Received: 10 February 2022 | Revised: 11 July 2022 | Accepted: 21 July 2022

DOI: 10.1111/bcp.15487

ORIGINAL ARTICLE

Dose optimization of cefotaxime as pre-emptive treatment in critically ill adult patients: A population pharmacokinetic study

Eveline E. Roelofsen[1,2] | Alan Abdulla[2] | Anouk E. Muller[3,4] | Henrik Endeman[6] | Diederik Gommers[6] | Annemieke Dijkstra[5] | Nicole G. M. Hunfeld[2,6] | Brenda C. M. de Winter[2] | Birgit C. P. Koch[2]

[1]Department of Hospital Pharmacy, Haaglanden Medical Center, The Hague, The Netherlands

[2]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

[3]Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands

[4]Department of Medical Microbiology, Haaglanden Medical Centre, The Hague, The Netherlands

[5]Department of Intensive Care, Maasstad Hospital, Rotterdam, The Netherlands

[6]Department of Intensive Care, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Eveline Roelofsen, Department of Hospital Pharmacy, Haaglanden Medical Centre, Postbus 432, 2501 CK The Hague, The Netherlands.
Email: e.roelofsen@haaglandenmc.nl

Funding information
The study was performed at the Erasmus MC and the Maasstad Hospital. The authors confirm that the Principal Investigators for this paper were Birgit Koch (Erasmus MC), Henrik Endeman (Erasmus MC) and Annemieke Dijkstra (Maasstad Hospital) and that they had direct clinical responsibility for patients.

Aims: To describe the pharmacokinetics (PK) of cefotaxime as pre-emptive treatment in critically ill adult patients, including covariates and to determine the probability of target attainment (PTA) of different dosage regimens for Enterobacterales and *Staphylococcus aureus*.

Methods: Five samples were drawn during 1 dosage interval in critically ill patients treated with cefotaxime 1 g q6h or q4h. PK parameters were estimated using NONMEM (v7.4.2). The percentage of patients reaching 100% $fT>MIC_{ECOFF}$ was used to compare different dosage regimens for Enterobacterales and *S. aureus*.

Results: This study included 92 patients (437 samples). The best structural model was a 2-compartment model with a combined error, interindividual variability on clearance, central volume and intercompartmental clearance. Correlations between interindividual variability were included. Clearance increased with higher estimated glomerular filtration rate (eGFR; creatinine clearance) and albumin concentration. For Enterobacterales, 1 g q8h reached 95% PTA and continuous infusion (CI) of 4 g 24 h^{-1} 100% PTA at the highest eGFR and albumin concentration. For *S. aureus* the predefined target of 95% PTA was not reached with higher eGFR and/or albumin concentrations. CI of 6 g 24 h^{-1} for *S. aureus* resulted in a minimum of 99% PTA.

Conclusion: Cefotaxime PK in critically ill patients was best described by a 2-compartment model with eGFR and albumin concentration as covariates influencing clearance. For Enterobacterales 1 g q8h or CI of 4 g 24 h^{-1} was adequate for all combinations of eGFR and albumin concentration. For *S. aureus* CI of 6 g 24 h^{-1} would be preferred if eGFR and albumin concentration exceed 80 mL min^{-1} and 40 g L^{-1} respectively.

KEYWORDS
β-lactam antibiotics, cefotaxime, cephalosporins, critically ill, pharmacokinetics, pharmacokinetic modelling, dosage regimens, pharmacometrics

1 | INTRODUCTION

In recent years, it has become increasingly clear that standard dosage of antibiotics in critically ill patients may result in inadequate exposure. Optimal dosage is complicated by the heterogeneity of the population and the altered pharmacokinetics (PK) in these patients compared to healthy volunteers or patients with less severe illnesses or infections.[1,2] Exposure to antibiotics in critically ill patients can be affected by changes in the PK due to altered renal function (dysfunction or augmented renal clearance) as well as altered liver function, volume of distribution and protein binding.[2–5] Underexposure can lead to decreased effectiveness and higher morbidity and mortality rates,[2,5–7] while overexposure can result in adverse effects.

Different strategies have therefore been suggested or utilized to optimize antibiotic dosage in critically ill patients, including an increased initial dose of ciprofloxacin, extended infusion or continuous infusion of β-lactams, and routine therapeutic drug monitoring of antibiotics in critically ill patients.[8–14] Key to these strategies is the development and use of PK and pharmacodynamic models in order to establish adequate target attainment, taking into account the high interpatient variability and the decreased susceptibility of the target microorganisms.

