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# Population pharmacokinetics of intravenous cefotaxime indicates that higher doses are required for critically ill children

Stan J. F. Hartman ⓘ [1], Parth J. Upadhyay[2], Ron A. A. Mathôt[3], Michiel van der Flier[4,5], Michiel F. Schreuder ⓘ [6], Roger J. Brüggemann ⓘ [7], Catherijne A. Knibbe ⓘ [2,8] and Saskia N. de Wildt ⓘ [1,9,10]*

[1]Department of Pharmacology and Toxicology, Radboud Institute of Health Sciences, Radboudumc, Nijmegen, The Netherlands; [2]Systems Biomedicine and Pharmacology, Leiden Academic Center for Drug Research, Leiden University, Leiden, The Netherlands; [3]Department of Clinical Pharmacology and Hospital Pharmacy - Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [4]Pediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Pediatric Infectious Diseases and Immunology, Amalia Children's Hospital, and Section Pediatric Infectious Diseases, Radboudumc, Nijmegen, The Netherlands; [6]Department of Pediatrics, Division of Pediatric Nephrology, Amalia Children's Hospital, Radboud Institute of Molecular Life Sciences, Radboudumc, Nijmegen, The Netherlands; [7]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands; [8]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands; [9]Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands; [10]Department of Intensive Care Medicine, Radboud Institute of Health Sciences, Radboudumc, Nijmegen, The Netherlands

*Corresponding author. E-mail: Saskia.deWildt@radboudumc.nl

**Background:** Cefotaxime is frequently used in critically ill children, however pharmacokinetic (PK) studies to support adequate dosing in this patient population are limited.

**Objectives:** To characterize cefotaxime PK in critically ill children and evaluate exposures achieved by current and alternative dosing regimens.

**Methods:** Children (0–18 years) admitted to the paediatric ICU, receiving intravenous cefotaxime (100–150 mg/kg/day, interval 6–8 h) were included (Clinicaltrials.gov NCT03248349). Total plasma cefotaxime concentrations were measured on multiple study days. Population-PK analysis was performed using nonlinear mixed effects modelling (NONMEM™). Dose evaluations were performed using typical patients across the paediatric age range and target attainment was determined for MICs of 0.5, 2 and 4 mg/L.

**Results:** 479 cefotaxime plasma concentrations from 52 children (median age 1.6, range 0.03–17.7 years) were used to describe cefotaxime PK. We describe a two-compartment structural model with interindividual variability, including bodyweight as covariate for volume of distribution and clearance. Model predicted exposure for 150 mg/kg/day (current dose) showed trough concentrations <0.5 mg/L in patients >4 years of age. The maximum cefotaxime doses (200 mg/kg/day, interval 6 h) proved adequate for MICs ≤0.5 mg/L across the whole age range. Similar daily doses with increased frequency (interval 4 h) covered MICs up to 2 mg/L, while a loading dose followed by continuous infusion regimens are needed to adequately treat MICs of 4 mg/L.

**Conclusions:** Higher cefotaxime doses are required for adequate exposure for most pathogens in critically ill children. A higher dose frequency or continuous infusion is advisable to improve target attainment for intermediately susceptible pathogens.

## Introduction

Cefotaxime is a third-generation cephalosporin antibiotic in the β-lactam family. Due to its broad antibiotic spectrum and high tissue penetration, cefotaxime is frequently prescribed in critically ill children with severe infections, including meningitis and severe sepsis of unknown origin. Despite its frequent use in critically ill children, pharmacokinetic (PK) data to support adequate dosing in this patient population are scarce.[1]

Critical illness in children introduces several pathophysiological changes, such as extensive fluid retention, organ dysfunction or augmented kidney clearance (AKC),[2] which can alter the PK profile of drugs. Additionally, PK in children differs from adults due to maturation processes involved in drug absorption, distribution, metabolism and excretion.[3] This interplay of factors impacting PK in critically ill children can result in increased or decreased drug exposure, potentially causing drug toxicity or therapy failure.[4] Adequate drug exposure of β-lactam antibiotics is defined as the proportion of time unbound concentrations (%*fT*) are above MIC of the pathogen. Several studies in critically ill adults and children report large intraindividual variability and suboptimal exposure of several different antibiotic agents,[1,4–6] including cefotaxime.[7] Optimizing dosing regimens in these populations is critical, as timely, adequate antibiotic exposure is associated with treatment success in critically ill adults.[5]

### Objectives

Hence, we aimed to characterize cefotaxime PK in critically ill children. Using these data, we aimed to evaluate the exposure achieved with current dosing guidelines in critically ill children and provide alternative dosing regimens where required.

