J Antimicrob Chemother 2022; **77**: 2227–2237
https://doi.org/10.1093/jac/dkac168 Advance Access publication 9 June 2022

Journal of Antimicrobial Chemotherapy

Optimal dosing of cefotaxime and desacetylcefotaxime for critically ill paediatric patients. Can we use microsampling?

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Received 20 December 2021; accepted 25 April 2022

Objectives: To describe the population pharmacokinetics of cefotaxime and desacetylcefotaxime in critically ill paediatric patients and provide dosing recommendations. We also sought to evaluate the use of capillary microsampling to facilitate data-rich blood sampling.

Methods: Patients were recruited into a pharmacokinetic study, with cefotaxime and desacetylcefotaxime concentrations from plasma samples collected at 0, 0.5, 2, 4 and 6 h used to develop a population pharmacokinetic model using Pmetrics. Monte Carlo dosing simulations were tested using a range of estimated glomerular filtration rates (60, 100, 170 and 200 mL/min/1.73 m^2) and body weights (4, 10, 15, 20 and 40 kg) to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets, including 100% $fT_{>MIC}$ with an MIC breakpoint of 1 mg/L.

Results: Thirty-six patients (0.2–12 years) provided 160 conventional samples for inclusion in the model. The pharmacokinetics of cefotaxime and desacetylcefotaxime were best described using one-compartmental model with first-order elimination. The clearance and volume of distribution for cefotaxime were 12.8 L/h and 39.4 L, respectively. The clearance for desacetylcefotaxime was 10.5 L/h. Standard dosing of 50 mg/kg q6h was only able to achieve the PK/PD target of 100% $fT_{>MIC}$ in patients >10 kg and with impaired renal function or patients of 40 kg with normal renal function.

Conclusions: Dosing recommendations support the use of extended or continuous infusion to achieve cefotaxime exposure suitable for bacterial killing in critically ill paediatric patients, including those with severe or deep-seated infection. An external validation of capillary microsampling demonstrated skin-prick sampling can facilitate data-rich pharmacokinetic studies.

Introduction

Severe infection can have long-term health consequences for paediatric patients, including impaired neurodevelopment and chronic disability.[1,2] Effective antimicrobial dosing is one of the cornerstones of care to ensure therapeutic success in the treatment of severe infection. However, critical illness can manifest as extreme physiological derangements and this has the potential to impact on drug exposure, leading to treatment failure and/or antimicrobial resistance.[3]

Cefotaxime—a semi-synthetic, third-generation cephalosporin—is one of the most prescribed antimicrobials used to treat severe infections in critically ill paediatric patients.[4–6] Approximately 43% of cefotaxime is bound to plasma proteins and it exhibits good penetration into body fluids and tissues.[7,8] Cefotaxime is a hydrophilic drug with approximately 50%–60% eliminated by the kidneys by glomerular filtration followed by tubular secretion.[9] Cefotaxime is metabolized by enzymatic hydrolysis of the O-acetyl group by an acetyl esterase in the liver to a pharmacologically active metabolite, desacetylcefotaxime.[10,11] The

metabolite is estimated as being between 0.5 and 10 times less microbiologically active than the parent compound, cefotaxime.[8]

Optimal cefotaxime dosing regimens target concentrations above the MIC throughout the dosing interval [pharmacokinetic/pharmacodynamic (PK/PD) $fT_{>MIC}$], with targets of ≥60% $fT_{>MIC}$ and ≥100% $fT_{>MIC}$ for critically ill patients,[12,13] and ≥100% $fT_{>4\times MIC}$ for critically ill patients with severe or deep-seated infection.[14] Cefotaxime can be used to treat infections caused by Gram-positive and Gram-negative organisms, including meningitis caused by *Escherichia coli*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Streptococcus pneumoniae*.[14] Of the pathogens treated with cefotaxime, the reported MIC value according to the EUCAST is 1 mg/L for meningitis and indications other than meningitis caused by *E. coli*.[15] Additionally, an MIC non-species-related breakpoint of 1 mg/L is commonly used for the treatment of a susceptible pathogen, with an MIC of ≥2 mg/L indicating a resistant pathogen.[15] Current cefotaxime dosing regimens of 50 mg/kg every 6 h, with a maximum dose of 2 g (a total daily dose of up to 8 g), are commonly used for critically ill paediatric patients (>1 month old of life).[16–18]

The primary aims of this study were: (i) to describe the population pharmacokinetics of cefotaxime and desacetylcefotaxime in critically ill paediatric patients and to provide dosing recommendations for this special patient population; and (ii) to describe the suitability of using capillary microsampling for blood sampling compared with samples collected from an indwelling arterial or venous cannula (conventional sampling) by performing an external validation.

Patients and methods

Study design

A prospective, open-label, pharmacokinetic study was conducted at the paediatric ICU at the Queensland Children's Hospital, Brisbane, Australia between March 2019 and September 2021. Critically ill patients between the ages of 1 month and 12 years and receiving intravenous cefotaxime, as prescribed by the treating physician, were included. Patients receiving extracorporeal membrane oxygenation, renal replacement therapy and peritoneal dialysis were excluded from this study. The research was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Human Research & Ethics Committee of the Queensland Children's Hospital (HREC/17/QRCH/45). Written informed consent was obtained from the parents or legal guardians prior to commencement of the study. Clinical characteristics were collected for patients including sex, age, height, weight, total bilirubin, haemoglobin, albumin, platelet count, white cell count, serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, prothrombin time, activated partial thromboplastin time, C-reactive protein, urinary creatinine, paediatric logistic organ dysfunction-2 (PELOD-2) score. For each patient, an estimated glomerular filtration rate (eGFR) was calculated using the bedside Schwartz equation (mL/min/1.73 m^2).[19,20]

Conventional blood sampling and capillary microsampling

Paired blood samples using conventional sampling (from an arterial or venous line) and capillary microsamples[21] (from a finger or heel prick) were simultaneously collected at five pre-defined timepoints: prior to administration of the cefotaxime dose (time 0), and then after the end of infusion at approximately 0.5, 2, 4 and 6 h. For capillary microsamples, the patient's finger was cleaned with alcohol and punctured using a lancet device (either Haemolance Plus®, low flow 25G × 1.4 mm or BD microtainer Quikheel Infant Lancet, 1 mm × 2.5 mm). The finger was gently massaged and held below the heart of the patient until approximately 50 μL of blood was collected into a heparinized plastic capillary tube. The capillary microsample was centrifuged at 2000 **g** for 10 min to obtain plasma. The capillary tube was then snipped with scissors to isolate the plasma. For conventional plasma samples, approximately 0.6 mL of blood was obtained and collected into a heparinized 3 mL blood collection tube and centrifuged at 1500 **g** for 10 min to obtain plasma. After centrifugation, all plasma samples were transferred into screw-capped 2 mL polypropylene tubes and stored at −80°C until analysis.