Cefotaxime is a third-generation cephalosporin, which is used in the critical care setting to treat infections caused by microorganisms such as Enterobacterales and *Staphylococcus aureus*. It is frequently used as the systemic component for selective digestive decontamination (SDD) in order to prevent infections with the above-mentioned microorganisms. SDD is indicated in patients admitted to the intensive care unit (ICU) who are expected to be mechanically ventilated for >48 hours or with an expected stay of >72 hours. Therefore, the population of patients on SDD is heterogeneous and includes patients with burns, trauma, as well as the general ICU population.

Cefotaxime PK in adults has mainly been investigated in the 1980s and early 1990s in healthy volunteers and patients with renal or liver insufficiency.[15–26] In these studies, cefotaxime showed a fast and predominant renal elimination with a half-life between 0.8 and 2.42 hours. In healthy volunteers, renal clearance of cefotaxime was higher than the glomerular filtration rate, suggesting the involvement of tubular secretion.[15–21] Renal insufficiency resulted in a significantly decreased clearance and increased half-life.[15,19,22] Approximately 20% of the cefotaxime dose is excreted renally as the metabolite desacetylcefotaxime, which exhibits approximately 12% of the activity of cefotaxime.[20,23,24] Liver dysfunction reduces the formation of desacetylcefotaxime and causes a slight accumulation of cefotaxime which is considered to be clinically irrelevant.[21,22] Protein binding in healthy volunteers ranged from 27–47%.[14,16,25,26] One study in ICU patients reported a median protein binding of approximately 30% for intermittent as well as continuous dosing.[11]

Although data on the PK of cefotaxime suggests that continuous infusion might be preferred, more detailed data on the PK and the probability of target attainment for different microorganisms is needed to optimize therapy.[11,27] Therefore, the aim of this study was to develop a population PK (popPK) model of cefotaxime as preemptive treatment in critically ill adult patients, including covariates in order to determine the probability of target attainment of different dosage regimens for Enterobacterales and *S. aureus*.

What is already known about this subject

- Only limited pharmacokinetics of cefotaxime is available in literature showing a predominant renal clearance and a protein binding of approximately 40%.
- Pharmacokinetics of β-lactam antibiotics, including cefotaxime in critically ill patients differ from healthy volunteers emphasizing the need for data in this specific population.
- Intermittent standard dosage of cefotaxime has a lower target attainment for *Enterobaterales* than continuous infusion.

What this study adds

- Cefotaxime pharmacokinetics was best described in a 2-compartment model with a combined error and interindividual variability on clearance, central volume and intercompartmental clearance.
- Cefotaxime pharmacokinetics in critically ill shows a large interindividual variability which can be partly explained by the covariates estimated glomerular filtration rate and albumin concentration on albumin.
- Intermitted dosages for the treatment *Staphylococcus aureus* need to be adjusted based on estimated glomerular filtration rate and albumin concentration, while a 6 g 24 h-1 continuous infusion suffices independent of these covariates.

2 | METHODS

The cefotaxime data were obtained as part of the EXPAT study, a prospective, observational PK/pharmacodynamic study of several antibiotics in the ICU departments of the Erasmus Medical Center and Maasstad Hospital, Rotterdam, the Netherlands.[14]

2.1 | Study design and population

Patients on intermittent intravenous cefotaxime were enrolled between January 2016 and June 2017 if they were ≥18 years and admitted to the ICU with an expected stay of >72 hours. Patients were excluded if written informed consent was not obtained, if admittance to the ICU was due to burn wounds, or if cefotaxime therapy was

discontinued prior to sampling. Cefotaxime was prescribed in a dosage of either 1 g every 6 hours (q6h) or 1 g q4h according to the SDD protocol and at the discretion of the attending physician for selective bowel decontamination with or without additional treatment.

2.2 | Blood sampling and assay

Five blood samples per patient were collected at 15–30 minutes before the start of a dose, 15–30 minutes after administration, 1 and 3 hours after the end of infusion, and just before the next administration. Blood samples were taken on day 2 after the start of cefotaxime. Cefotaxime was infused in 1 minute up to 1 hour. Blood samples were centrifuged and plasma was stored at −80°C until analysis. Exact sampling times were recorded as well as the time of dosage administration and infusion rate. Total cefotaxime plasma concentrations were measured using a multianalyte ultraperformance liquid chromatography–tandem mass spectrometry assay,[28] validated in accordance with the Food and Drug Administration guidance on bioanalytical method validation.[29] Samples above the linearity of the calibration curves (0.25–12.5 mg L^{-1}, R^2 > 0.99) were diluted according to standard dilution protocol.

