and Laboratory Standards Institute (CLSI) ceftriaxone breakpoint for *Enterobacteriaceae* and *Streptococcus pneumoniae* of 1 μg/ml (40).

Statistical analysis. Statistical analyses were performed using the statistical software R studio, version 1.2.1335. Medians of continuous variables were compared using a Wilcoxon rank sum test. Paired nonparametric variables were compared using Wilcoxon signed rank test. Categorical variables were compared using Fisher's exact test or chi-squared test. Statistical significance was met at a P value of <0.05.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 3.4 MB.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Child Health and Development Cincinnati Pediatric Clinical Pharmacology Postdoctoral Training Program (5T32HD069054-09); National Center for Advancing Translational Sciences of the National Institutes of Health (award number 5UL1TR001425); the Cincinnati Children's Hospital Medical Center Arnold W. Strauss Fellow Award; the Cincinnati Children's Hospital Medical Center Hospital Medicine Fellow Award; and the Gerber Foundation Novice Research Award. The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, et al. 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377. https://doi.org/10.1007/s00134-017-4683-6.
2. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, Nadkarni VM, Thomas NJ, Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. 2015. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 191:1147–1157. https://doi.org/10.1164/rccm.201412-2323OC.
3. Sime FB, Udy AA, Roberts JA. 2015. Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol 24:1–6. https://doi.org/10.1016/j.coph.2015.06.002.
4. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA. 2012. Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2:35. https://doi.org/10.1186/2110-5820-2-35.
5. Garot D, Respaud R, Lanotte P, Simon N, Mercier E, Ehrmann S, Perrotin D, Dequin PF, Le Guellec C. 2011. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. Br J Clin Pharmacol 72:758–767. https://doi.org/10.1111/j.1365-2125.2011.04005.x.
6. Schaad UB, Stoeckel K. 1982. Single-dose pharmacokinetics of ceftriaxone in infants and young children. Antimicrob Agents Chemother 21:248–253. https://doi.org/10.1128/AAC.21.2.248.
7. Fukumoto K, Aida S, Oishi T, Ueno K. 2009. Pharmacokinetics of ceftriaxione, a third-generation cephalosporin, in pediatric patients. Biol Pharm Bull 32:1139–1141. https://doi.org/10.1248/bpb.32.1139.
8. Iida S, Kawanishi T, Hayashi M. 2011. Indications for a ceftriaxone dosing regimen in Japanese paediatric patients using population pharmacokinetic/pharmacodynamic analysis and simulation. J Pharm Pharmacol 63:65–72. https://doi.org/10.1111/j.2042-7158.2010.01179.x.
9. Hartman SJF, Upadhyay PJ, Hagedoorn NN, Mathot RAA, Moll HA, van der Flier M, Schreuder MF, Bruggemann RJ, Knibbe CA, de Wildt SN. 2021. Current ceftriaxone dose recommendations are adequate for most critically ill children: results of a population pharmacokinetic modeling and simulation study. Clin Pharmacokinet https://doi.org/10.1007/s40262-021-01035-9.
10. Tang Girdwood SC, Tang PH, Murphy ME, Chamberlain AR, Benken LA, Jones RL, Stoneman EM, Kaplan JM, Vinks AA. 2020. Demonstrating feasibility of an opportunistic sampling approach for pharmacokinetic studies of beta-lactam antibiotics in critically ill children. J Clin Pharmacol https://doi.org/10.1002/jcph.1773.
11. Nicholson JP, Wolmarans MR, Park GR. 2000. The role of albumin in critical illness. Br J Anaesth 85:599–610. https://doi.org/10.1093/bja/85.4.599.
12. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL, International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases. 2014. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14:498–509. https://doi.org/10.1016/S1473-3099(14)70036-2.
13. Popick AC, Crouthamel WG, Bekersky I. 1987. Plasma protein binding of ceftriaxone. Xenobiotica 17:1139–1145. https://doi.org/10.3109/00498258709167406.
14. Khan MW, Wang YK, Wu YE, Tang BH, Kan M, Shi HY, Zheng Y, Xu BP, Shen AD, Jacqz-Aigrain E, Tian LY, Zhao W. 2020. Population pharmacokinetics and dose optimization of ceftriaxone for children with community-acquired pneumonia. Eur J Clin Pharmacol 76:1547–1556. https://doi.org/10.1007/s00228-020-02939-4.
15. Sandoz Inc. 2021. Ceftriaxone for injection, USP. Drug insert. Sandoz Inc, Hozkirchen, Germany.

16. Pollack MM, Patel KM, Ruttimann UE. 1996. PRISM III: an updated pediatric risk of mortality score. Crit Care Med 24:743–752. https://doi.org/10.1097/00003246-199605000-00004.
17. Wang YK, Wu YE, Li X, Tian LY, Khan MW, Tang BH, Shi HY, Zheng Y, Hao GX, van den Anker J, You DP, Zhao W. 2020. Optimal dosing of ceftriaxone in infants based on a developmental population pharmacokinetic-pharmacodynamic analysis. Antimicrob Agents Chemother 64:e01412-20. https://doi.org/10.1128/AAC.01412-20.
18. Anderson BJ, Holford NH. 2009. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 24:25–36. https://doi.org/10.2133/dmpk.24.25.