## Patients and methods

### Study design and setting

A single centre, prospective, population PK (pop-PK) study (POPSICLE-study, NCT03248349) to identify the PK of antibiotics in critically ill children was performed on the level 3 paediatric intensive care unit (PICU) of the Radboudumc (Nijmegen, the Netherlands) between June 2017 and May 2019. Children aged 0–18 years were included if they received an intravenous antibiotic agent, had an arterial or central venous line in place for clinical reasons and if informed or deferred consent was provided by parents/caregivers with the consent/assent of the child depending on the child's age and/or capabilities. Exclusion criteria consisted of inability to read or understand the informed consent form or concomitant treatment with extra-corporeal membrane oxygenation (ECMO) or kidney-replacement therapy.

The local Medical Ethics Review Board (MERB) (CMO Arnhem-Nijmegen, protocol number 2016-3085) waived the need for formal ethics approval according to the Dutch Law on Human Research for the POPSICLE study. For the current analysis, all patients were selected who received intravenous cefotaxime during the study period and had at least one plasma sample taken within 24 h after a cefotaxime dose.

### Patient data collection

Patient characteristics were collected during the study period to describe the patient population and covariates in the PK model. Postnatal age, weight (WT), height, gender and main reason for ICU admission (stratified into nine categories) were collected at baseline. Clinical data including co-medication (such as vasopressive drugs), mechanical ventilation, validated paediatric disease severity scores [Pediatric Index of Mortality 2 (PIM-II, range 0%–100%)[8]], Pediatric RISk for Mortality 3 (PRISM-3, range 0–74)[9] and daily Pediatric Logistic Organ Dysfunction 2 (PELOD-2, range 0–31)[10] were also collected. Laboratory values were obtained from electronic health records during the whole study period, including serum concentrations of creatinine (SCr), cystatin C (CysC), urea, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), albumin, bilirubin, and C-reactive protein (CRP). Glomerular filtration rate (eGFR) was estimated using two equations published by Schwartz *et al.*, including either SCr and height[11] or Scr, height, gender, CysC and blood urea nitrogen concentrations.[12]

### Cefotaxime dosing

Cefotaxime was administered either at a prophylactic dose (100 mg/kg/day, maximum 4 g per day, as part of the local ICU protocol for selective decontamination of the digestive tract) or a therapeutic dose (150 mg/kg/day, maximum 12 g per day), and administered as three or four bolus intravenous infusions per day (as intravenous push), in concordance with national dosing guidelines.[13] The exact date and time of cefotaxime administration were recorded on a dedicated case report form.

### Blood sampling, handling and analysis

Patients underwent a rich blood sampling scheme for PK analysis. This included three or four daily 0.5 mL anticoagulated EDTA samples from the indwelling line in the first 3 days of the study period, and one daily 0.5 mL EDTA sample from day 4 until the end of the study. The end of the study period was marked by either the cessation of antibiotic therapy, removal of arterial or central venous line, discharge from PICU or after a maximum number of 14 sampling days. Samples were drawn randomly throughout the dosing interval, with the aim of at least one trough concentration per patient, to facilitate model building. The EDTA-samples were centrifuged and plasma was stored at −80°C until drug concentration analysis in November 2019.

Additionally, scheduled blood samples were obtained for this study on day 1 and 4 for complete blood count, urea, SCr, ASAT, CRP, albumin concentrations, and CysC, if not already taken on that day for clinical indications. Total cefotaxime concentrations were analysed in plasma samples using a validated liquid chromatography with tandem mass spectrometry method with a lower (LLOQ) and upper limit of quantification (ULOQ) of 0.100–250 mg/L, respectively, with accuracy ranging from 99.2%–104.2%. Samples with concentrations <LLOQ were handled by using the M6 method, where the first sample of a patient <LLOQ is retained in the dataset at LLOQ/2 and any subsequent samples <LLOQ from that patient are excluded. Details of these analyses and handling of LLOQ/ULOQ samples is presented in the Supplementary data (available at *JAC* Online).

### PK analysis

Cefotaxime concentration–time data were analysed using non-linear mixed effect modelling on NONMEM v. 7.4 (ICON, Ellicott, Maryland, USA). Model building included three main steps: (1) identifying the structural and statistical model; (2) covariate analysis on PK parameters; and (3) model evaluation. Additional details of the PK model development, covariate analysis and model evaluation are presented in the Supplementary data.

### Structural model development

Nested models, which differ only for a single factor, were compared by their objective function value (OFV), which is proportional to the sum of the difference between observations and model predictions, squared. For nested models a decrease in OFV of ≥3.84, corresponding with a $P < 0.05$, for one degree of freedom was considered statistically significant. Additionally, general goodness-of-fit plots and other model diagnostics [distribution of interindividual variability (IIV) and conditionally weighted residuals (CWRES) for potential covariates, goodness-of-fit split for weight or kidney function quartiles, precision and shrinkage of parameter estimates] were used to evaluate model performance and potential bias.