2.3 | Clinical data collection

Clinical and other data collected were age, sex, weight, height, serum creatinine concentration, estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, urea concentration, C-reactive protein, albumin concentration, body temperature, white blood cell count, continuous renal replacement therapy (CRRT), SOFA (Sequential Organ Failure Assessment) score, APACHE II, Acute Physiology and Chronic Health Evaluation II, and fluid balance.

2.4 | Structural model

Parametric popPK modelling and simulations were performed using NONMEM (nonlinear mixed effects modelling v 7.4.2, ICON Development Solutions, Ellicot City, MD, USA). To evaluate and visualize the different models, R Studio (version 1.1.463), R (version 3.5.2), Xpose (version 4.6,1) and PsN (version 4.8,1), were used in combination with the graphical user interface Pirana (version 2.9.7).

Data were used untransformed. The first-order conditional estimation method was used to analyse data. Samples below the level of quantification were not taken into account, but were confirmed after model development by simulating the concentration.

2.5 | PK analysis and model evaluation

One-, 2- and 3-compartment models were tested to fit the cefotaxime concentration data, using first order elimination by terms of clearance (CL), volume of distribution of the central compartment (V1) and peripheral compartments (V2 and V3), and the intercompartmental clearance of cefotaxime between the central and peripheral compartments (Q1 and Q2). Model fit was evaluated using the precision of parameter estimates, objective function value (OFV), shrinkage values (below 20% was considered acceptable),[30] as well as visual inspection of the goodness of fit (GOF) plots, visual predictive check and normalized prediction distribution error. The interindividual variability (IIV) was tested on all parameters as was covariance between random effects by means of omega block. An exponential model was used to estimate the IIV on each parameter. IIV was considered log-normally distributed and η-values normally distributed.

A combined proportional and additive model was used for the residual variability.

2.6 | Covariate analysis

Covariate analysis was subsequently performed to study whether part of the IIV in the data could be explained by inclusion of 1 or more of the parameters as described under data collection. Continuous covariates were normalized to the population median and implemented by use of an exponential model. For binary variables a proportional model was used. Significant covariates were identified by forward inclusion followed by backward elimination. The level of significance used for forward inclusion was 0.05 (decrease in OFV of at least 3.84) and 0.001 (decrease in OFV of at least 10.83) for backward elimination.

2.7 | Determination of the probability of target attainment

Monte Carlo simulations ($n = 5000$) were performed on steady state concentrations with the final model to determine probability of target attainment (PTA) for a range of minimum inhibitory concentration (MIC) values. Covariates were evaluated in the range in which they predominantly occurred in the dataset, to avoid extrapolation: for eGFR 10, 30, 50, 80, and 100-mL min^{-1} were used; and for albumin concentration 20, 30, and 40 g L^{-1}. A protein binding of 30% was used.[11] Different intermittent dosage regimens were simulated, including the dosing regimens in our study population (1 g q6 h and 1 g q4h) and the regimens recommended by the EUCAST (1 g q8h, 2 g q8h and 2 g q6h).[31] For all intermittent dosage regimens, a duration of infusion of 15 minutes was used.

Finally, continuous infusion of 4 and 6 g/d was simulated.

The percentage of patients reaching 100% *f*T>MIC was used to determine target attainment of the different dosage regimens for Enterobacterales (such as *Escherichia coli* and *Klebsiella pneumoniae*, but excluding those with chromosomal AmpC-enzymes) and *S. aureus*. For these microorganisms, the epidemiological cut-off (MIC_{ECOFF}) of 0.25 and 4 mg L^{-1}, respectively, were used.[31] A target attainment of 95% of patients reaching 100% *f*T>MIC was considered adequate.

3 | RESULTS

3.1 | Study population

In total, 93 patients were included. One patient was excluded due to an impossible concentration–time profile (no increase in cefotaxime concentration after presumed administration of cefotaxime), leaving 92 patients in the final analysis. A total of 453 blood samples were analysed. Seven samples were not drawn. Sixteen samples were excluded: 9 samples were drawn after a second administration of cefotaxime with an unknown administration time; 4 samples were drawn during administration of cefotaxime; 2 samples were below level of quantification (0.5%); and 1 sample was physiologically impossible (998 mg L^{-1}), resulting in a total of 437 observations in the final database. 80 patients received 1 g q6h and 12 patients 1 g q4h. Basic patient characteristics showed a large variability among patients (Table 1).

