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Ceftriaxone Pharmacokinetics and Pharmacodynamic Target Attainment for Three Pediatric Patients Receiving Continuous Kidney Replacement Therapy

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Ceftriaxone is used commonly for sepsis, including in children requiring continuous kidney replacement therapy (CKRT). No reports exist of pharmacokinetic (PK) parameters for children receiving ceftriaxone on CKRT. We enrolled children admitted to our pediatric intensive care unit (PICU) who received CKRT for >24 hours and received >1 dose of ceftriaxone while on and off CKRT. We measured free ceftriaxone concentrations from residual blood samples then used Bayesian estimation with PK modeling software to generate concentration-time profiles and determine PK parameters and the percentage of time free ceftriaxone concentrations were above 1× or 4× MIC (% *f*T >MIC). Three patients aged 2 to 17 years were included; all were anuric at CKRT initiation and received 50 mg/kg (max 2000 mg) ceftriaxone every 12 to 24 hours. Total ceftriaxone clearance (CL) was 0.50 to 3.67 L/hr while receiving CKRT and 0.29 to 2.71 L/hr while off, indicating CKRT provided 25% to 42% of total ceftriaxone CL. All achieved 100% *f*T >1× and 4× MIC using an estimated MIC (1 mg/L) for patients 1 to 2 (no culture data) and a measured MIC (0.016 mg/L) for patient 3. Therefore, CKRT contributed significantly to total ceftriaxone clearance in 3 children though the dosing strategies used in each patient attained PD targets.

ABBREVIATIONS AKI, acute kidney injury; CKD, chronic kidney disease; CKRT, continuous kidney replacement therapy; CL, clearance; CLSI, Clinical Laboratory and Standards Institute; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; *f*T >, time free concentration exceeds; IRB, institutional review board; MIC, minimum inhibitory concentration; PICU, pediatric intensive care unit; PD, pharmacodynamic; PK, pharmacokinetic; PRISM, Pediatric Risk Mortality Score; UFR, ultrafiltration rate; Vc, central volume of distribution

KEYWORDS acute kidney injury; ceftriaxone; continuous renal replacement therapy; extracorporeal clearance

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Introduction

Sepsis is the leading cause of acute kidney injury (AKI) in critically ill children, including severe AKI requiring continuous kidney replacement therapy (CKRT).[1–3] Children with sepsis requiring CKRT are a high-risk population; appropriate antimicrobial dosing, balancing adequate microbiologic effect while avoiding toxicity, is critical. However, there is a paucity of data regarding antimicrobial dosing for children receiving CKRT.[4] Multiple CKRT parameters, including filter size, blood flow, dialysis modality, and effluent flow rates can impact drug clearance.[5] Yet, published guidelines recommend a one-size-fits-all approach for drug dosing regardless of CKRT prescription.[5] There is an unmet need to identify the factors that influence drug pharmacokinetic/pharmacodynamic (PK/PD) parameters for pediatric patients receiving CKRT.

Ceftriaxone is commonly used for sepsis treatment and is the most frequently prescribed beta-lactam antibiotic in our pediatric intensive care unit (PICU), which is a 48-bed PICU based at Cincinnati Children's Hospital Medical Center, a tertiary/quaternary care children's hospital in Cincinnati, OH.[6] Ceftriaxone efficacy is based on the time free drug concentrations are above the minimum inhibitory concentration (*f*T>MIC), with some recommending a target of 100% *f*T> 4× MIC to maximize efficacy for severe infections.[7,8] Ceftriaxone has 70% to 90% protein binding and therefore should have relatively insignificant removal via extracorporeal dialysis modalities, given that drugs with high degrees of protein binding are less susceptible to extracorporeal clearance.[9,10] However, small PK studies in adults have shown that ceftriaxone has non-negligible extracorporeal clearance.[11,12] One study of anuric adults receiving continuous venovenous hemofiltration (CVVH) suggested dosing ceftriaxone every 48 to 72 hours to achieve the PD target of 100% *f*T>2 mg/L.[11] However, guidelines recommend anywhere from 1 to 2 g every

12 to 24 hours[13] or even no change from typical dosing.[14] There is no literature recommendation for ceftriaxone dosing for pediatric patients receiving CKRT.[5] Pediatric patients receiving CKRT represent a unique population with varying body sizes, which affect CKRT prescription, and may also impact drug clearance. In addition, children 2 years and younger have maturation-related changes in renal and hepatic metabolism, which can further impact clearance.[15] Thus, we sought to examine achievement of ceftriaxone PK/PD targets in 3 pediatric patients receiving CKRT.