Analysis of samples

Cefotaxime and desacetylcefotaxime concentrations were measured using a validated ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) bioanalytical method[22] in accordance with the guidelines provided by the EMA[23] and the U.S. FDA.[24] The linear concentration range was 0.5–500 mg/L and 0.2–10 mg/L for cefotaxime and desacetylcefotaxime, respectively. All intra-assay and inter-assay accuracy and precision were within 15% of acceptance criteria.

Pharmacokinetic model

Pmetrics version 1.5.0 (Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA, USA) in RStudio (version 0.99.9.3) as a wrapper for R (version 3.3.1), Xcode (version 2.6.2) and the Intel Parallel Studio Fortran Compiler XE 2017 was used to develop a population pharmacokinetic model. One- and two-compartment models were constructed using non-parametric adaptive grid (NPAG) algorithms with total plasma cefotaxime and desacetylcefotaxime concentrations. A stepwise approach was followed to build the model to establish: (i) the structural base model, (ii) the best-fit error model, and (iii) development of a covariate model. Elimination from the central compartment and the rate of formation of the metabolite were modelled as first-order processes, and rate of formation of the metabolite was also tested for Michaelis–Menten kinetics. Lambda (additive) and gamma (multiplicative) error models were evaluated using a polynomial equation for SD as a function of observed concentration with observation weighting performed as error = SD × gamma or error = $(SD^2 + lambda^2)^{0.5}$.

Pharmacokinetic model evaluation

Models were evaluated by the combination of diagnostic goodness-of-fit plots and statistical analysis. Diagnostic plots included scatter plots of observed-versus-predicted concentrations, visual predictive check plots. Statistical evaluation to compare different models was based on the regression coefficient r^2, bias and imprecision, the log-likelihood ratio (−2*LL) and Akaike information criterion (AIC). The bias was measured using the mean weighted predicted − observed error. Imprecision was measured by using bias-adjusted and the mean weighted squared predicted − observed error. The percentage of shrinkage was measured using the total variation in the probability of each model.

Covariate screening

Covariate model building was performed using sequential assessment of biologically plausible clinical characteristics. Covariates were tested individually against the primary pharmacokinetic parameters and rate of metabolite formation, with inclusion based upon a statistically significant improvement in the AIC and −2*LL. The covariates evaluated, using allometric or linear scaling, against pharmacokinetic parameters were the clinical characteristics obtained for each patient and are listed in the Supplementary material (Table S1, available as Supplementary data at *JAC* Online).

External validation

An external validation was performed to describe the correlation between the measurement of cefotaxime concentrations obtained from capillary microsamples compared with the concentrations obtained using conventional sampling. For the external validation, the model developed using conventional sampling was used as a prior and Bayesian posterior simulations were calculated for each subject. A linear regression, the goodness-of-fit and the coefficient of determination were used to assess the correlation between the observed and predicted concentrations. Prediction errors were evaluated to describe bias (calculated as mean weighted prediction error, MWPE) and precision (Root Mean Square Predication error, RMSE) using Pmetrics. The acceptance criteria to establish validity were set to a bias of 20%, which has also been applied in a study by Guo *et al*. (2019).[25] Scatter plots and Bland–Altman plots were used to visually inspect the predicted (model-simulated or measured conventional sampling) and observed (capillary microsampling) cefotaxime and desacetylcefotaxime concentrations for systematic bias.

Dosing simulations

Cefotaxime dosing regimens administered as a bolus dose every 4 or 6 h, as a 2 or 3 h extended infusion (EI), or as a continuous infusion (CI) across a range of eGFR (60, 100, 170 and 200 mL/min/1.73 m^2) and a range of body weights (4, 10, 15, 20 and 40 kg) were evaluated using Monte Carlo simulations ($n=1000$) in Pmetrics. Cefotaxime protein binding at 40% was used to calculate the probability of target attainment (PTA).[26] For each dosing regimen, the PTA was calculated as the percentage of patients achieving a $\geq$60% $fT_{>MIC}$, $\geq$100% $fT_{>MIC}$ or $\geq$100% $fT_{>4\times MIC}$ with MIC non-species-related breakpoint of 1 mg/L[15] targeting success at 90%.

Table 1. Clinical characteristics and patient information

Demographic data	Median[a]
Total patients	36
Sex, female/male, *n* (%)	14/22 (39/61)
Age (months)	30.4 (8.2–65.8)
Height (cm)	86.5 (68.5–109)
Weight (kg)	11.7 (8.1–18.2)
BSA (m^2)	0.5 (0.4–0.7)
Albumin (g/L)	30 (24–33)
Bilirubin (μmol/L)	6.0 (3.5–9.5)
Haemoglobin (g/L)	106 (97–116)
Platelet count ($\times 10^9$/L)	251 (189–306)
Serum creatinine (mL/min)	24.0 (17.5–28.5)
eGFR (mL/min/1.73 m^2)	143 (109–259)
Illness severity score PELOD-2 score (on admission to the ICU)	4 (2–6)
Patient mechanically ventilated at the time of dosing, *n* (%)	23 (64)
Invasive ventilation at the time of dosing, *n* (%)	22 (61)
Vasopressors/Inotropes at the time of dosing, *n* (%)	8 (22)
Number of doses prior to PK sampling interval[b]	4 (2–11)
Dose prior to PK sampling interval (mg)[b]	605 (404–910)
Daily total dose (mg)[b]	2420 (1615–3640)

PELOD-2 score, Paediatric Logistic Organ Dysfunction; eGFR, estimated glomerular filtration rate (indexed to BSA 1.73, calculated using bedside Schwartz equation).
[a]Data displayed as mean with IQR (Q1–Q3) or *n* (%) as appropriate.
[b]Data displayed as mean (minimum – maximum).