### Covariate model development

Covariate influence on PK parameters was assessed using stepwise forward inclusion, using an OFV difference of >6.64 ($P < 0.01$) as cut-off value. After forward inclusion steps, a backward elimination step was performed to test the relevance of each covariate for the final model, using an OFV increase of <10.8 to justify retaining the covariate in the final model ($P < 0.001$). Tested covariates on cefotaxime clearance (CL) and volume of distribution (Vd) included metrics of age and body size, disease severity scores, clinical data (including prophylactic or therapeutic treatment), kidney function parameters and other laboratory data. The covariate relationship for weight was tested both as an estimated exponent as well as fixed exponents at 0.75 for CL and 1.0 for Vd, according to typical allometric scaling of these parameters.[14]

### Model evaluation

The final model was internally validated using normalized prediction distribution errors (NPDE). Parameter precision was analysed by bootstrap resampling ($n = 500$).

### Dose evaluation

We used 100% %$fT_{>MIC}$ as the therapeutic PK target for cefotaxime, which is a frequently used PK target for cephalosporins in critically ill patients.[15] Unbound concentrations were assumed to be 60% of total cefotaxime concentrations. As cefotaxime is most frequently used empirically in patients with severe sepsis of unknown origin, we aimed to cover the majority of pathogens for our final assessment of cefotaxime dose evaluations. We used MIC cut-off values of 0.5, 2 and 4 mg/L, based on epidemiological cut-off values (ECOFFs) provided by the EUCAST. Coverage for MICs up to 0.5 mg/L ensures the appropriate treatment of the majority of susceptible pathogens, while MICs of 2 and 4 mg/L should be used for empirical or targeted therapy of intermediately-susceptible pathogens.[16]

The final model was used to estimate median cefotaxime exposure for typical patients of 1 week, and 1, 4, 8 and 18 years of postnatal age, with a normal weight for age (3.775, 9.75, 17.125, 26.75 and 60.5 kg, respectively) based on Dutch national growth charts. We tested the exposure achieved by the currently used therapeutic dosing regimens (150–200 mg/kg/day, as bolus infusion, dose interval 6–8 h) with a maximum dose of 12 g/day, in concordance with maximum doses in the Summary of Product Characteristics (SmPC) for patients with severe sepsis or meningitis.[17] Additionally, alternative dosing regimens with a higher frequency of bolus infusions (dose interval 4 h), extended infusions (infusion in 1, 2 and 4 h) and continuous infusion regimens (including a loading dose of 25 mg/kg, with a maximum of 1000 mg) were simulated. Steady-state trough concentrations, used as a surrogate marker for %$fT_{>MIC}$, were assessed at 24 h after the first dose.

## Results

Total plasma cefotaxime concentrations were determined in 485 plasma samples from 52 patients, with a median of 10 samples per patient. Concentrations ranged from <0.100 to 670 mg/L, with large interindividual variability as shown by an over 10-fold range in cefotaxime trough concentrations. There were 18 samples <LLOQ, of which 12 were retained in the final dataset as $0.5 \times$ LLOQ and 6 were excluded from analysis, leaving 479 samples included in the final model. Six samples >ULOQ were diluted and remeasured. Demographic and clinical characteristics of the patient cohort are shown in Table 1.

### Model results

Cefotaxime concentrations were best described by a two-compartment model with IIV on cefotaxime CL and central Vd