TABLE 1 Patient characteristics

Characteristics	$n = 92$
Demographic data	
Sex (M/F)	57/35
Age (y)	64 (23–85)
Body weight (kg)	76 (45–150)
Height (cm)	171 (143–196)
BMI (kg/m^2)	26 (17.8–46.3)
Clinical data	
APACHE II	23 (7–71)
SOFA score	13 (1–21)
Biological data	
Serum creatinine (μmol L^{-1})	98 (5–913)
eGFR (mL min^{-1}/1.73m^2)	57 (4–347)
Albumin (g L^{-1})	26 (11–47)
C-reactive protein (mg L^{-1})	127 (0–488)
Leucocytes ($\times 10^9$ cells L^{-1})	13 (0.9–100)
Extracorporeal circuits	
CRRT	5 (5.4%)

Data are expressed as *n* (%) or median (range) M, male; F, female; BMI, body mass index; SOFA score, Sequential Organ Failure Assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; eGFR, estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; CRRT, continuous renal replacement therapy.

3.2 | PopPK model

The best structural model was a 2-compartment model with a combined error and an IIV on CL, V1 and Q. The model control stream is available as Supplementary data (S1). Correlations between the IIV were included using an omega block. CL increased with higher eGFR and higher albumin. No other significant covariates were found. The covariates could explain 48% of the IIV on clearance. Table 2 shows the parameter estimates of the final model including covariates and the structural model. Clearance of cefotaxime is described by the following formula, in which the eGFR and albumin concentration are divided by the median.

$$CL = 7.08^{*}\,(\text{eGFR}/57)^{0.477^{*}}(\text{albumin concentration}/26)^{0.64}.$$

3.3 | Model evaluation

Figure 1 shows the goodness of fit plots of the final model including covariates. Both the individual and population predictions showed an equal distribution around the line of unity when plotted against the

TABLE 2 Model parameters and estimates

	Base model		Final model including covariates	
Parameter	Estimate	Rel. SE (%SE)	Estimate	Rel. SE (%SE)
CL (L h^{-1})	6.76	7.7	7.08	5.4
V1(L)	15.5	6.6	15.70	6.2
V2 (L)	24.8	34.3	25.00	37.0
Q (L h^{-1})	5.11	22.7	4.81	15.2
Additive error (mg L^{-1})	0.618	52.8	0.617	25.9
Proportional error	0.196	9.8	0.191	8.6
Covariate eGFR on CL	-	-	0.477	15.7
Covariate albumin concentration on CL	-	-	0.640	24.8
Variability on CL, % [shrinkage]	69.6 [1.1]	9.0	50.3 [2.2]	11.8
Variability on V1, % [shrinkage]	35.8 [10.1]	18.9	34.9 [13.3]	16.1
Variability on Q, % [shrinkage]	76.2 [14.2]	20.3	92.1 [17.3]	13.8

Model parameters of the final model including covariates and the structural model. CL, clearance of cefotaxime; V1, volume of distribution in the central compartment; V2, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; IIV, interindividual variability; eGFR, estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; Rel SE, relative standard error.

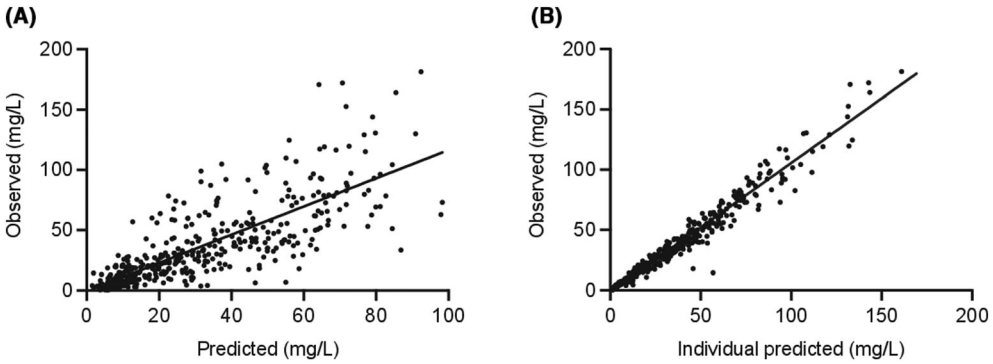

FIGURE 1 Goodness-of-fit plots final model including covariates. (A) Observed concentrations plotted against population predicted concentrations. (B) Observed concentrations set against population predicted concentrations. The line identifies the line of identity.