Materials and Methods

Patient Identification and Enrollment. Patients were enrolled as part of a prospective study of β-lactam antibiotics in critically ill patients at a single large quaternary PICU from 2018–2021. Patients were included in this series if they received at least 24 hours of CKRT, received at least 1 ceftriaxone dose while on and off CKRT, and had residual blood samples available for analysis of at least 2 ceftriaxone concentrations while receiving CKRT and 2 concentrations while not receiving CKRT. Samples were collected up until 30 hours after the final dose of ceftriaxone.

Sample Collection and Processing. Ceftriaxone concentrations were measured using residual blood scavenged from clinical samples, as previously described.[16] Briefly, patients who received at least 1 ceftriaxone dose during their PICU admission were screened for whether the clinical team had ordered laboratory tests following ceftriaxone administration. Residual blood from lithium-heparin or ethylenediaminetetraacetic acid tubes was requisitioned. Samples were requested daily until ceftriaxone discontinuation for up to 7 days. Previous stability studies demonstrated that total ceftriaxone does not degrade >15% over a period of 7 days when stored at 4°C; samples used in this study were obtained under the same conditions, that is, after being used for clinical purposes, the samples were stored at 4°C and subsequently frozen at −80°C within 7 days of sample collection.[7] Samples were centrifuged (2060 x g, 10 to 20°C, 10 minutes; Eppendorf 5417R) and the supernatant was removed and stored at −80°C until ceftriaxone measurement. Both total and free ceftriaxone concentrations were measured via validated HPLC method with a ~5% precision, as reported previously by Tang Girdwood et al.[7,17]

Chart Review. EMRs were reviewed for information regarding demographics, medical conditions, cause of AKI, and identified infections. Timing of CKRT initiation and cessation, blood and dialysate flow rates, pre/post convective fluid replacement rates, and filter types were identified. Net UFR was calculated as the difference between total ultrafiltrate and CKRT input fluid (priming volume) and averaged over the hours while patients were on circuit. Total effluent flow rate was calculated as the sum of dialysate flow rate, substitution fluid rate, and net UFR.[18]