**Table 1.** Overview of demographic and clinical characteristics of the total patient cohort ($n = 52$)

| Characteristic | Median [IQR] or $n$ (%) | Range |
|---|---|---|
| Postnatal age (years) | 1.61 [0.17–8.63] | 0.03–17.69 |
| Postnatal age (categories), $n$ (%) | | |
|   0–3 months | 17 (32.7%) | |
|   3–12 months | 6 (11.5%) | |
|   1–2 years | 7 (13.5%) | |
|   2–4 years | 4 (7.7%) | |
|   4–8 years | 5 (9.6%) | |
|   8–12 years | 6 (11.5%) | |
|   12–18 years | 7 (13.5%) | |
| Weight (kg) | 10.95 [5.2–28.5] | 2.7–80 |
| Height (m) | 0.83 [0.58–1.31] | 0.50–1.90 |
| Gender, $n$ (%) | | |
|   Male | 32 (61.5%) | |
|   Female | 20 (38.5%) | |
| Main reason for ICU admission, $n$ (%)[e] | | |
|   Respiratory failure | 33 (63.5%) | |
|   Neurological impairment | 9 (17.3%) | |
|   Circulatory failure | 5 (9.6%) | |
|   Surgery | 2 (3.8%) | |
|   Metabolic impairment | 2 (3.8%) | |
|   Burns | 1 (1.9%) | |
| PRISM-3 score[a] | 6 [3–9] | 0–16 |
| PIM-2 expected mortality rate | 3.2% [1.0%–7.2%] | 0.1%–88.4% |
| Baseline PELOD-2 score[a] | 5 [5–6] | 0–15 |
| Vasopressive co-medication during study period, $n$ (%) | 19 (36.5%) | |
| Mechanical ventilation during study period, $n$ (%) | 47 (90.4%) | |
| Cefotaxime dose (mg/kg/day) | 100 [99.2–105.1] | 50–151.1 |
| Therapeutic dose (150 mg/kg/day), $n$ (%) | 11 (21.2%) | |
| Baseline SCr (μmol/L)[a] | 28 [23–40] | 8–87 |
| Baseline eGFR (mL/min/1.73 m$^2$)[a,d] | 89 [74–106] | 46–398 |
| Baseline Albumin (g/L)[a,b] | 27 [22–31] | 15–36 |
| Baseline CRP (mg/L)[a,c] | 18 [6–54] | 1–343 |

ICU, intensive care unit; PRISM, Pediatric Risk of Mortality score; PIM, Pediatric Index of Mortality; PELOD, Pediatric Logistic of Organ Dysfunction; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.
[a]Baseline values determined as first entry for each individual patient.
[b]Based on 48 patients.
[c]Based on 50 patients.
[d]Estimated by equation published by Schwartz in 2012 [eGFR (mL/min/1.73 m$^2$) = 42.3*(Height in m/Creatinine in mg/dL)^0.79].[12]
[e]Categories 'Malignancy', 'Infection', and 'Congenital defects' not included due to no patients with this category as main reason for ICU admission.

(V1), including an omega block matrix to account for correlation between CL and V1. A proportional error model best described residual variability. Additional or combined error models did not
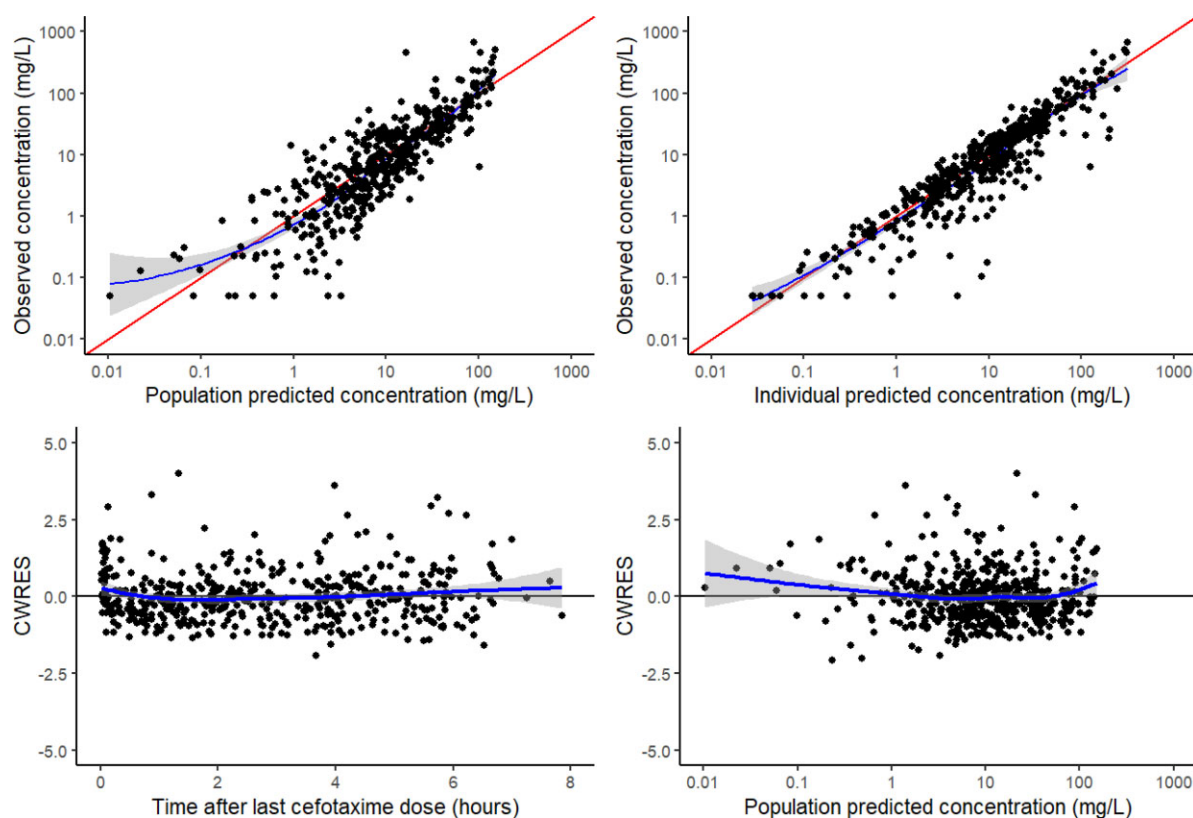
**Figure 1.** Goodness of fit plots of the final cefotaxime two compartment model. Diagnostic plots for cefotaxime: observations versus population predictions (PRED) and individual predictions (IPRED) and conditional weighted residuals (CWRES) versus time after the last dose and PRED for the final model. This model included inter-individual variability on cefotaxime clearance and central volume of distribution, with weight included as a covariate on both parameters. The red line represents the line of unity, with the blue line representing the moving average between model predictions and observations and predictions. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