19. Anderson BJ, Holford NH. 2011. Tips and traps analyzing pediatric PK data. Paediatr Anaesth 21:222–237. https://doi.org/10.1111/j.1460-9592.2011.03536.x.
20. Girdwood ST, Kaplan J, Vinks AA. 2020. Methodologic progress note: opportunistic sampling for pharmacology studies in hospitalized children. J Hosp Med 15:E1–E3. https://doi.org/10.12788/jhm.3380.
21. Granich GG, Krogstad DJ. 1987. Ion pair high-performance liquid chromatographic assay for ceftriaxone. Antimicrob Agents Chemother 31:385–388. https://doi.org/10.1128/AAC.31.3.385.
22. Slater A, Shann F, Pearson G, Paediatric Index of Mortality Study Group. 2003. PIM2: a revised version of the paediatric index of mortality. Intensive Care Med 29:278–285. https://doi.org/10.1007/s00134-002-1601-2.
23. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, Slater A, Group APS, the Paediatric Intensive Care Audit Network. 2013. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care. Pediatr Crit Care Med 14:673–681. https://doi.org/10.1097/PCC.0b013e31829760cf.
24. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. 2005. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 6:2–8. https://doi.org/10.1097/01.PCC.0000149131.72248.E6.
25. National Institute of Diabetes, Digestive and Kidney Diseases. 2021. Bedside IDMS-traceable Schwartz GFR calculator for children. https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/children-conventional-units.
26. National Institute of Diabetes, Digestive and Kidney Diseases. 2021. CKD-EPI adults (conventional units). https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units.
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. 2009. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381. https://doi.org/10.1016/j.jbi.2008.08.010.
28. Mizuno T, Gist KM, Gao Z, Wempe MF, Alten J, Cooper DS, Goldstein SL, Vinks AA. 2019. Developmental pharmacokinetics and age-appropriate dosing design of milrinone in neonates and infants with acute kidney injury following cardiac surgery. Clin Pharmacokinet 58:793–803. https://doi.org/10.1007/s40262-018-0729-3.
29. Mizuno T, Fukuda T, Emoto C, Mobberley-Schuman PS, Hammill AM, Adams DM, Vinks AA. 2017. Developmental pharmacokinetics of sirolimus: implications for precision dosing in neonates and infants with complicated vascular anomalies. Pediatr Blood Cancer 64:26470. https://doi.org/10.1002/pbc.26470.
30. Ette EI. 1997. Stability and performance of a population pharmacokinetic model. J Clin Pharmacol 37:486–495. https://doi.org/10.1002/j.1552-4604.1997.tb04326.x.
31. Mouton JW, Punt N, Vinks AA. 2007. Concentration-effect relationship of ceftazidime explains why the time above the MIC is 40 percent for a static effect in vivo. Antimicrob Agents Chemother 51:3449–3451. https://doi.org/10.1128/AAC.01586-06.
32. Mouton JW, Schmitt-Hoffmann A, Shapiro S, Nashed N, Punt NC. 2004. Use of Monte Carlo simulations to select therapeutic doses and provisional breakpoints of BAL9141. Antimicrob Agents Chemother 48:1713–1718. https://doi.org/10.1128/AAC.48.5.1713-1718.2004.
33. Mouton JW, Punt N. 2001. Use of the t > MIC to choose between different dosing regimens of beta-lactam antibiotics. J Antimicrob Chemother 47:500–501. https://doi.org/10.1093/jac/47.4.500.
34. Rodríguez-Tudela JL, Almirante B, Rodríguez-Pardo D, Laguna F, Donnelly JP, Mouton JW, Pahissa A, Cuenca-Estrella M, 2007. Correlation of the MIC and dose/MIC ratio of fluconazole to the therapeutic response of patients with mucosal candidiasis and candidemia. Antimicrob Agents Chemother 51:3599–3604. https://doi.org/10.1128/AAC.00296-07.
35. Centers for Disease Control and Prevention National Center for Health Statistics. 2016. NHANES questionnaires, datasets, and related documentation. Centers for Disease Control and Prevention, Atlanta, GA.
36. Piepsz A, Tondeur M, Ham H. 2006. Revisiting normal (51)Cr-ethylenediaminetetraacetic acid clearance values in children. Eur J Nucl Med Mol Imaging 33:1477–1482. https://doi.org/10.1007/s00259-006-0179-2.
37. Schwartz GJ, Work DF. 2009. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol 4:1832–1843. https://doi.org/10.2215/CJN.01640309.
38. Van Der Heggen T, Dhont E, Peperstraete H, Delanghe JR, Vande Walle J, De Paepe P, De Cock PA. 2019. Augmented renal clearance: a common condition in critically ill children. Pediatr Nephrol 34:1099–1106. https://doi.org/10.1007/s00467-019-04205-x.
39. Barreto EF, Webb AJ, Pais GM, Rule AD, Jannetto PJ, Scheetz MH. 2021. Setting the beta-lactam therapeutic range for critically ill patients: is there a floor or even a ceiling? Crit Care Explor 3:e0446. https://doi.org/10.1097/CCE.0000000000000446.
40. CLSI (ed). 2018. Performance standards for antimicrobial disk susceptibility tests. CLSI standard M02. Clinical and Laboratory Standards Institute, Wayne, PA.