Results

A total of 36 critically ill paediatric patients [median age: 30.4 months (IQR age: 8.2–65.8 months)] with 160 conventional samples were included in the model development. Two plasma samples were below the lower limit of quantification for both cefotaxime and desacetylcefotaxime and these missing values have been simulated by Pmetrics during the analysis. Five samples were excluded from comparative paired analysis as the capillary microsample was haemolysed.[27] In accordance with the clinical protocol, cefotaxime was administered to 34 patients as an intermittent infusion (duration mean, range: 0.19 h, 0.02–0.65 h) of 50 mg/kg every 6 h, two patients (weights 52.0 and 60.2 kg) received the maximum 2 g dose, with one of these patients receiving their dose as an EI over 3.75 h. Actual cefotaxime doses, including total daily doses, are reported in Table 1.

From the total study cohort, 58% of the patients ($n=21$) had augmented renal function (eGFR >130 mL/min/1.73 m^2), 33% ($n=12$) of the patients had normal renal function (eGFR ranging between 80 and 130 mL/min/1.73 m^2), while 8% ($n=3$) of the patients had impaired renal function (eGFR values <80 mL/min/1.73 m^2). Of the patients recruited, 39% ($n=14$) weighed less than 10 kg, 47% of the patients weighed between 10 and 30 kg ($n=17$) and 14% of the patients ($n=5$) had a body weight above 30 kg. The baseline clinical characteristics and patient information are presented in Table 1.

Plasma–concentration data were best described using a one-compartmental model with first-order elimination for both cefotaxime and desacetylcefotaxime. For the model, empirical inclusion of weight normalized to 70 kg with allometric scaling (0.75) on clearance and linear scaling on volume of distribution was used on cefotaxime. As the volume of distribution for desacetylcefotaxime could not be estimated, it was assumed to be equal to the volume of distribution of cefotaxime.[28] The inclusion of the patient population mean-adjusted eGFR (eGFR/150) was accepted as a covariate on cefotaxime clearance (CL1) as it resulted in a decrease in log-likelihood of 11.0. The inclusion of normalized body surface area (BSA/1.73 m^2) as a covariate on desacetylcefotaxime clearance decreased the log-likelihood by 15.0. The goodness-of-fit of the final models were confirmed with the diagnostic plots shown in Figure 1. The final Pmetrics model and the results obtained for the log-likelihood and AIC during the model development are provided in the Supplementary material (Tables S1 and S2, respectively). The support points of the final covariate model are provided in the Supplementary material (Table S3).

The primary pharmacokinetic parameters are summarized in Table 2 and the visual predicted check plots for cefotaxime and desacetylcefotaxime are provided in the Supplementary material (Figure S1). Based on the visual predictive check, 94.7% of the observations for cefotaxime and 96.6% of the observations for desacetylcefotaxime were within the 5th and 95th of simulated percentiles. Individual plots are presented in

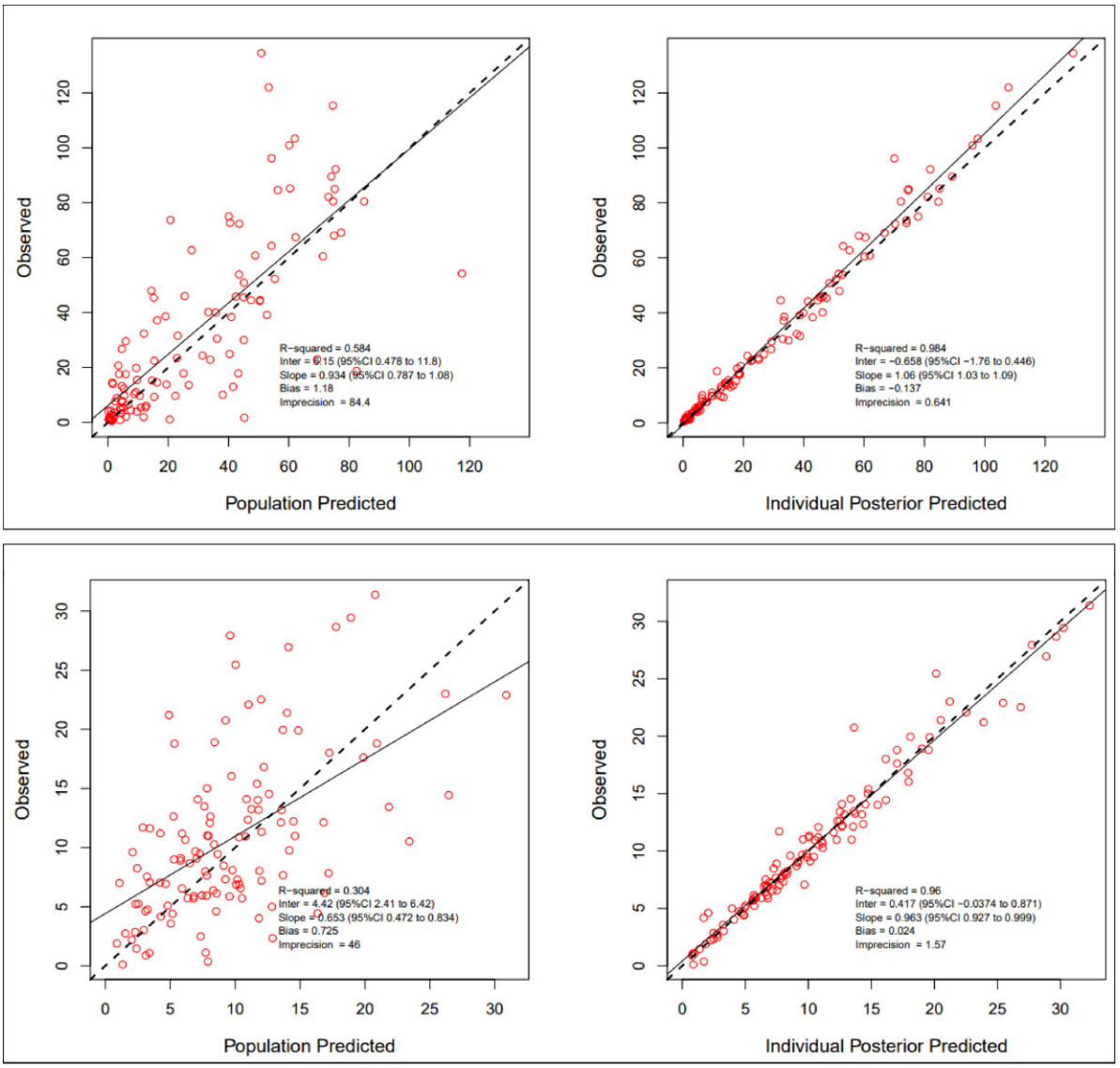

Figure 1. Diagnostic plots for the final covariate model for plasma concentrations (mg/L) of cefotaxime (top) and desacetylcefotaxime (bottom). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

the Supplementary material (Figures S2–S5). A dose selection flow chart is provided in Figure 2. PTA values for cefotaxime are presented across a range of patient weight and eGFR based on the PK/PD targets of ≥60% $fT_{>MIC}$ (Table 3), ≥100% $fT_{>MIC}$ (Table 4) and ≥100% $fT_{>4\times MIC}$ (Table 5).