show significant improvements in OFV. Forward covariate inclusion showed bodyweight as a covariate for CL and V1, for which the relationship was best described using a power function with estimated allometric exponents. After inclusion of these covariate functions, the model showed no inherent bias in different weight groups (Figure S1). The addition of these covariates showed a reduction in IIV from 155.6% on CL and 163.4% on V1 in the structural model, to 65.7% and 88.8% in the final model, respectively. None of the other tested covariates improved the model beyond this point, and none of the included covariates were removed during backward elimination. Despite inclusion of bodyweight as covariate, we observed large variability in cefotaxime PK in our cohort, with individual CL values corrected per kilogram ranging from 0.02 to 0.66 L/kg/h across the population (Figure S2). Plots of the IIV and tested covariates are presented for our structural model (without covariates) and our final model (with covariates) in Figures S3 and S4.

Final model goodness of fit plots are shown in Figure 1. Conditionally weighted residuals were evenly distributed over cefotaxime concentration and time after last dose (Figure 1). Parameter estimates of the final model and bootstrap evaluation are presented in Table 2. Additional details regarding the PK analysis and final model are described in the Supplementary data.

### Bootstrap and internal evaluation of the final model

Median bootstrap estimates were comparable to final model estimates, indicating low bias in our model. Bias for all bootstrapped median parameters was between −8% and +2%, except for IIV on V1 (−17.8%). The 95% CI of bootstrap parameter estimates overlapped completely with the final model estimates. Minimization was successful in 491 out of 500 (98.2%) bootstrap runs.

The NPDE analysis showed a slight deviation around the median, with accurate predictions in the extremes (Figure S5). As weight was the only included covariate, we proceeded by performing dose evaluations for typical patients with a normal weight for their age.

### Dose simulation and evaluation

Concentration–time profiles were simulated for typical patients ranging from 3.775 to 60.5 kg, corresponding with the median weight for patients of 1 week and 18 years of age, respectively (Figure 2 and Figure S6). On average, simulated cefotaxime trough concentrations were highest in patients 1 week of age, and decreased with age. Model predicted exposure for 150 mg/kg/day (current dose) showed trough concentrations <0.5 mg/L in

**Table 2.** Pharmacokinetic parameter estimates from final cefotaxime model and bootstrap run

| Model parameters | Final model estimate | RSE (%) | Bootstrap estimates ($n=500$) median (% bias) | Bootstrap 95% CI |
|---|---|---|---|---|
| $CL_i = CL_{pop}*\left(\frac{WT_i}{10.95}\right)^{\Theta_1}$ | | | | |
| $CL_{pop}$ (L/h) | 2.8 | 8.5 | 2.724 (−0.6%) | 2.195–3.205 |
| $\Theta_1$ | 1.11 | 8.5 | 1.106 (+0.5%) | 0.901–1.362 |
| $V1_i = V1_{pop}*\left(\frac{WT_i}{10.95}\right)^{\Theta_2}$ | | | | |
| $V1_{pop}$ (L) | 2.62 | 10.5 | 2.60 (−0.8%) | 1.641–3.721 |
| $\Theta_2$ | 1.18 | 9.3 | 1.11 (−0.9%) | 0.683–1.647 |
| $Q_{pop}$ (L/h) | 1.15 | 18.3 | 1.148 (−3.6%) | 0.321–1.865 |
| $V2_{pop}$ (L) | 1.55 | 16.3 | 1.571 (+2.0%) | 1.093–2.439 |
| Interindividual variability | | | | |
| CL | 0.359 | 21.2 | 0.291 (−6.4%) | 0.105–0.671 |
| Block matrix | 0.305 | | 0.169 (−7.7%) | 0.022–0.387 |
| V1 | 0.581 | 20.9 | 0.351 (−17.8%) | 0.126–0.731 |
| Residual variability | | | | |
| Proportional error | 0.307 | 15.5 | 0.298 (−4.2%) | 0.220–0.390 |