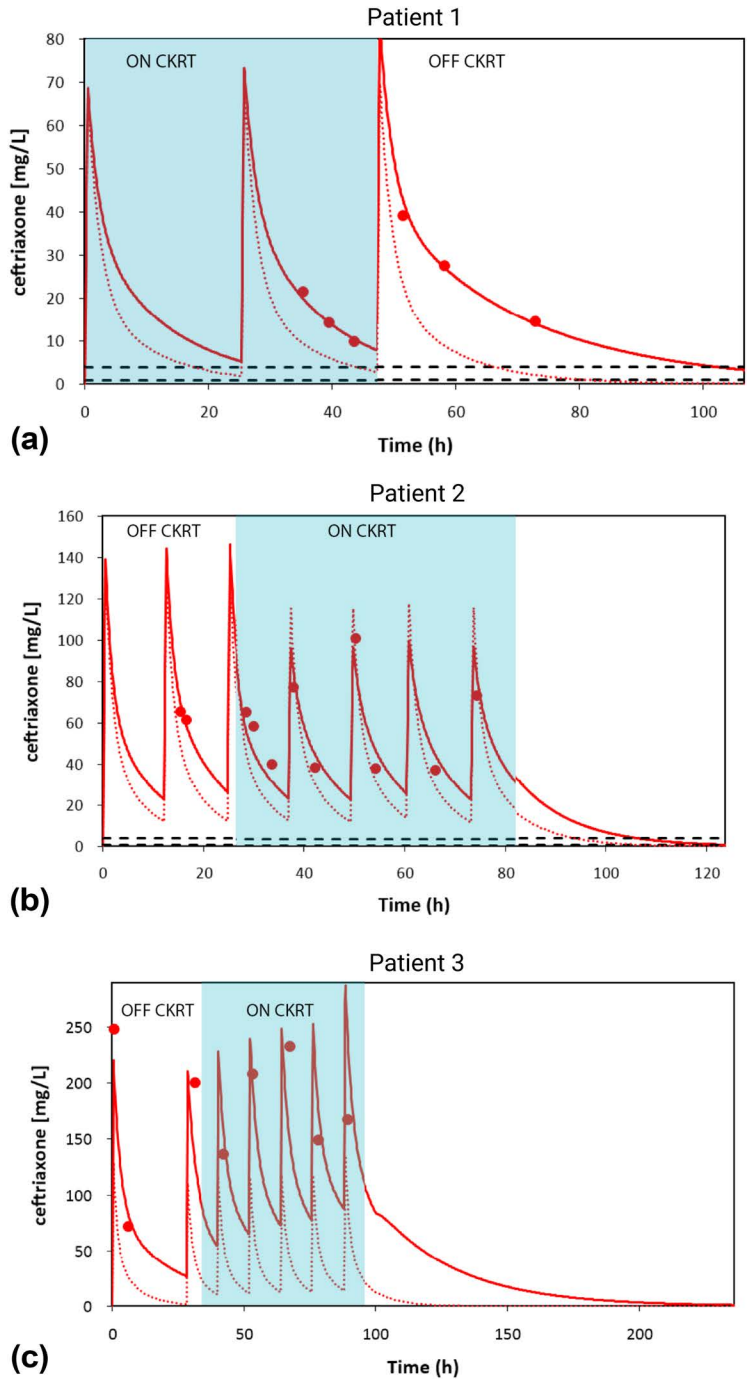
Modeling. Ceftriaxone PK parameters during and before or after CKRT were estimated with Bayesian estimation using MwPharm++ (Mediware, Czech Republic) with a previously published population PK model of free ceftriaxone in critically ill pediatric patients as the Bayesian prior.[7] The model was adapted to exclude serum creatinine as a covariate given that serum creatinine concentrations while receiving CKRT are not reflective of native kidney function. Thus, the reference/normalized patient is an older patient with negligible maturation effect of 70 kg, with Pediatric Risk Mortality Score (PRISM) III score of 0 and without fever, with a CL of 6.54 L/hr/70 $kg^{0.75}$. The measured free ceftriaxone concentrations were fitted using Bayesian estimation assuming a 5% assay error in accordance with the inter- and intraday precision reported above and concentration vs. time profiles were generated. For all patients, CL values were estimated with Bayesian estimation, standardized by allometrically scaled body weight (L/hr/$kg^{0.75}$) and normalized to the reference patient.[7]

Due to variations in sample availability around peak concentrations, Vc estimation was handled differently for each patient. For patient 1, there were no scavenged samples near the peak while on or off CKRT (Figure 1a), making it difficult to estimate Vc accurately. Thus, we fixed Vc to the population mean (25.4 L/70 kg). For patient 2, there were no samples near the peak while off CKRT (Figure 1b), so, Vc was fixed to the mean. While on CKRT, there was robust sampling around multiple peaks (Figure 1b), and Vc was estimated. For patient 3, there was adequate sampling around peaks while on and off CKRT (Figure 1c); Vc was estimated with Bayesian estimation. For the 2 patients for whom ceftriaxone was used as empiric coverage, the CLSI breakpoint of 1 mg/L for *Enterobacterales* was chosen as the PD target.[19] For the patient with an identified bloodstream infection (*Neisseria meningitidis*), the reported MIC of 0.016 mg/L was used. The percentage of time free ceftriaxone concentrations were above 1× and 4× MIC (% *f*T>1× and 4× MIC) during each dosing interval were calculated.

