Urinary Biomarkers and Attainment of Cefepime Therapeutic Targets in Critically Ill Children

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Background: Critically ill children are at risk for subtherapeutic antibiotic concentrations. The frequency of target attainment and risk factors for subtherapeutic concentrations of cefepime in children have not been extensively studied.

Methods: We performed an observational study in critically ill children receiving a new prescription of standard dosing of cefepime for suspected sepsis (≥2 systemic inflammatory response syndrome criteria within 48 hours of cefepime start). Three plasma cefepime concentrations were measured at steady state and, a urine sample was collected prior to pharmacokinetics (PK) sampling for measurement of urinary biomarkers. Bayesian analysis determined cefepime PK for each individual, and simulations were used to estimate time above minimum inhibitory concentration ($fT > MIC$) for 8 μg/mL (breakpoint for *Pseudomonas*). Clinical factors and urinary biomarkers were compared between patients who did and did not achieve 100% $fT > MIC$. Correlations between covariates and cefepime PK parameters, as well as optimal cut points to identify <100% $fT > MIC$, were evaluated.

Results: Twenty-one subjects were enrolled and PK sampling occurred after a median of 5 doses (range, 3–9); 43% of children achieved 100% $fT > MIC$ for an MIC of 8 μg/mL. Younger age and lower urinary biomarkers (neutrophil gelatinase-associated lipocalin and kidney injury molecule-1) were significantly associated with failure to attain 100% $fT > 8$ μg/mL. Urinary neutrophil gelatinase-associated lipocalin (<122.1-ng/mg creatinine) best identified individuals who failed to attain this putative target (positive predictive value, 91.7%).

Conclusions: A large proportion of critically ill children failed to attain target concentrations for empiric treatment of *Pseudomonas aeruginosa* with cefepime. Urinary biomarkers may be a noninvasive means to identify those at higher risk for increased cefepime clearance and subtherapeutic concentrations.

Key Words: augmented renal clearance, biomarkers, target attainment, pharmacokinetics, sepsis

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Critical illness alters the volume of distribution (V_d), protein binding and drug clearance (CL), affecting the pharmacokinetics (PK) and pharmacodynamics of antibiotics.[1,2] β-lactam exposures in critically ill adults are often low, contributing to poor outcomes.[3,4] Similarly, standard dosing is frequently inadequate in critically ill children,[5,6] especially for the treatment of more resistant gram-negative pathogens.[7] Pediatric sepsis and septic shock have an in-hospital mortality of roughly 6% to 26%,[8–10] with delayed antimicrobial administration being associated with increased mortality and organ dysfunction.[10,11] Optimizing antibiotic exposures early in pediatric sepsis contributes to improved patient outcomes.

Cefepime, a renally excreted fourth-generation cephalosporin, is used as empiric antibiotic coverage in many critically ill children with suspected sepsis. Its efficacy is defined by the fraction of time of the dosing interval for which the free (unbound) concentration is maintained above the minimum inhibitory concentration ($fT > MIC$) of the infecting pathogen.[12] While the optimal $fT > MIC$ associated with clinical efficacy in critically ill children is unknown, the recommended therapeutic target for critically ill adults is $fT > MIC$ of 100%.[13] Meanwhile, microbiological cure and suppression of resistance selection have been associated with a more robust target of 100% $fT > 4\times$ MIC.[14] Few studies have evaluated cefepime target attainment in critically ill children.

Therapeutic drug monitoring (TDM) is typically reserved for drugs with a narrow therapeutic window to optimize safety (primarily), as well as efficacy. Although cefepime neurotoxicity occurs with high minimum concentration (C_{min}) in adults,[15] it is a rare occurrence in children. However, a potential rationale for β-lactam TDM in children is to identify those with lower concentrations who may be at higher risk of treatment failure. Because β-lactam TDM is not routinely available at most pediatric institutions, recognition of children at higher risk for subtherapeutic concentrations could allow for implementation of alternative dosing strategies to optimize attainment of $T > MIC$ targets, such as extended or continuous infusions.

Traditional methods for estimating renal function and drug CL using serum creatinine (SCr)–based equations[16] do not readily identify children with augmented renal CL or changing glomerular filtration in the setting of acute kidney injury (AKI). Novel urinary biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), can detect AKI earlier and correlate better with glomerular filtration rate (GFR) and drug CL than SCr.[17–19] Thus, they could identify patients with impaired renal CL at risk for supratherapeutic drug concentrations. Conversely, low levels of biomarkers, signifying the absence of

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kidney injury, may detect children at higher risk for faster drug elimination and subtherapeutic drug exposures. In this prospective observational study, we hypothesized that biomarkers would correlate with cefepime concentrations in critically ill children with suspected sepsis.