$CL_i$, individual clearance; $CL_{pop}$, population clearance; Q, intercompartmental clearance; RSE, relative standard error; $V1_i$, individual central volume; $V1_{pop}$, population central volume; $V2_i$, individual peripheral volume; $V2_{pop}$, population peripheral volume; WT, bodyweight in kg.
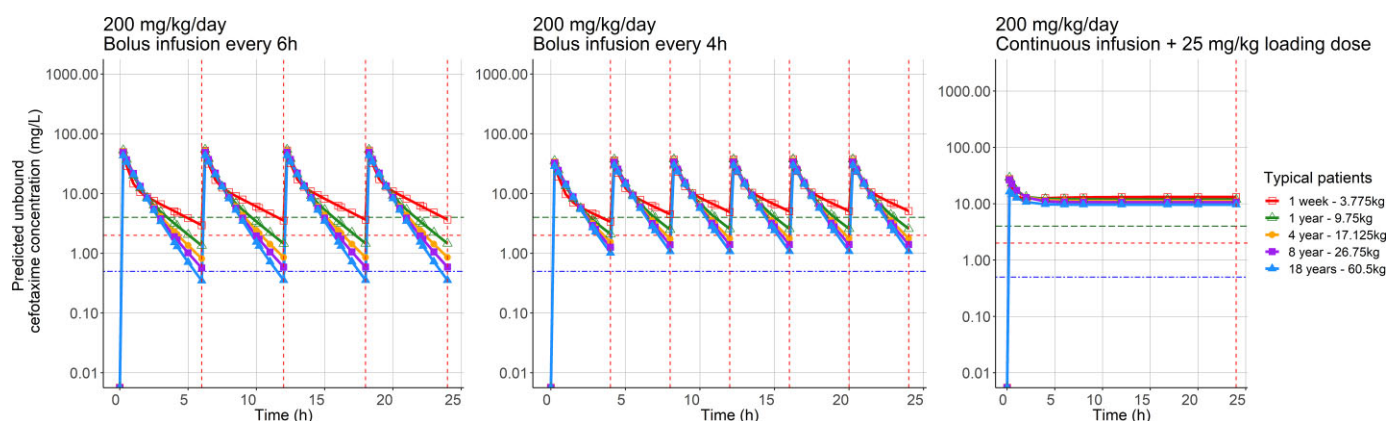


**Figure 2.** Simulated unbound cefotaxime concentrations in typical patients aged 1 week–18 years for three selected dosing regimens. Concentration–time profile of unbound cefotaxime in five typical patients across the paediatric age range with a normal weight for age for three selected dosing regimens. The current dose (200 mg/kg/day, bolus infusions, q6h) is depicted in the left panel, with alternative dosing regimens in the middle (200 mg/kg/day, bolus infusions, q4h) and right panel (200 mg/kg/day, continuous infusion with a 25 mg/kg loading dose). Solid lines represent a concentration time profile of a typical patient, with colour and shape indicating different typical patients (see the key). Horizontal lines represent target MICs of 0.5 (blue, dash-dotted), 2 (red, dashed) and 4 mg/L (green, long dash), respectively. Vertical dotted lines represent the timing of a new dose. Additional concentration–time profiles of other dosing regimens (e.g. with extended infusions or lower daily doses) can be found in the Supplementary data. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

patients >4 years of age (Figure S6), indicating non-target attainment ($fT_{>MIC}$ below 100%) of cefotaxime for pathogens with an MIC of 0.5 mg/L or higher.

The current maximum SmPC dose (200 mg/kg/day, interval 6 h, bolus infusion) results in trough concentrations above the MIC for all typical patients for MICs up to 0.5 mg/L, with patients <1 year also reaching this target for MICs up to 2.0 mg/L. A similar daily dose with a higher dosing frequency (200 mg/kg/day, interval 4 h, bolus infusion) leads to adequate trough concentrations for MICs up to 2.0 mg/L in all typical patients, with patients <1 year also covered for MICs up to 4.0 mg/L. To ensure

adequate exposure for MICs of 4.0 mg/L for patients >1 year of age, a 25 mg/kg loading dose followed by a 200 mg/kg/day continuous infusion is advised. We provide a schematic dosing rationale based on our evaluations in typical patients, including target pathogens, in Table 3 and Figure 3.