Results

There were 5 patients in our cohort who were on CKRT and received 1 or more doses of ceftriaxone. We excluded 1 patient who received extracorporeal membrane oxygenation and another who had insufficient sampling. Our final cohort included 3 patients. Patient characteristics, CKRT prescriptions and urine output are presented in Table 1. Patients ranged from 2 to 17 years; all were previously healthy. Patient 1 had acute interstitial nephritis due to minocycline, patient 2 had hemolytic uremic syndrome due to *Shiga*-toxin-producing *Escherichia coli*, and patient 3 had meningococcemia.

Figure 1. (a–c) PK Model-based Predicted Concentration-Time Profile for Patients 1–3 While on and Off of CKRT



Dashed black lines represent 1× and 4× MIC based on MIC of 1 mg/L (CLSI breakpoint for Enterobacteriaceae*) for Patients 1–2 and measured MIC of 0.016 mg/L for Patient 3's isolate of* Neisseria meningitidis*. Dotted red curves represent expected concentration-time profiles based on population PK model and patient covariates. Solid red curves represent simulated concentration-time profiles using Bayesian estimation after incorporating observed concentrations. Simulations of concentration-time profiles were performed separately for time on and off of CKRT then juxtaposed for clarity of presentation.*

Table 1. Patient Characteristics and CKRT Prescriptions

Patient	Age, yr and Sex	PICU Admit Weight/ CKRT Initiation Weight, kg	Height, cm/ BSA, m^2	Cause of AKI	Known CKD?	UOP for 24 hr pre-CKRT Initiation, mL (mL/kg/hr)	Mean daily UOP While on CKRT, mL (mL/kg/hr)	UOP for 24 hr post-CKRT, mL (mL/kg/hr)	% Fluid Overload at CKRT Initiation
1	16.9 M	74.5 / 74.5	180 / 1.94	Acute interstitial nephritis from minocycline	No	0 (0)	0 (0)	675 (0.38)	1.7
2	2.2 F	11.7 / 11.7	87 / 0.53	Hemolytic-uremic syndrome due to *Shiga*-toxin *Escherichia coli*	No	5 (0.018)	0 (0)	0 (0)	19.5
3	5.3 F	18.7 / 22.5	112 / 0.84	Septic shock from meningococcemia	No	0 (0)	0 (0)	0 (0)	17.3

Patient	Filter	CKRT Mode / Dialysis and Replacement Fluids	Qb, mL/min (mL/kg/ min)	Qd, mL/hr	Qpre, mL/hr	Qpost mL/hr	Net UF*, mL/hr	Qef, mL/hr (mL/ kg/hr)	Qef, mL/hr/ 1.73 m^2
1	HF1000	CVVHD / PrismaSATE/ PrismaSOL BGK 2/0	200 (2.7)	2000	0	50	524	2574 (34.6)	2295
2	M100	CVVHDF / PrismaSATE/ PrismaSOL BGK 2/0 for first 48 hr, then Phoxillum B22K 4/0	60 (5.1)	300	300	50	175	825 (70.5)	2693
3	M100	CVVHDF / PrismaSATE/ PrismaSOL BGK 2/0	100 (5.3)	500	450	50	283	1283 (68.6)	2642

AKI, acute kidney injury; BSA, body surface area; CKD, chronic kidney disease; CKRT, continuous kidney replacement therapy; post-CKRT, clearance estimate was determined using ceftriaxone concentrations obtained after CKRT discontinuation; pre-CKRT, clearance estimate was determined using ceftriaxone concentrations obtained prior to CKRT initiation; Qb, blood flow rate; Qd, dialysate flow rate; Qef, total effluent flow rate; Qpost, post-substitution fluid rate; Qpre, pre-replacement fluid rate; UF, ultrafiltration rate; UOP, urine output