METHODS

Subjects and Setting

We performed a prospective observational study in children (<19 years of age) admitted to the pediatric intensive care unit (PICU) of the Children's Hospital of Philadelphia. Children were eligible if prescribed standard dosing of cefepime (50 mg/kg/dose every 8 hours if <40 kg; 2000 mg/dose every 8 hours if ≥40 kg) and had ≥2 systemic inflammatory response syndrome (SIRS) criteria present within 48 hours prior to initiation of cefepime;[20] SIRS criteria are described in the Table, Supplemental Digital Content 1, http://links.lww.com/INF/G120. Cefepime was administered routinely as a 30-minute infusion at our hospital, but infusion times were not prespecified for this study. Children receiving extracorporeal membrane oxygenation, renal replacement therapy or plasmapheresis were excluded. The institutional review board approved the study protocol with a waiver of documented assent; verbal assent was obtained, when possible. Documented written informed consent was obtained from the subject or parents/legal guardians.

Cefepime PK Sampling

Following enrollment and administration of at least 3 cefepime doses, 3 blood samples were collected during a single dosing interval at 3, 4.5 and 6 hours (±60 min) after completion of a dose; sampling times were chosen to facilitate the calculation of elimination rate constants using noncompartmental methods, as needed. All sampling was completed within 72 hours of therapy to reflect drug concentrations early in cefepime therapy. Each blood sample was promptly centrifuged (2326 × g for 15 minutes) following collection, and the plasma portion was aliquoted and stored at −80 °C. Total cefepime concentrations in plasma were determined in the Bioanalytical Core Laboratory of the Center for Clinical Pharmacology using high-performance liquid chromatography and tandem mass spectrometry, as previously described.[21] The lower limit of quantification for the assay was 0.01 μg/mL, with a range of 0.01 to 25 μg/mL; samples above the limit of quantification were diluted 50× for analysis.

Kidney Biomarkers

Following enrollment and prior to blood sampling, a single urine sample was collected for measurement of urinary biomarkers. Fresh urine was collected from the subject using an indwelling urinary catheter, clean intermittent catheterization or urine bag. Samples were kept on ice or refrigerated at 4 °C until centrifugation (2737 × g at 4 °C for 15 minutes). The supernatants were then divided and stored at −80 °C. Urine biomarkers were measured at the CHOP Translational Core Lab via Quantkine ELISA (NGAL, KIM-1, osteopontin and cystatin C; R&D Systems, Inc, Minneapolis, MN) and the Luminex platform (clusterin; R&D Systems, Inc, Minneapolis). Biomarker concentrations that were out of the range of the assay (Table, Supplemental Digital Content 2, http://links.lww.com/INF/G120) were assigned the maximum or minimum of the assay, as appropriate. Urine creatinine was also measured on each sample by a 2-point end enzymatic method (Roche Diagnostics, Indianapolis, IN). Biomarker results were reported as values adjusted for urine creatinine because specimens were not timed collections.

SCr was collected per standard of care and measured in the CHOP Chemistry Laboratory using the 2-point rate spectrophotometric method (Vitros5600 analyzer, Ortho Clinical Diagnostics, Markham, ON); SCr was rounded to 0.1 if reported as <0.2 mg/dL, which was the lower limit of quantification for the assay during the study period. Estimated GFR (eGFR) was calculated for each subject at cefepime initiation, and at the time, the urinary biomarkers' sample was collected using the bedside Schwartz equation.[22] Renal impairment was defined as eGFR <60 mL/min/1.73 m^2.

Bayesian Estimation and Target Attainment

Individual PK parameters were determined for each subject by fitting total plasma cefepime concentrations using Bayesian estimation in Monolix 2024R1 (Lixoft, Antony, France). A published population PK model of cefepime in critically ill children[23] served as prior information for maximum a posteriori estimation (Table, Supplemental Digital Content 3, http://links.lww.com/INF/G120). Briefly, this published model described total plasma cefepime PK via one compartment with first-order elimination and a proportional residual error structure. Fixed effect parameters were allometrically scaled with an exponent of 0.75 on CL and 1 on V_d; eGFR was included as a covariate on CL. Relative standard errors of the parameters[23] were used to calculate the standard deviations for Bayesian estimation.