A linear regression of the model-predicted (using conventional sampling) versus observed (capillary microsampling) cefotaxime and desacetylcefotaxime concentrations are presented in Figure 3. The 95% CI for the intercept for cefotaxime and desacetylcefotaxime are −1.8 to 0.45 and −0.04 to 0.87 mg/L, respectively, and the slope of the regression line is close to 1 for both cefotaxime (95% CI 1.03 to 1.09) and desacetylcefotaxime (95% CI 0.927 to 0.999). The regression line crosses the line of equality for both cefotaxime and desacetylcefotaxime. The results of the external validation found for cefotaxime there was a bias (MWPE) of −0.137 mg/L ($P=0.1129$, different than 0) and a precision (RMSE) of 14.6% and for desacetylcefotaxime there was a bias (MWPE) of −0.024 mg/L ($P=0.0967$, different than 0) and a precision (RMSE) of 12.9%, when comparing the observed concentrations (capillary microsampling) with the model-predicted concentrations (using conventional sampling). Bland–Altman weighted residual plots of the observed concentrations (capillary microsampling) to the model-predicted concentrations (using conventional sampling) are presented in Figure 4. Scatter plots and Bland–Altman plots of the measured cefotaxime and desacetylcefotaxime concentrations from paired conventional samples and capillary microsamples are presented in Figure 5.

Discussion

This study enhances our understanding of the pharmacokinetics of cefotaxime and its active metabolite, desacetylcefotaxime, and optimized dosing in critically ill paediatric patients,[28–30] through the use of rich blood sampling to build the pharmacokinetic profiles ($n = 5$ samples/patient, range 3 to 5). Based on this study design, we have developed a model that supports the inclusion of eGFR on the clearance of cefotaxime and BSA on the clearance of desacetylcefotaxime. Additionally, our blood sampling strategy has demonstrated that the application of capillary microsampling to obtain blood from a finger or heel prick correlates with concentrations obtained using conventional sampling techniques.

A one-compartmental model with first-order elimination best fitted the data to describe the pharmacokinetics of cefotaxime and desacetylcefotaxime. In paediatric patients only one other study has used a population pharmacokinetic approach, which used a similar approach applied here, with a one-compartmental model and setting the volume of distribution of desacetylcefotaxime to equal that of cefotaxime.[28] Studies of β-lactam antimicrobials in critically ill adults have described the pharmacokinetics using a two-compartment model[31–34] and this difference may be due to the use of a single dosing event in the paediatric studies.

Cefotaxime clearance was similar to that previously reported in critically ill paediatric patients, where clearance ranged from 6.9 to 13.7 L/h.[28–30] All studies report variable cefotaxime clearance in critically ill patients. Desacetylcefotaxime clearance was higher in our study, compared with the study by Beranger

Table 2. Population pharmacokinetic primary parameters of cefotaxime and desacetylcefotaxime concentrations of critically ill paediatric patients

Parameter	Mean	SD	CV (%)	Median	Shrink (%)
CL1 (L/h)	12.8	6.17	48.3	11.7	0.312
CL2 (L/h)	10.5	6.91	65.9	9.75	0.985
V1 (L)	39.4	20.7	52.6	34.0	1.08
K12 (h^{-1})	0.199	0.155	77.7	0.169	0.686

CL1, cefotaxime clearance; CL2, desacetylcefotaxime clearance; V1, central volume of cefotaxime; K12, rate of formation of desacetylcefotaxime; CV, coefficient of variation; Shrink %, model shrinkage.
Clearance and volume of distribution are standardized for an adult patient body weight of 70 kg

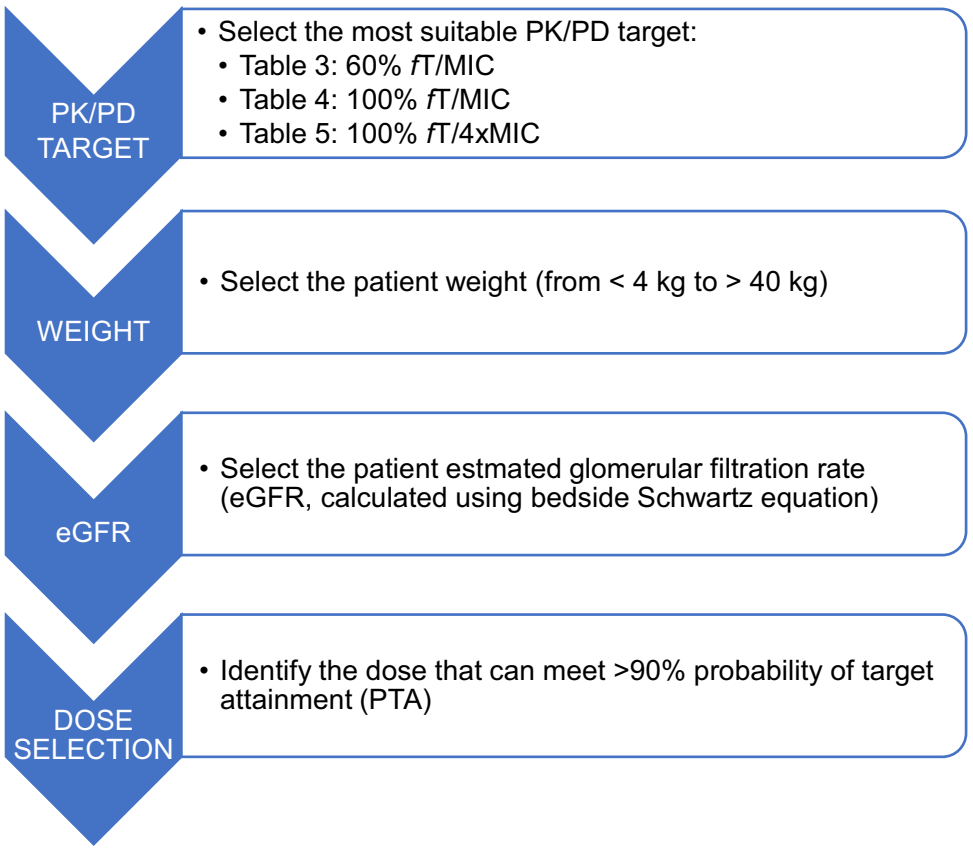

Figure 2. Flow chart to support dosing recommendations in Tables 3–5. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 3. Dose simulations (with PTA results, %) for pathogens susceptible to cefotaxime (MIC target of 1 mg/L) to achieve a PK/PD target of 60% $fT_{>MIC}$