* Net UF is calculated for time on CKRT during which we analyzed ceftriaxone concentrations. Dialysis fluids for all 3 patients were of similar composition; the chief difference between PrismaSATE/SOL and Phoxillum is that PrismaSATE/SOL has a potassium concentration of 2 mEq/L and a bicarbonate concentration of 32 mEq/L, while Phoxillum has a potassium concentration of 4 mEq/L and a bicarbonate concentration of 22 mEq/L. Full electrolyte compositions are available at usrenalacute.baxter.com. Patient 2 was switched from Phoxillum to SATE/SOL to address metabolic alkalosis. %FO was calculated as (Fluid intake in L since ICU admission-output in L since ICU admission)/ICU admission weight in kg*100% as per literature standard.[26]

All patients were anuric at the time of CKRT initiation, implying minimal residual kidney function. Patients 2 and 3 remained anuric during and after CKRT, while patient 1, who received corticosteroids for treatment of AIN, had recovery of kidney function and began urinating in the first 24 hours after CKRT discontinuation. All patients were connected to Prismaflex machines (Baxter, USA) in standard fashion for CKRT using a double-lumen dialysis-capable catheter placed in a central vein. Patient 1 received CVVHD using a polyarylethersulfone-containing HF1000 hemodiafilter (Baxter, surface area 1.1 m^2) while patients 2 and 3 both received CVVHDF using an AN 69-containing M100 filter (Baxter, surface area 0.9 m^2) with clearance modality evenly split between convective and dialytic modes. All patients received regional citrate anticoagulation. As detailed in Table 1, blood flow rates ranged from 2.7 to 5.3 mL/kg/min. Total effluent flow rates ranged from 2300 to 2700 mL/hr/1.73 m^2, similar to the 2000 to 2500 mL/hr/1.73 m^2 generally prescribed for pediatric AKI.[20] Patient 1, who had the lowest total effluent flow per body surface area, was nearly 17 years old and had a total effluent flow of 35 mL/kg/hr, within the 25 to 40 mL/kg/hr generally prescribed for adults receiving CKRT.[21]

Ceftriaxone dosing regimens and clearance while on and off CKRT, culture data and PD target attainment are summarized in Table 2. Concentration-time profiles while on and off CKRT for each patient are in Figures 1a–c. Patient 1 received every 24-hour dosing, patient 2 received every 12-hour dosing, and patient 3 received every 12-hour dosing while on CKRT and

Table 2. Ceftriaxone Dosing and PK/PD Parameters

Patient	Ceftriaxone Dosing Regimen While on CKRT, mg (mg/kg*)	Ceftriaxone Dosing Regimen While Off CKRT, mg (mg/kg*)	Ceftriaxone Clearance, L/hr (L/hr/70 $kg^{0.75†}$) While on CKRT	Ceftriaxone Clearance, L/hr (L/hr/70 $kg^{0.75†}$) While Off CKRT	Additional Clearance Provided by CKRT, L/hr (% of Total Clearance on CKRT)	CKRT Qef, L/hr	CKRT-Attributable Ceftriaxone Clearance/ Qef
1	2000 (26.8) q24h	2000 (26.8) q24h	3.67 (3.91)	2.71 (2.85), post CKRT	0.96‡ (26.1)	2.57	0.37
2	580 (49.6) q12h	580 (49.6) q12h	1.02 (5.11)	0.77 (4.28), pre CKRT	0.25 (24.5)	0.825	0.30
3	1000 (53.5) q12h	1000 (53.5) q24h	0.50 (1.78)	0.29 (0.95), pre CKRT	0.21 (42.0)	1.28	0.19

Patient	Positive Cultures	Off CKRT			On CKRT		
		C_{min} range, mg/L	% *f*T >1×MIC§	% *f*T >4×MIC§	C_{min} range, mg/L	% *f*T >1×MIC§	% *f*T >4×MIC§
1	None	13.7¶	100%	100%	5.4–7.91	100%	100%
2	Stool culture: *Shiga* toxin-producing *Escherichia coli* 0157:H7	22.9–26.4	100%	100%	23.2–26.1	100%	100%
3	Blood culture: *Neisseria meningitidis*, ceftriaxone MIC 0.016 mg/L	34.7	100%	100%	57.7–116.3	100%	100%

CKRT, continuous kidney replacement therapy; MIC, minimum inhibitory concentration; Qef, total effluent flow