## Discussion

We here present pharmacokinetics and optimized dosing regimens for cefotaxime in critically ill children. Interindividual variability could be largely explained by variation in body weight. At
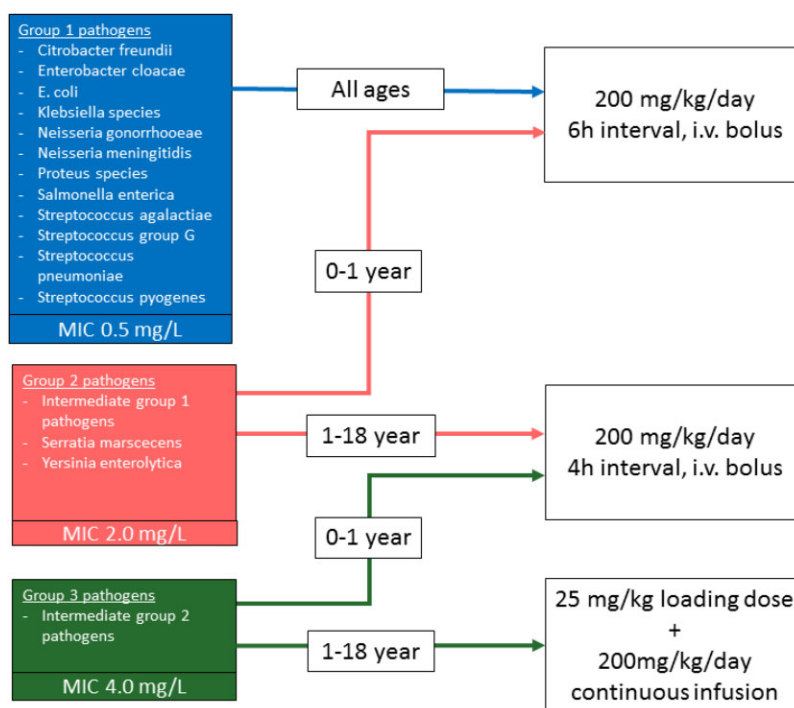
**Figure 3.** Cefotaxime dose advice for cefotaxime in critically ill children for covering different pathogens, stratified according to epidemiological cut-off (ECOFF) values of MIC of 0.5, 2.0 and 4.0 mg/L. Dose advice is based on dose evaluations with typical patients. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

the same time, a significant proportion of variability remained and could not be explained by the other co-variates tested. This unexplained variability could be caused by interindividual variance in fluid balance, protein binding or genetic disposition that was not included in our covariate analysis.

Our model-based simulations in typical patients with various weights highlight that the currently used dose of 150 mg/kg/day leads to insufficient trough concentrations in patients >4 years of age, while the SmPC maximum dose (200 mg/kg/day, interval 6 h) only covers MICs up to 0.5 mg/L when given as a bolus injection. While this includes the susceptible range for the majority of pathogens, some frequently encountered pathogens and intermediately susceptible pathogens are not adequately covered with this dose advice. Cefotaxime exposure is lowest for

**Table 3.** Dose advice for cefotaxime in critically ill children for covering different MIC values in different age groups

| Pathogen MIC (mg/L) | Age groups | |
|---|---|---|
| | 0–1 year | 1–18 years |
| 0.5 | 200 mg/kg/day 6 h interval, IV bolus | 200 mg/kg/day 6 h interval, IV bolus |
| 2 | 200 mg/kg/day 6 h interval, IV bolus | 200 mg/kg/day 4 h interval, IV bolus |
| 4 | 200 mg/kg/day 4 h interval, IV bolus | 25 mg/kg loading dose + 200 mg/kg/day continuous infusion |

patients >1 year of age, putting them at risk for subtherapeutic concentrations in case of these pathogens. We therefore provide individualized dosing regimens for specific ages and target MICs: (1) 200 mg/kg/day, interval 6 h, bolus infusions; (2) 200 mg/kg/day, interval 4 h, bolus infusion; and (3) a 25 mg/kg loading dose followed by 200 mg/kg/day as continuous infusion.

### Comparison with the literature

In our pop-PK model, we identified and quantified the influence of weight as a covariate of cefotaxime CL and central Vd, which is consistent with the existing literature in critically ill children.[7,18] In addition to bodyweight, these two studies also included an effect of postnatal and/or gestational age on drug CL. However, including age as a covariate did not significantly improve our model, which might be due to the non-linear relationship between weight and cefotaxime CL we observed in our cohort. Cefotaxime is mainly excreted in urine (20%–36%) as unchanged cefotaxime, while 15%–25% is metabolized to the major (active) metabolite desacetyl-cefotaxime and 20%–25% to inactive M2 and M3 metabolites.[19] Although the specific enzymes involved in cefotaxime metabolism remain unclear, it is known that the ontogeny of drug-metabolizing enzymes can show different maturation patterns in the first years of life,[20] which might influence cefotaxime CL in young infants. In addition, cefotaxime is a substrate for organic anion transporters (OAT) 1, 3 and 4, which facilitate drug transport in both the kidney and liver of which, OAT1 and OAT3 show low activity and/or expression at birth.[21] Additionally, a genetic polymorphisms of the OAT3 gene