		eGFR			
Dosing regimen	WT	60	100	170	200
50 mg/kg q6h	4	**98.4**	**91.8**	69.3	56.7
	10	**100**	**96.3**	84.3	74.7
	15	**100**	**97.5**	87.5	81.3
	20	**100**	**98.0**	89.1	84.5
	40	**100**	**98.7**	**92.3**	89.3
50 mg/kg q4h	4	**100**	**100**	**90.1**	85.3
	10	**100**	**100**	**96.4**	**91.3**
	15	**100**	**100**	**99.5**	**94.4**
	20	**100**	**100**	**99.8**	**96.7**
	40	**100**	**100**	**100**	**99.8**
50 mg/kg EI q6h	4	**100**	**100**	**100**	**100**
	10	**100**	**100**	**100**	**100**
	15	**100**	**100**	**100**	**100**
	20	**100**	**100**	**100**	**100**
	40	**100**	**100**	**100**	**100**
50 mg/kg EI q4h	4	**100**	**100**	**100**	**100**
	10	**100**	**100**	**100**	**100**
	15	**100**	**100**	**100**	**100**
	20	**100**	**100**	**100**	**100**
	40	**100**	**100**	**100**	**100**
50 mg/kg CI	4	**99.7**	**98.7**	**96.5**	**96.4**
	10	**100**	**98.7**	**97.2**	**96.5**
	15	**100**	**99.2**	**98.7**	**96.8**
	20	**100**	**100**	**99.4**	**97.5**
	40	**100**	**99.9**	**98.7**	**98.7**

$fT_{>MIC}$, fraction of time (fT) where the drug exceeds the MIC; WT, weight (kg); q6h, dosed every 6 h; q4h, dosed every 4 h; EI, extended infusion for half the total dosing interval; CI, continuous infusion with dose calculated as total daily dose.
PK/PD targets ≥90% $fT_{>MIC}$ have been highlighted in bold.

Table 4. Dose simulations (with PTA results, %) for pathogens susceptible to cefotaxime (MIC target of 1 mg/L) to achieve a PK/PD target of 100% $fT_{>MIC}$

		eGFR			
Dosing regimen	WT	60	100	170	200
50 mg/kg q6h	4	89.7	55.8	29.1	18.4
	10	**93.0**	74.0	41.6	33.0
	15	**94.9**	81.3	46.5	38.2
	20	**95.9**	86.4	49.2	42.2
	40	**97.2**	**91.4**	58.6	49.7
50 mg/kg q4h	4	**97.2**	88.1	59.5	51.6
	10	**98.1**	**91.4**	76.0	64.2
	15	**99.3**	**94.9**	81.7	71.2
	20	**99.8**	**96.5**	84.7	76.3
	40	**100**	**97.5**	88.8	85.0
50 mg/kg EI q6h	4	**97.3**	89.0	56.3	47.6
	10	**97.6**	**92.8**	75.9	60.5
	15	**97.9**	**95.4**	81.9	69.1
	20	**98.2**	**96.2**	84.7	76.2
	40	**99.1**	**97.4**	**90.0**	85.4
50 mg/kg EI q4h	4	**100**	**99.7**	85.8	79.9
	10	**100**	**100**	**91.5**	87.9
	15	**100**	**100**	**94.8**	**90.4**
	20	**100**	**100**	**96.7**	**91.5**
	40	**100**	**100**	**99.8**	**96.9**
50 mg/kg CI	4	**99.7**	**98.7**	**96.5**	**96.4**
	10	**100**	**98.7**	**97.2**	**96.5**
	15	**100**	**99.2**	**98.7**	**96.8**
	20	**100**	**100**	**99.4**	**97.5**
	40	**100**	**99.9**	**98.7**	**98.7**

$fT_{>MIC}$, fraction of time (fT) where the drug exceeds the MIC; WT, weight (kg); q6h, dosed every 6 h; q4h, dosed every 4 h; EI, extended infusion for half the total dosing interval; CI, continuous infusion with dose calculated as total daily dose.
PK/PD targets ≥90% $fT_{>MIC}$ have been highlighted in bold.

et al.,[28] which reported a clearance of 4.2 L/h. Both studies had patients with a similar median renal function, so this may be a result of the increased definition allowed through the use of 2–4 samples per patient during the elimination phase in our study. Both our study and the study by Beranger *et al.*[28] have found the clearance of the active metabolite was highly variable. Cefotaxime and desacetylcefotaxime are eliminated by the kidneys and estimated creatinine clearance was able to be included on the clearance of cefotaxime. This finding concords with data from critically ill adult patients that have shown clearance to be proportional to estimated creatinine clearance.[35] The use of eGFR calculated with the bedside Schwartz equation in this paediatric model is advantageous as it includes a factor for age as a descriptor for renal maturation. No other studies have found an association between BSA and clearance of desacetylcefotaxime, although a relationship between BSA and liver volume has been recently identified in children[36] and this may account for the relationship identified for the metabolite in our study.