After model fitting, we recorded the individual estimates for V_d and CL for each subject. Individual predicted concentrations showed a good fit to the observed concentrations (Figure, Supplemental Digital Content 4, http://links.lww.com/INF/G120), supporting the accuracy of the estimated individual PK parameters. The final population PK parameters (Bayesian posteriors) are shown in Table, Supplemental Digital Content 3, http://links.lww.com/INF/G120. The final model and each subject's estimated individual PK parameters were then exported to Simulx 2024R1 (Lixoft, Antony, France), and unbound cefepime plasma concentrations were simulated from time 0 to 52 hours, assuming 20% protein binding.[23,24] Each subject's cefepime dosing information (amount and timing), along with known covariate information (weight, eGFR), was utilized for simulations. If a subject received <48 hours of cefepime, additional doses at 8-hour intervals were incorporated so that C_{min} closest to 48 hours could be recorded. In addition, each subject's fraction of time above MIC ($fT > MIC$) from 24 to 48 hours was calculated for MIC values of 1, 2, 4, 8 and 16 μg/mL.

Data Analysis

We tested the association between covariates (clinical characteristics and biomarkers) and 100% $fT > MIC$ for an MIC of 8 μg/mL, the Clinical and Laboratory Standards Institute breakpoint for *Pseudomonas aeruginosa*, using χ^2 and Wilcoxon rank-sum tests. *Pseudomonas* is often targeted with empiric cefepime therapy in the critical care setting, and this MIC breakpoint has been utilized in prior evaluations of the adequacy of initial cefepime dosing among critically ill adults[25] and immunocompromised children.[26]

We evaluated the Spearman correlation between continuous covariates, including biomarkers and cefepime PK parameters (V_d, CL and C_{min}). The eGFR closest and prior to 24 hours was used for these tests of association because T > MIC from 24 to 48 hours was used for target attainment. For biomarkers, including eGFR, which were significantly correlated with C_{min} or CL, we calculated the Youden index using the *cutpointr* package in R to identify the optimal cutoff point to predict attainment of $C_{min} < 8$ μg/mL and the test performance [sensitivity, specificity, negative predictive value and positive predictive value (PPV)] of the cutoff point.

Data management and analyses were conducted using R version 4.3.1 (Vienna, Austria). No formal sample size

calculations were made a priori because this was an exploratory study and convenience sampling/enrollment was done during the time period.

RESULTS

Study Population

Thirty-one children were enrolled from May 2018 to December 2019. Two became ineligible following consent (one was started on plasmapheresis and the other transferred out of the PICU). Eight additional children were withdrawn from the study due to inadequate venous access. As a result, 21 children fully participated in the study (Table 1). The median number of SIRS criteria met upon initiation of cefepime was 3: 6 met 2 criteria, 7 met 3 and 8 met all 4. Eighteen children received cefepime for suspected sepsis, 2 had fever with a central line and 1 had neutropenic fever.

TABLE 1. Characteristics of the Study Population

Characteristics	Value (n = 21)
Female sex, n (%)	8 (38)
Age, yr; median (range)	10.6 (0.7–18.7)
Weight, kg; median (range)	30.9 (6.6–127.5)
Height, cm; median (range)	129.0 (62.2–180.0)
Indication for PICU admission, n (%)	
Respiratory distress/failure	8 (38)
Cardiac arrest	2 (10)
Fever/shock	4 (19)
Central nervous system pathology*	5 (24)
Postoperative care	1 (5)
Electrolyte disturbance	1 (5)
Underlying comorbidities, n (%)	
Neurologic disorder	8 (38)
Lung disease	3 (14)
Cancer	7 (33)
Neutropenia	3 (14)
Stem cell transplant	1 (5)
Initial cefepime dosing, mg/kg/dose; median (range)	44.4 (15.7–51.3)
Receipt of maximum cefepime dose (2000 mg), n (%)	9 (43)
Severity of illness (PELOD-2) score at start of cefepime, median (range)	7 (4–13)
Mechanical ventilation at start of cefepime, n (%)	17 (81)
On vasopressor/inotrope support	
At cefepime start, n (%)	8 (38)
At the time of PK sampling, n (%)	6 (29)
eGFR at cefepime initiation, mL/min/1.73 m^2; median (IQR)	147 (122–182)
Renal impairment (eGFR <60 mL/min/1.73 m^2), n (%)	1 (5)
eGFR at biomarker collection, mL/min/1.73 m^2; median (IQR)	144 (109–208)
Renal impairment (eGFR <60 mL/min/1.73 m^2), n (%)	1 (5)
Number of cefepime doses prior to PK sampling, median (range)	5 (3–9)
Cefepime dose prior to PK sampling given as a bolus infusion,† n (%)	5 (24)
Pharmacokinetic parameters,‡ median (range)	
V_d, L/kg	0.54 (0.23–1.02)
CL, L/h/kg	0.15 (0.04–0.29)
C_{min},‡ µg/mL	6.2 (0.9–89.1)