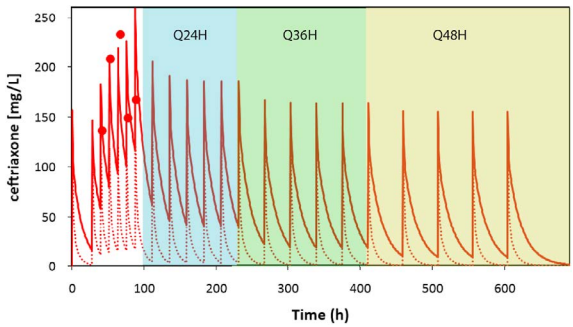
* Mg/kg based on PICU admit weight.
† This allometrically scaled clearance is normalized to the reference patient in reference 7 (an older patient of 70 kg with negligible maturation effect, with Pediatric Risk Mortality Score ([PRISM] III score of 0, and without fever) with a clearance of 6.54 L/hr/70 $kg^{0.75}$.
‡ Indicates additional clearance provided by CKRT may be an underestimate due to residual kidney function during time off CKRT.
§ Based on MIC of 1 mg/L (CLSI breakpoint for Enterobacteriales) for patients 1 and 2.
¶ Extrapolated based on presumed continuation with every 24-hour dosing, though ceftriaxone was discontinued.

Table 3. Serum Albumin, Ceftriaxone Concentrations, and Protein Binding

Patient	Mean Serum Albumin During Study Interval, g/dL	Range of Total Ceftriaxone Concentrations, mg/L	Range of Free Concentrations, mg/L	Median % Protein Binding (IQR)*
1	2.2	47.0–120	10.0–75.0	66 (59–71)
2	1.9	97.7–365	30.9–183	66 (64–69)
3	2.3	165–329	72.2–165	25 (24–49)

* Percent protein binding was calculated as 1 – (free concentration/total concentration)*100%. Patient 3 had the lowest degree of protein binding despite the highest mean serum albumin.

Figure 2. PK Model-based Predicted Concentration-Time Profile for Patient 3 While on CKRT Followed by Simulations of 1 g Ceftriaxone Every 24 Hours (Blue), Every 36 Hours (Green), and Every 48 Hours (Yellow)



Dotted red curves represent expected concentration-time profiles based on population PK model and patient covariates. Solid red curves represent simulated concentration-time profiles using Bayesian estimation after incorporating observed concentrations. C_{min} range 40.2–61.3 mg/L for q24h, 17.9 to 21.2 mg/L for q36h, and 8.8 to 9.5 mg/L q48h.

every 24 hours while off. Reasoning for dosing variability was not provided in clinical notes. Using the difference between ceftriaxone clearances on and off CKRT, we estimated the proportion of overall ceftriaxone clearance provided by CKRT, which ranged from 25% to 42% of overall ceftriaxone clearance. CKRT-attributable clearance corresponded to 19% to 37% of total effluent flows, which are a measure of the overall dialysis dose provided. All patients had 100% *f*T >1×MIC and *f*T >4×MIC, using 1 mg/L for patients 1 and 2 and the measured MIC of 0.016 mg/L for *N meningitidis* for patient 3. Patient 3 had evidence of gradual ceftriaxone accumulation, with free C_{min} increasing from 57.7 mg/L upon CKRT initiation to 116.3 mg/L at the end of our sampling period. This occurred despite patient 3 having the lowest median percent protein binding (25% compared with 66% in patients 1 and 2; see Table 3). Using the clearance estimates obtained from patient 3's time on CKRT, we simulated dosing 1 g ceftriaxone every 24, 36, and 48 hours (Figure 2); each of these simulations achieved 100% *f*T >4×MIC.