The volume of distribution for cefotaxime was variable in our patient cohort, but similar to other studies in critically ill paediatric patients, which have reported it ranging from 21.4 to 96 L.[28,30] Studies in critically ill patients have found the volume of distribution of hydrophilic antimicrobials, such as cefotaxime, can be highly altered due to a distribution of fluids into the interstitial space.[37] This may occur in patients suffering from capillary leak syndrome caused by severe sepsis or critically ill patients requiring extensive fluid resuscitation.[12]

Based on a PK/PD target of ≥100% $fT_{>MIC}$, with a non-species-related breakpoint MIC of 1 mg/L for susceptible organisms,[38] 14% of patients ($n=5$) failed to achieve a target of 1 mg/L for cefotaxime and 39% of patients ($n=14$) failed to achieve a target of 4 mg/L across the dosing interval. In our study cohort, 58% of patients had augmented renal clearance (defined as eGFR values above 130 mL/min/1.73 m^2).[39] This result concords with other studies of both critically ill adults and paediatric patients.[39–41]

Table 5. Dose simulations (with PTA results, %) for pathogens susceptible to cefotaxime (MIC target of 1 mg/L) to achieve a PK/PD target of 100% $fT_{>4\times MIC}$

		eGFR			
Dosing regimen	WT	60	100	170	200
50 mg/kg q6h	4	48.0	30.8	3.7	5.0
	10	59.9	39.1	13.9	6.7
	15	67.9	42.0	19.0	10.7
	20	72.6	43.7	23.5	14.6
	40	83.6	51.5	32.3	23.9
50 mg/kg q4h	4	89.1	58.0	30.3	20.9
	10	**92.3**	75.6	43.4	34.1
	15	**94.5**	83.4	48.3	40.6
	20	**96.1**	86.1	51.3	43.9
	40	**97.0**	**90.1**	60.5	51.4
50 mg/kg EI q6h	4	86.4	51.1	24.4	14.3
	10	**92.7**	66.4	37.8	28.5
	15	**93.9**	73.6	43.3	34.7
	20	**95.3**	79.9	45.9	38.2
	40	**97.2**	88.7	53.4	46.5
50 mg/kg EI q4h	4	**96.9**	88.0	56.0	47.9
	10	**97.0**	**91.7**	70.3	59.3
	15	**97.0**	**94.3**	79.0	66.6
	20	**97.0**	**96.6**	82.9	71.6
	40	**97.4**	**97.0**	89.4	83.3
50 mg/kg CI	4	80.1	46.9	20.7	12.4
	10	85.7	65.4	30.2	23.5
	15	88.3	72.0	35.1	27.7
	20	89.2	75.7	39.1	30.9
	40	**90.0**	81.9	49.6	39.9
100 mg/kg CI	4	**95.5**	**90.4**	75.3	60.5
	10	**96.4**	**93.0**	85.1	80.1
	15	**96.4**	**94.2**	86.2	84.3
	20	**96.4**	**94.7**	87.9	85.1
	40	**96.5**	**95.9**	**90.7**	88.3
200 mg/kg CI	4	**99.7**	**98.7**	**96.5**	**96.4**
	10	**100**	**98.7**	**97.2**	**96.5**
	15	**100**	**99.2**	**98.7**	**96.8**
	20	**100**	**99.4**	**98.7**	**97.5**
	40	**100**	**99.9**	**98.7**	**98.7**

$fT_{>MIC}$, fraction of time (fT) where the drug exceeds the MIC; WT, weight (kg); q6h, dosed every 6 h; q4h, dosed every 4 h; EI, extended infusion for half the total dosing interval; CI, continuous infusion with dose calculated as total daily dose.
PK/PD targets ≥90% $fT_{>4\times MIC}$ have been highlighted in bold.

Dosing simulations, using a range of weights and eGFR, support the use of shorter dosing intervals to achieve a PK/PD target of ≥60% $fT_{>MIC}$. For critically ill paediatric patients with normal or impaired renal function, to achieve a PK/PD target of ≥100% $fT_{>MIC}$ a 4 hourly dosing interval or an EI with a 6 hourly interval was able to provide sufficient cefotaxime coverage (using) for most patient weight and eGFR ranges. However, critically ill patients with augmented renal clearance, or neonatal patients with normal renal clearance required both a 4 hourly dosing interval combined with a 2 h EI to achieve the PK/PD target of ≥100% $fT_{>MIC}$. More aggressive PK/PD targets (≥100% $fT_{>4\times MIC}$) that may be suitable for critically ill patients with severe or deep-seated infection were not achieved using standard dosing of 50 mg/kg every 6 h. For critically ill paediatric patients with normal or impaired renal function a 4 hourly dosing interval combined with a 2 h EI achieved target in all patient weight ranges, except for neonatal patients with normal renal function. For critically ill patients with augmented renal clearance or neonatal patients with normal renal clearance, an CI with a total daily dose of 100–200 mg/kg was required to achieve this PK/PD target. Previous studies have demonstrated the challenge of achieving effective PK/PD targets for cefotaxime[28] and other β-lactam antimicrobials[42–45] in critically ill paediatric patients with higher eGFR. The study by Beranger *et al.*,[28] targeting ≥100% $fT_{>MIC}$ and ≥100% $fT_{>4\times MIC}$ for pathogens with an MIC of 0.5 mg/L, recommended the use of CI to achieve PK/PD targets in a similar patient population.

From the external validation, there is no systematic bias evident when comparing the concentration results of cefotaxime or desacetylcefotaxime obtained by conventional sampling to samples obtained by finger or heel prick using capillary microsampling and the calculated bias met the pre-established acceptance criteria, both when performed using the external validation methodology and as demonstrated in the Bland–Altman analysis of the measured concentrations. While the Bland–Altman plots of weighted residual error over the predicted concentration range show a greater imprecision at low cefotaxime and desacetylcefotaxime concentrations, the histograms show that, overall, there is a normal distribution of bias for both cefotaxime and desacetylcefotaxime across the predicted concentration range.

This study has several limitations. We measured total cefotaxime and desacetylcefotaxime concentrations in plasma samples and have not quantified the unbound concentrations. A consequence of this is that we have been unable to calculate protein binding for our patients and have set cefotaxime protein binding to 40% for the purpose of performing the PTA calculations and this may impact on the accuracy of the resultant dosing recommendations. Additionally, we did not collect and isolate the pathogens that caused the infections in the patients enrolled in the study and have therefore applied the PK/PD non-species-related breakpoints from the EUCAST[38] as targets to derive suitable dosing recommendations.