*Includes seizures (n = 3), cerebellar hemorrhage (n = 1), shunt malfunction (n = 1) and altered mental status (n = 1).

†Bolus infusion defined by infusion time <15 minutes.

‡C_{min} determined at 8 hours post-dose.

IQR indicates interquartile range; PELOD-2, Pediatric Logistic Organ Dysfunction-2.

Ten children were clinically diagnosed with a bacterial infection and received a definitive course of treatment, including 6 with a lower respiratory tract infection, 3 with bacteremia and 1 with a urinary tract infection; the remainder received cefepime empirically. Six individuals had gram-negative bacteria isolated on culture: *Serratia marcescens* (blood, cefepime MIC ≤ 1 µg/mL), *Escherichia coli* (blood, cefepime MIC ≤ 1 µg/mL), *P. aeruginosa* (n = 3, all respiratory tract isolates; cefepime MIC ≤ 1, 2 and 16 µg/mL) and *Providencia stuartii* (urine, cefepime MIC 1 µg/mL). Two patients had MRSA isolated from a respiratory tract culture, 1 had *Enterococcus faecalis* isolated from a urine culture, 1 had MSSA bacteremia and another had MSSA isolated from a respiratory tract culture.

The median time of urine sample collection following cefepime start was 25.8 (interquartile range, 22.9–38.5) hours; the median time from urine sample collection to first PK measurement was 8.9 (interquartile range, 1.0–15.6) hours. Three participants had clusterin concentrations, and 3 had KIM-1 concentrations that were below the limit of quantification of the assay. Two and 1 individuals had NGAL and osteopontin concentrations above the upper limits of the assay ranges, respectively.

Cefepime PK and Target Attainment

Median individual V_d and CL estimates among subjects, assuming 20% protein binding, were 16.9 (range, 5.0–66.3) L and 3.23 (1.55–14.57) L/h, respectively. The median cefepime C_{min} closest to 48 hours was 6.2 (range, 0.9–89.1) µg/mL. Almost all children maintained free concentrations above an MIC of 1 and 2 µg/mL for 100% of the dosing interval from 24 to 48 hours, but less than half had $fT > MIC$ of 100% using MICs ≥ 4 µg/mL (Table 2).

Twelve children (57%) failed to meet the a priori target of 100% $fT > MIC$ for an MIC of 8 µg/mL. These patients were younger and had higher eGFR at 24 hours after cefepime initiation (Table 3). Children who failed to have 100% $fT > 8$ µg/mL had higher weight-adjusted CL (in L/h/kg) and larger V_d (in L/kg), as well as lower NGAL and KIM-1 urinary concentrations. Age, eGFR at 24 hours, urinary clusterin, NGAL and KIM-1 were significantly correlated with cefepime C_{min} at 48 hours (Table 4). Age and weight, as well as NGAL and KIM-1, were also significantly correlated with cefepime CL. Scatterplots of biomarkers versus C_{min} and CL are shown in Figure 1 and Figure, Supplemental Digital Content 5, http://links.lww.com/INF/G120, respectively.