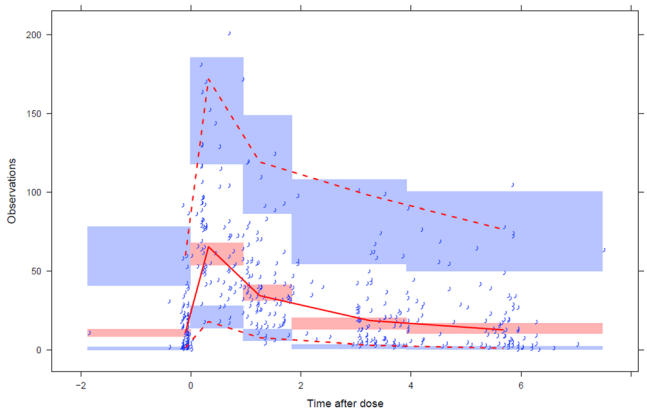

FIGURE 2 Visual predictive check final model including covariates. Observed cefotaxime concentration–time after dose and the visual predictive check of the final model. Blue brackets, observed concentrations; red line, observed median; dotted red lines, the 5th and 95th percentiles of the observed data; red shaded area, the 95% confidence interval of the model-predicted median; blue shaded areas, the 95% confidence intervals of the model-predicted 5th and 95th percentiles.

observed concentrations. The visual predictive check (Figure 2) shows that most of the median observations were within the 95%CI of the models' predictions, indicating a good model predictability. The normalized prediction distribution error shows no relevant trend or deviation (Figure S2).

3.4 | PTA

For Enterobacterales, 100% *f*T>MIC is reached in almost all intermittent dosage regimens and eGFR and albumin concentration combinations, with even the lowest dosage regimen of 1 g q8h reaching 95% PTA at the highest eGFR and albumin concentration. Figure 3 shows the percentage of patients reaching 100% *f*T>MIC of the different dosage regimens for *S. aureus* (MIC_{ECOFF} 4 mg L^{-1}) plotted against different combinations of eGFR and albumin concentration.

For *S. aureus* the target is only reached at fairly low eGFR and/or albumin concentration in all intermittent dosage regimens. The 1 g q8h regimen does not reach the target of 95% of patients reaching 100% *f*T>MIC when the eGFR or albumin concentration is higher than 10 mL min^{-1} and 30 g L^{-1}, respectively. A combination of an eGFR of 100 mL min^{-1} and albumin concentration of 40 g L^{-1} reduces the percentage of patients reaching target to 14%. Increasing the interval or the dose to 2 g q8h, 1 g q6h, 2 g q6h, or 1 g q4h results in percentages of 34, 25, 54, and 54%, respectively, for the same combination of eGFR and albumin concentration. At the approximately median eGFR (50 mL min^{-1}) and albumin concentration (30 g L^{-1}) percentages were 48% (1 g q8h), 77% (2 g q8h), 70% (1 g q6h), 90% (2 g q6h) and 86% (1 g q4h).

However, continuous infusion of 4 g/d would be adequate for Enterobacterales (PTA of 100% for the highest eGFR and albumin concentration), and would also suffice for *S. aureus* at an eGFR of 80 mL min^{-1} or less and albumin concentration of 40 g L^{-1} or less. Otherwise, 6 g CI/d would be needed.

4 | DISCUSSION

The aim of this study was to describe the PK with a popPK model of cefotaxime as pre-emptive treatment in critically ill adult patients, including covariates and subsequently recommend optimal dose regimen for Enterobacterales and *S. aureus*.

The PK of cefotaxime in 92 critically ill patients included in this study was best described by a 2-compartmental model with a combined error and IIV on CL, V1 and Q. Both the eGFR and the albumin concentration were positively related to clearance of cefotaxime. eGFR and albumin concentration accounted for 48% of the IIV. Consequently, high eGFR and albumin concentration resulted in a decrease in target attainment even for Enterobacterales (MIC_{ECOFF} 0.25 mg L^{-1}) in the lower intermittent dosage regimen (1 g q8h). Continuous infusion of 4 g/d would suffice for Enterobacterales. For *S. aureus* (MIC_{ECOFF} 4 mg L^{-1}) target attainment of 100% *f*T>MIC could only be reached at low eGFR and albumin concentration, while a 6 g/d continuous infusion would cover *S. aureus* at all combinations of eGFR and albumin concentration in this study.