The strengths of this study are that it is the first known pharmacokinetic study describing cefotaxime and desacetylcefotaxime in critically ill paediatric patients using rich sampling for blood collection. Additionally, we demonstrate that the use of capillary microsampling can be used perform pharmacokinetic studies and there is the potential for this to facilitate more studies in neonatal and paediatric patients.[46]

Standard dosing of 50 mg/kg every 6 h was only able to achieve the PK/PD target commonly used in intensive care of 100% $fT_{>MIC}$ in patients >10 kg and with impaired renal function or patients of 40 kg with normal renal function. Dosing

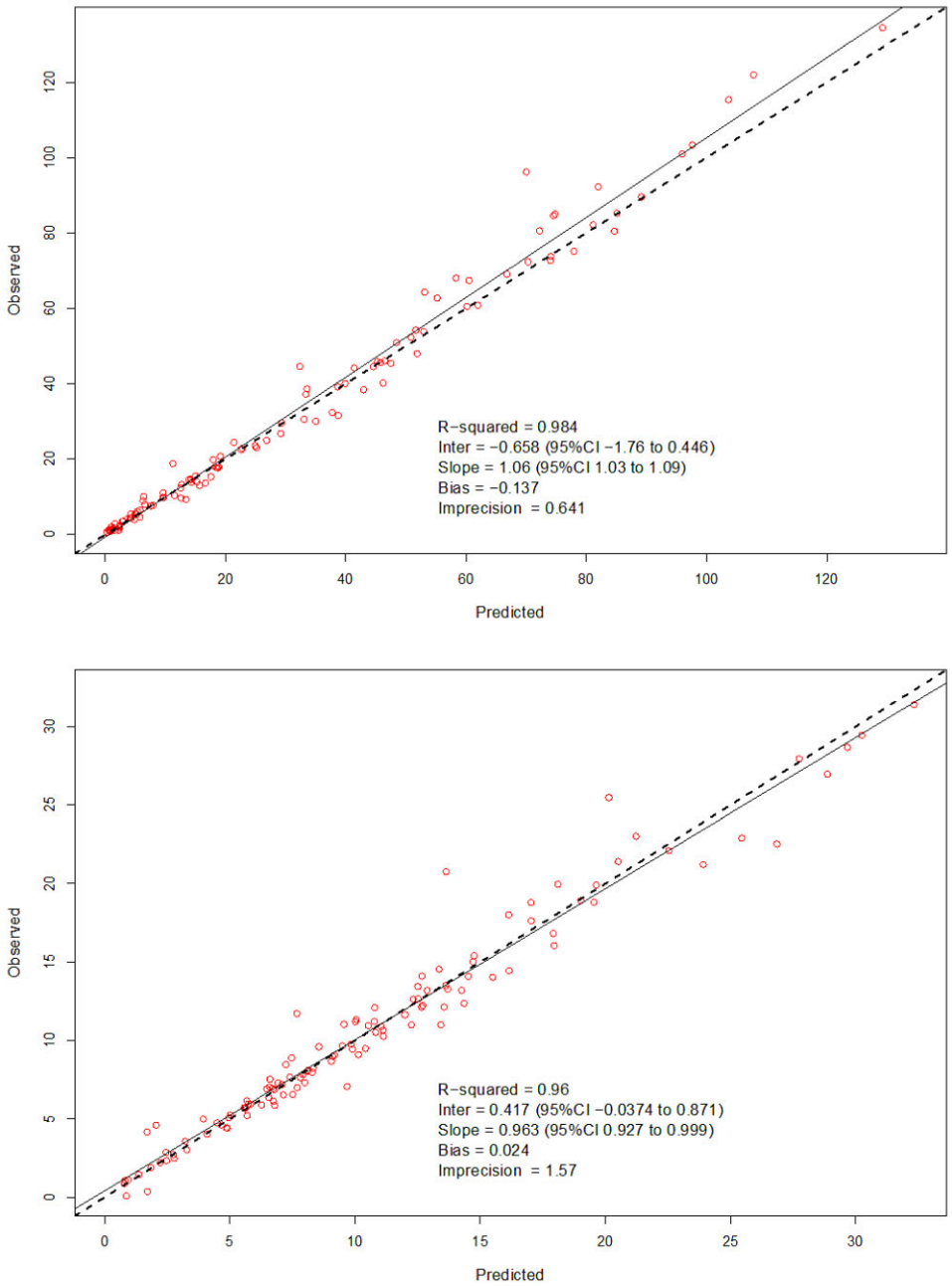

Figure 3. External validation linear regression plots of cefotaxime (top) and desacetylcefotaxime (bottom) comparing observed concentrations (capillary microsampling) with model-predicted concentrations (using conventional sampling). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

recommendations support the use of shorter intervals or EI or CI to achieve cefotaxime exposure suitable for bacterial killing in critically ill paediatric patients, including patients with severe or deep-seated infection. Further research is required to confirm the suitability of these dosing recommendations. If implemented, we would recommend supporting patient care with therapeutic drug monitoring. Capillary microsampling for blood collection was externally validated and demonstrated the application of a finger/heel prick sample can facilitate data-rich pharmacokinetic studies.