The optimal cutoff point of eGFR at 24 hours to predict failure to attain 100% $fT > 8$ µg/mL was ≥89 mL/min/1.73 m^2 (Youden index, 0.44). The PPV of this cutoff point (ie, the likelihood of <100% $fT > 8$ µg/mL if eGFR was ≥89 mL/min/1.73 m^2) was 0.705. The optimal NGAL measurement to predict 100% $fT > 8$ was ≤122.1-ng/mg Cr (Youden index, 0.81), which had a PPV of 0.917 (ie, the likelihood of <100% $fT > 8$ µg/mL was 0.917 if NGAL ≤122.1). For KIM-1, the optimal cutoff point was 3.2 ng/

TABLE 2. Target Attainment for Subjects Treated With Cefepime

MIC (µg/mL)	100% $fT \geq$MIC, n (%)	100% $fT \geq 4\times$ MIC, n (%)
1	20 (95.2)	10 (47.6)
2	20 (95.2)	9 (42.9)
4	10 (47.6)	7 (33.3)
8	9 (42.9)	4 (19.0)
16	7 (33.3)	2 (9.5)

Target attainment was determined based on simulated concentrations from 24 to 48 hours after the start of cefepime for each individual. The free fraction of cefepime was assumed to be 80% in all subjects.

TABLE 3. Comparison Between Factors and 100% *f*T >8 µg/mL

Factor	<100% *f*T >MIC (n = 12)	100% *f*T >MIC (n = 9)	*P* value
Age, yr; median (IQR)	2.9 (1.0–11.5)	16.6 (14.4–17.2)	**0.006**
Weight, kg; median (IQR)	16.3 (9.6–51.1)	45 (29.8–49.9)	0.11
Dosage, mg/kg/dose; median (IQR)	45.0 (39.1–47.6)	40.9 (40.1–46.3)	0.48
eGFR at start of cefepime, mL/min/1.73 m^2; median (IQR)	155 (135–214)	122 (94–182)	0.21
eGFR closest and prior to 24 hours after start of cefepime, mL/min/1.73 m^2; median (IQR)	164 (135–316)	109 (80–167)	0.08
Severity of illness (PELOD-2) score at start of cefepime, median (IQR)	7.5 (7–9.5)	7 (6–8)	0.37
Receipt of vasopressors/inotropes at start of cefepime, n (%)	9 (25%)	5 (55%)	0.20
PK parameters*			
V_d, L/kg; median (IQR)	0.59 (0.52–0.63)	0.44 (0.42–0.52)	0.11
CL, L/h/kg; median (IQR)	0.22 (0.16–0.24)	0.07 (0.05–0.09)	**<0.001**
Urinary biomarkers, ng/mg urine creatinine; median (IQR)			
Cystatin C	141.0 (60.9–225.2)	863.9 (169.2–18010.9)	0.08
Clusterin	204.2 (99.1–859.6)	814.1 (368.3–1440.9)	0.19
NGAL	57.1 (39.3–88.4)	826.7 (217.2–5217.9)	**0.004**
Osteopontin	5075.2 (2514.0–9117.3)	3728.8 (2802.3–4480.0)	0.65
KIM-1	1.9 (0.8–3.1)	8.9 (4.1–11.5)	**0.05**

Wilcoxon rank-sum tests were used for comparisons of continuous variables; Fisher exact tests were used for comparisons of categorical variables.
Bolded *P* values represent statistical significance at ≤0.05.
*PK parameters derived for each individual subject based on fitting of total drug concentrations via Bayesian estimation.
IQR indicates interquartile range; PELOD-2, Pediatric Logistic Organ Dysfunction-2.

TABLE 4. Spearman Correlation Analyses Between Covariates and Individual Cefepime PK Parameters

Factor	C_{min}*	V_d (L/kg)†	CL (L/h/kg)†
Age, yr	0.52‡	−0.45‡	−0.69§
Weight, kg	0.40	−0.63§	−0.65§
eGFR at the start of cefepime	−0.35	0.40	0.22
eGFR at 24 hours	−0.55‡	0.57§	0.41
PELOD-2 score at start of cefepime	0.09	−0.05	−0.11
Urinary biomarkers (adjusted for urine creatinine)			
Cystatin C	0.38	0.03	−0.32
Clusterin	0.45‡	0.03	−0.38
NGAL	0.52‡	0.03	−0.45‡
Osteopontin	0.18	0.13	−0.09
KIM-1	0.60§	−0.23	−0.45‡

*C_{min} defined as the lowest estimated concentration closest to 48 hours based on simulated concentration-time profiles for each subject, assuming 20% protein binding.
†Estimated V_d and CL estimated for each individual subject based on fitting of total drug concentrations via Bayesian estimation.
‡$P < 0.05$.
§$P < 0.01$.
PELOD-2 indicates Pediatric Logistic Organ Dysfunction-2.

mg Cr (Youden index, 0.61; PPV, 0.833), while, for clusterin, the optimal cutoff point was 262.7 ng/mg Cr (Youden index, 0.47; PPV, 0.875). Full test characteristics, as well as test performance for *f*T > 4 and 16 µg/mL, are shown in the appendix (Table, Supplemental Digital Content 6, http://links.lww.com/INF/G120).