(OAT3-Ile305Phe) has shown to influence cefotaxime CL in healthy adult volunteers of Asian descent.[22]

Typical PK parameter values in our study were approximately 20% higher when compared with a study by Berangér et al.,[7] who also assessed cefotaxime PK in a critically ill paediatric population (0.26 versus 0.21 L/kg/h, respectively for CL and 0.38 L/kg versus 0.31 L/kg, respectively for Vd). These differences could be explained by slight differences in the included patient populations, as our cohort showed significantly higher disease severity [higher PELOD-2 scores (1 versus 5), more mechanical ventilation (90.4% versus 32.7%) and vasopressive co-medication (36.5% versus 4.1%)] which might have impacted PK parameters. Additionally, we included a higher number of samples per patient (median 10 versus 1 in the Béranger study[7]), which allows for more-accurate estimates of Vd in our population. Reported cefotaxime PK in non-critically ill children show a wide range of values for CL and Vd, ranging from 0.166–0.364 L/kg/h and 0.129–0.637 L/kg, respectively.[18,23–25] Differences between the results from these studies might possibly be attributed to differences in study populations. For example, both studies by Leroux et al.[18] and Maksoud et al.[23] reported a higher Vd (0.44 and 0.637 L/kg, respectively), but studied only neonates[18] or sickle cell disease patients receiving hyperhydration.[23]

### Clinical application of our findings

Using our dose simulations we developed individualized dosing regimen for cefotaxime for critically ill children, which should lead to optimized trough concentrations (as a surrogate marker for $\%fT_{>MIC}$) for patients in order to adequately treat intermediately susceptible pathogens. This dose advice addresses starting doses in different age groups that can be applied in clinical practice and can be tailored for settings with various pathogens and local cefotaxime resistance patterns that clinicians aim to cover. While these dose regimens address PK variation in age and different target MICs, the large unexplained variability in our model may still leave some patients with subtherapeutic or supratherapeutic exposure. Hence, in selected patients therapeutic drug monitoring (TDM) could be considered, e.g. in case of high suspicion of infection with an intermediately susceptible pathogen, immunocompromised patient or signs of (neuro)toxicity.

### Limitations

Our study has some limitations to address. Firstly, this was a single centre study in a critically ill population with relatively low incidence of acute kidney injury (AKI), augmented kidney clearance (AKC) or other alterations in organ function. Additionally, our cohort predominantly included Caucasian children (>90%) and it is known that genetic polymorphisms can influence cefotaxime CL. Therefore, results in other populations (e.g. Asians with a higher incidence of the OAT3-Ile305Phe polymorphism) could be different. Secondly, the majority of our cohort was treated with a prophylactic dose of cefotaxime, from which PK parameters were used to simulate therapeutic exposure. Although baseline characteristics and PK parameters in patients treated therapeutically and prophylactically were similar, this could still have added to the high variability in our cohort. Additionally, we were not able to measure free concentrations of cefotaxime, account for reduced protein binding in hypoalbuminaemic patients, use measured GFR values or include changes in fluid balance that could have been used to further improve our findings. Thirdly, as mentioned, we used dosing simulations for typical patients with a normal weight for age, which may limit validity in patients with abnormal weight for age (e.g. obese patients or small for gestational age infants).

### Conclusions

We determined the PK of cefotaxime in critically ill children and present individualized dose advice for this patient population. The maximum authorized doses of cefotaxime (200 mg/kg/day) are sufficient to cover the majority of pathogens, but a higher dosing frequency or continuous infusion is advisable in cases where cefotaxime is given for intermediately susceptible pathogens. Additionally, these doses can be combined with TDM to improve exposure after the start of treatment in selected patients.

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## Transparency declarations

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### Author contributions

Development of POPSICLE research protocol (S.J.F.H., R.J.B., M.v.d.F., M.F.S. and S.d.W.), including patients and collection of samples POPSICLE study (S.J.F.H.), bioanalysis of samples (R.A.A.M.), data-analysis and population pharmacokinetic modelling (S.J.F.H., P.J.U., C.A.K., S.d.W.), writing first version of manuscript (S.J.F.H., P.J.U., C.A.K., S.d.W.), completing final version of manuscript (S.J.F.H., P.J.U., R.A.A.M., M.v.d.F., M.S., R.J.B., C.A.K. and S.d.W.)

## Supplementary data

Additional Methods information plus Table S1 and Figures S1 to S6 are available as Supplementary data at JAC Online.

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