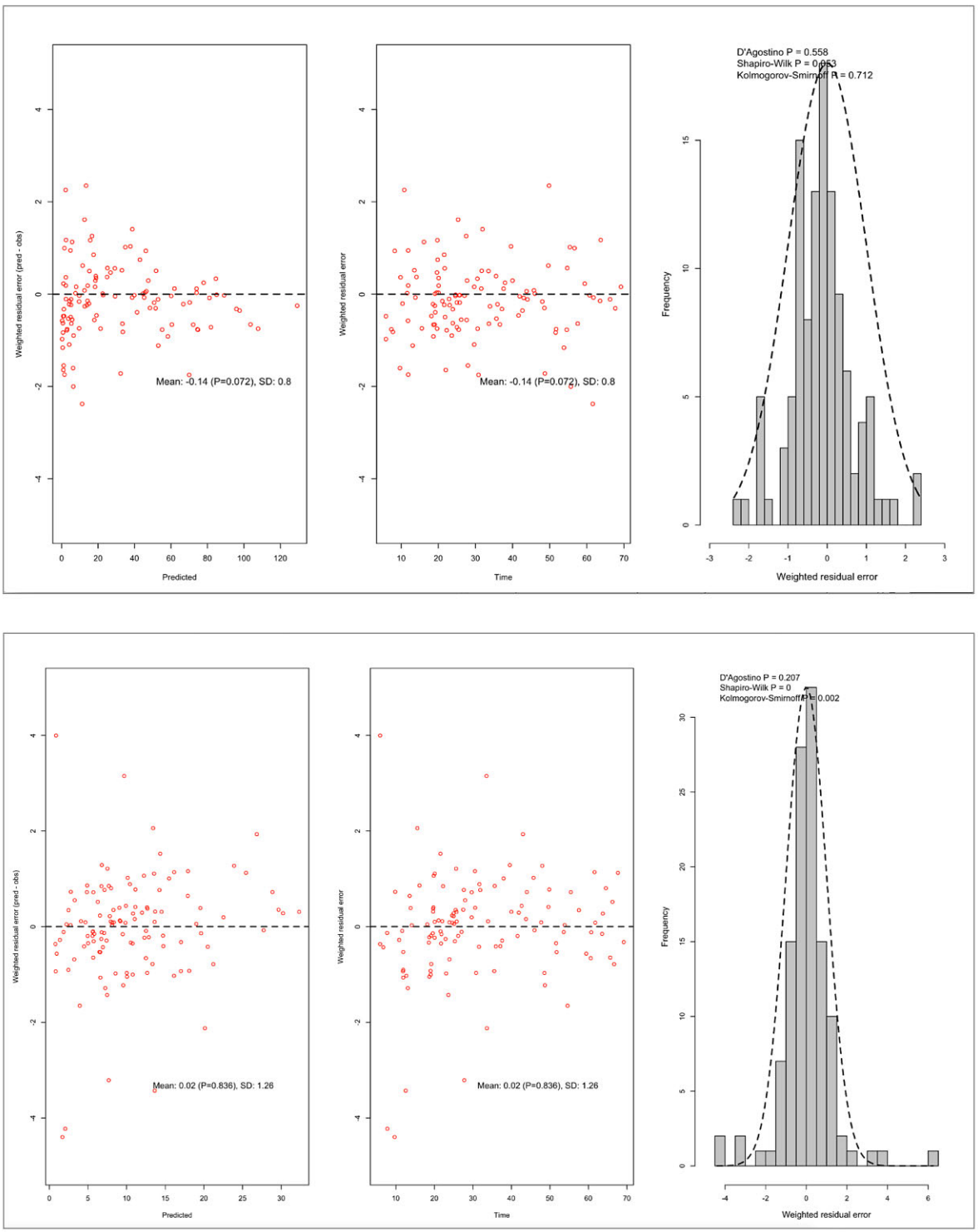

Figure 4. Bland–Altman weighted residual plots for external validation of cefotaxime (top) and desacetylcefotaxime (bottom) comparing observed concentrations (capillary microsampling) with model-predicted concentrations (using conventional sampling). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

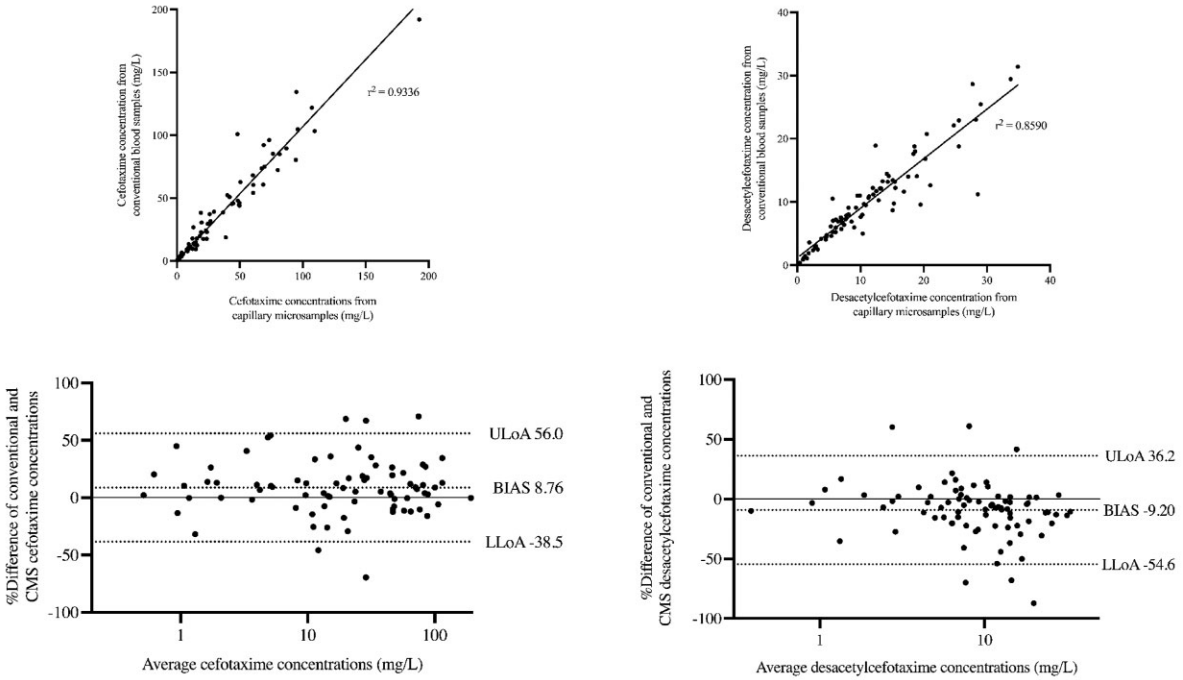

Figure 5. Scatter plots (top) and Bland–Altman plots (bottom) of conventional sampling and capillary microsampling (CMS) of cefotaxime (left) and desacetylcefotaxime (right). ULoA, upper 95% limit of agreement; LLoA, lower 95% limit of agreement.

Acknowledgements

We would like to acknowledge the critically ill children who participated in the study, their parents or legal guardians and the research nurses of the PICU at the Queensland Children's Hospital, Brisbane, Australia for their support and assistance with sample collection and other relevant tasks for this study. We also acknowledge the assistance of the staff of the Mass Spectrometry Facility of UQ Centre for Clinical Research, Brisbane, Australia.

Funding

This study was funded by a grant from the Children's Hospital Foundation, Queensland. Y.C.G.V. is a recipient of a Research Training Scholarship from The University of Queensland. S.L.P. is a recipient of an Early Career Research Fellowship from the Australian National Health and Medical Research Council (APP1142757). J.A.R. is a recipient of an Australian National Health and Medical Research Council Fellowship (APP1048652).

Transparency declarations

None to declare.

Supplementary data

Tables S1 to S3 and Figures S1 to S5 are available as Supplementary data at *JAC* Online.

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