Discussion

We present a novel report of ceftriaxone PK and PD target attainment in pediatric patients receiving CKRT. We noted excellent PD target attainment among all patients with evidence of ceftriaxone accumulation in one patient receiving every 12-hour dosing. In our cohort, CKRT accounted for 26% to 42% of total clearance, and ranged from 19% to 37% of prescribed total effluent flows. In other words, our findings imply that for a given increase in CKRT clearance, ceftriaxone clearance may increase by 20% to 40% of that incremental increase in CKRT/circuit clearance. Since ceftriaxone typically has 70% to 90% protein binding, it is only partially susceptible to extracorporeal clearance, which may explain why a given increment in circuit clearance was associated with a smaller increase in ceftriaxone clearance. That said, large changes in extracorporeal clearance may still have a significant impact on ceftriaxone clearance, and may need to be considered when prescribing ceftriaxone to pediatric patients on CKRT.

However, even with the additional clearance provided by CKRT, allometrically scaled clearance was less for each patient than the population mean clearance of 6.54 L/hr/70 $kg^{0.75}$ for critically ill children, which is consistent with excellent PD target attainment, even for the patients receiving every 24-hour dosing.[7] Given that patients in this study were hypoalbuminemic (mean daily serum albumin ranged from 1.9–2.5 g/dL during the study period), and the observed median degree of protein binding was 25% to 66%, ceftriaxone may have been more susceptible to extracorporeal removal. Notably, due to inadequate sampling prior to CKRT initiation, our off-CKRT clearance estimates for patient 1 were obtained using ceftriaxone concentrations obtained shortly after CKRT discontinuation, at which point the patient had had some return of native kidney function. Therefore, our estimate of the contribution of extracorporeal clearance to total clearance while on CKRT for patient 1 is likely an underestimate.

There was notable variation in dosing strategies in this cohort. Given that all patients achieved 100% *f*T >4×MIC assuming a MIC of 1 mg/L, and patient 3 had evidence of ceftriaxone accumulation, it is possible

that every 24-hour dosing may be sufficient for target attainment for anuric pediatric patients receiving standard-dose CKRT, assuming ceftriaxone is not being used for treatment of infections in sites where ceftriaxone concentrations may be significantly lower than those in the blood, for example, the cerebrospinal fluid in treatment of meningitis.[22] Moreover, as previously reported, and based on our simulations for patient 3, there may be patients with sufficiently low intrinsic ceftriaxone CL that dosing every 48 hours would be sufficient to achieve PD targets, though the specific patient factors that would predict success of every 48-hour dosing cannot be determined from this small case series.[11]

We had heterogeneity in ages, indications, and dosing regimen in our study population. Additional studies would enrich our understanding of patient-specific factors that may impact ceftriaxone clearance while on CKRT, such as fluid accumulation/overload, presence or absence of septic shock, degree of fluid resuscitation, filter type, and greater variation in effluent flows. In addition, the variation herein suggests a possible role for model-informed precision dosing, given the risk of biliary sludging with excessive ceftriaxone exposure.[23–25]

This study has a few strengths. We had samples available throughout most of the dosing interval both on and off CKRT, facilitating accurate model-informed estimation of ceftriaxone CL, C_{min}, and %*f*T>MIC. In addition, we demonstrated that dosing ceftriaxone every 12 hours in an anuric patient may lead to ceftriaxone accumulation, though this finding was only seen for 1 of the 2 patients given every 12-hour dosing (patient 3), so further studies should be performed to assess patient-, disease-, and CKRT-specific factors that may have contributed to this finding. At the same time, there are notable limitations worthy of discussion. The small sample size limits the scope of our conclusions. Moreover, we had few samples around peak concentrations, limiting our ability to estimate Vc consistently. Thus, while our estimates of clearance are likely accurate given adequate sampling close to trough concentrations, we are not able to make significant conclusions regarding central volume of distribution, which may have been larger than normal in these critically ill, hypoalbuminemic patients. In addition, only one of the patients in this case series had an identified bacterial infection, thus the PD target attainment data reported are mostly theoretical in nature.

Future work will include prospective sample collections of timed peripheral blood, post-filter blood, and effluent concentrations to allow for multicompartmental analysis and more accurate estimation of PK/PD parameters. Larger studies will help examine the effect of patient-level variables (e.g., age, weight, fluid overload) on PK parameters, target attainment, and hard clinical outcomes such as microbial eradication, PICU length of stay, and mortality.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board, who granted a waiver of informed consent.

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