No children died during cefepime treatment or as a complication of their infection. Among the 6 children who had gram-negative infections, 3 had recurrences of their infections within 30 days of diagnosis. However, all 6 children had 100% *f*T > MIC for the MIC of their infecting pathogen.

DISCUSSION

In our study, a substantial proportion of critically ill children failed to attain putative therapeutic targets for cefepime with standard, intermittent dosing. Only 43% of patients maintained estimated free cefepime concentrations above 8 µg/mL, an empiric target for treatment of *P. aeruginosa*.[26,27] Younger age, faster drug CL and lower urinary biomarker concentrations (NGAL and KIM-1) were associated with decreased cefepime concentrations.

In US PICUs, cefepime is the second-most prescribed β-lactam antibiotic.[28] Unfortunately, β-lactam assays are not available locally at most pediatric institutions, and cefepime TDM requires sending samples to a reference laboratory, which is costly and difficult to timely apply to clinical care. Administration of β-lactams as prolonged or continuous infusions can increase *f*T > MIC but is technically challenging in young patients who often have limited vascular access points. While TDM-directed dose adjustments and extended infusions can promote β-lactam efficacy, identification of the right candidates for these interventions (eg, patients with known resistant pathogens and those with increased drug elimination) is important.

In our study, patients with higher eGFR were more likely to fail to attain the *f*T > MIC target although this association was not statistically significant. A relationship between higher eGFR and decreased probability of *f*T > MIC target attainment for cefepime has been reported in other pediatric studies.[26] However, in our analyses, an eGFR of 89 mL/min/1.73m^2 best distinguished children who did and did not attain the *f*T > MIC target. This cutoff point for SCr-based eGFR is consistent with "low" GFR for children and adolescents over the age of 2 years[29] and is more reflective of impaired cefepime elimination rather than augmented CL. In a recent observational study of critically ill children, AKI was a significant predictor of cefepime C_{min} and identified patients with elevated cefepime exposures (C_{min} and area under the curve).[30] Thus, SCr-based eGFR may perform better in identifying critically ill children at risk for high rather than low concentrations.

Urinary biomarkers have been studied extensively for the detection of AKI,[31,32] where higher concentrations are reflective of injury. Low values are typically less informative but may have utility when it comes to understanding renal drug elimination. In our study, urinary biomarkers were inversely correlated with cefepime CL, which has also been described with other drugs including milrinone,[33] tobramycin[19] and vancomycin.[34] We found that NGAL had the best predictive ability to identify children with <100% *f*T > MIC for all MICs tested based on the Youden index. Furthermore, 92% of patients with NGAL below 122.1- and 166.4-ng/mg creatinine had cefepime concentrations that fell below 8 and 16 µg/mL,

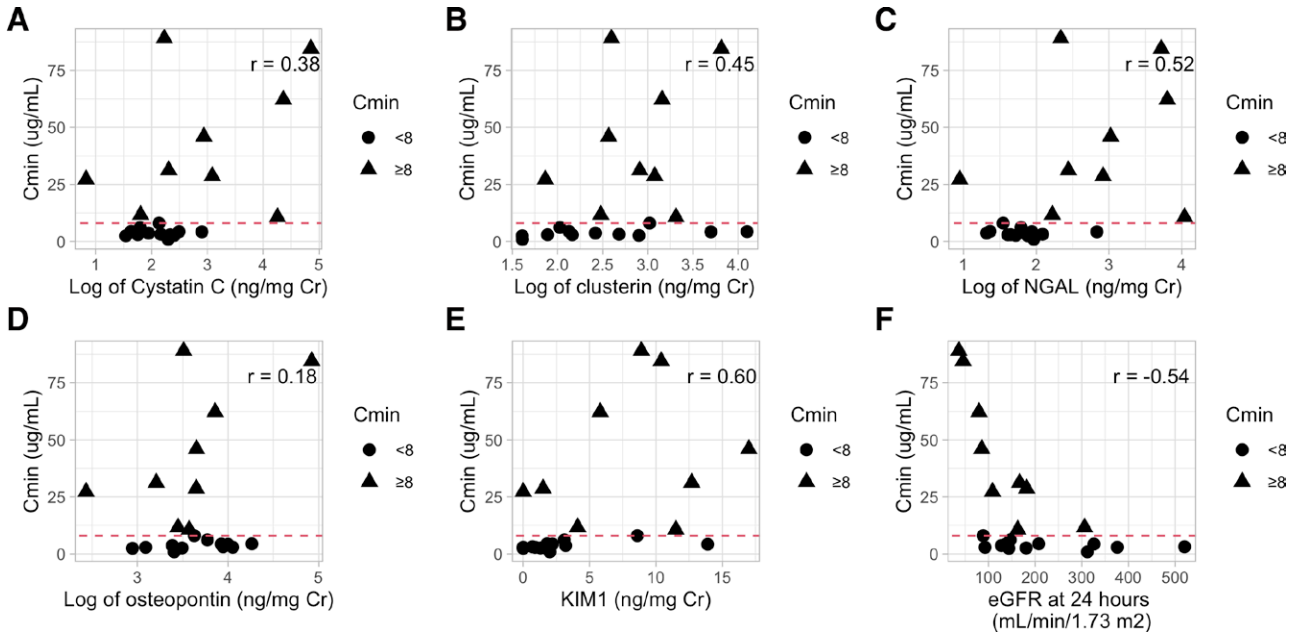

FIGURE 1. Scatterplots of biomarkers (A–E) and eGFR (F) versus C_{min}. Biomarkers (NGAL, osteopontin, cystatin C and clusterin) were log-transformed to allow for plotting. Correlations were determined using the Spearman correlation test. The horizontal dashed line represents C_{min} of 8 µg/mL. Triangles reflect concentrations ≥8 µg/mL, while circles represent concentrations <8 µg/mL.

respectively. However, NGAL's performance declined when using a lower MIC of 4 µg/mL (PPV, 75%), as with eGFR and the other biomarkers. Larger studies are needed to further evaluate these findings, but urinary biomarkers may serve as useful noninvasive screening tests beyond AKI.

It is noteworthy that traditional population PK analysis methods would be an alternative way to evaluate the relationship between biomarkers and cefepime PK (ie, examining biomarkers as covariates on cefepime CL). Population PK approaches would ideally involve serial urine collection, including samples close to cefepime initiation, to capture changes in biomarkers and organ function early in sepsis. Unfortunately, this was not feasible for us. Furthermore, our PK sampling times were selected to allow the calculation of elimination rate constants and *f*T > MIC via linear regression in each subject, if needed. Although these sampling times were suitable for the Bayesian estimation in our final analyses, alternative sampling times might be preferable to describe cefepime PK in critically ill children. Future studies with longitudinal urine and PK sampling may better tease out the dynamic relationships between biomarkers and cefepime PK.

There are other limitations to our study. First, due to our small sample size, we explored only a limited number of factors that we believed influenced cefepime PK (eg, renal function, the severity of illness indicators and dosing information). It is possible that other unexamined factors could also be influential. Second, our laboratory measured total cefepime concentrations, and we estimated the free fraction based on published literature.[24] Direct measurement of free drug concentrations could impact target attainment or the correlation between PK parameters and biomarkers/eGFR. Third, we did not specify when urine samples should be collected in relation to cefepime concentration sampling as collection of urine at precise times would not be practical clinically. Furthermore, we chose to collect PK samples after at least 3 cefepime doses as a proxy for steady state, but kidney function in critically ill patients is highly dynamic, potentially resulting in fluctuations of drug concentrations from dose to dose. The use of Bayesian estimation and evaluation of target attainment at 48 hours in all subjects should help account for the differential timing of PK sampling in our study. Finally, timed urine collection may be a more reliable method for measuring urinary biomarker excretion but is less practical and prone to collection errors. We provided values adjusted for urinary creatinine, which can help account for urine dilution.

In conclusion, a significant proportion of critically ill children failed to attain empiric cefepime targets in plasma using standard, intermittent dosing. Although all children received recommended dosing for treatment of serious infections, less than half maintained concentrations above the MIC breakpoint for *Pseudomonas*. Younger age and lower urinary biomarkers (NGAL and KIM-1) were associated with higher cefepime CL and with lower C_{min}. Urinary biomarkers may help identify patients at the highest risk for subtherapeutic cefepime concentrations.

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