The analysis was focused on Enterobacterales and *S. aureus*, since those are the target bacteria in SDD. However, the results for Enterobacterales can also be used for other species with lower MIC_{ECOFF},

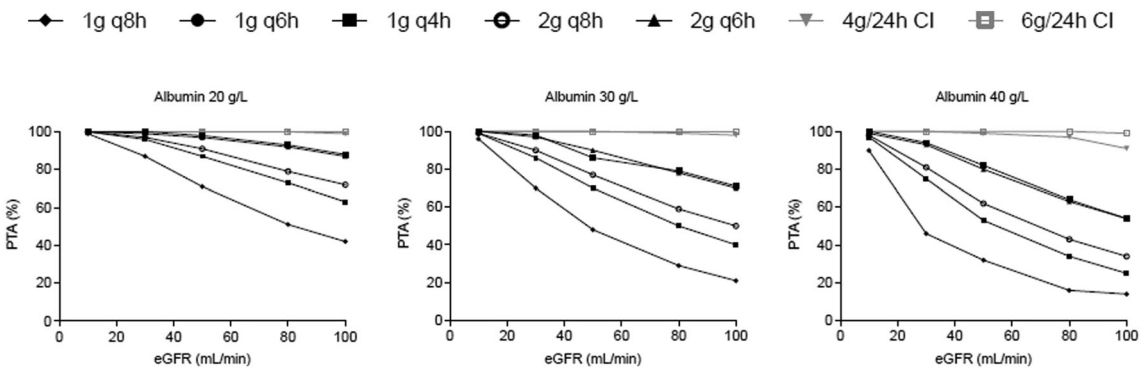

FIGURE 3 PTA of different dosage regimens and combinations of eGFR and albumin concentration for *Staphylococcus aureus* (MIC_{ECOFF} 4 mg L^{-1}). PTA, probability of target attainment (percentage) of patients who reached 100% *f*T>MIC; eGFR, estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; CI, continuous infusion.

such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (both MIC_{ECOFF} 0.064 mg L^{-1}).

Compared to previous studies on the PK of cefotaxime, clearance of cefotaxime in our study in critically ill patients was markedly lower than in healthy volunteers, namely 12.7–23.5 L h^{-1} compared to 7.08 L h^{-1}.[16–20] This might be explained by the high eGFR in healthy volunteers of 129 mL min^{-1} on average, while the median eGFR in this study population was 57 mL min^{-1}.[16–20] Total volume of distribution was almost twice as high in critically ill patients, 40.7 *vs*. 21.6 L on average in healthy volunteers, which is probably due to expansion of the interstitial space because of capillary leakage combined with fluid loading.[4,16–20] Compared to a previous popPK study of cefotaxime as empirical treatment in critically ill patients, clearance was lower and volume of distribution higher.[32] The former might be explained by the high median eGFR of the patients included by Swartling *et al*. namely 94 mL min^{-1} compared to 57 mL min^{-1} in our population. The latter could be caused by a sample size difference, as the model of Swartling *et al*. was based on mid and trough samples only, resulting in a less precise description of the PK.

In this heterogeneous study population, 2 significant covariates were found to be positively related to an increase in clearance, namely the eGFR and the albumin concentration. The effect of the eGFR is probably explained by the predominant renal clearance of cefotaxime and has also been identified by the studies of Swartling *et al*. and Aardema *et al*.[11,32]

In the study of Swartling *et al*., a change in eGFR of 10 mL min^{-1} increased clearance by 0.74 L h^{-1} for eGFRs at or below 120 mL min^{-1}. In our exponential model, the increases in clearance are consistent with these result ranging from 0.42–0.99 L h^{-1} per 10 mL min^{-1} with a smaller increase in clearance at higher eGFRs.

Comparing our data to those of Aardema *et al*. we find similar results as well. Aardema *et al*. reported that the eGFR was significantly higher in patients who did not reach the target of a total concentration of 4 mg L^{-1} compared to patients who did. The median eGFR was of 114 mL min^{-1} (interquartile range [IQR] 84–173 mL min^{-1}) *vs*. 65 mL min^{-1} (IQR 30–99 mL min^{-1}), respectively. In our population, we find a median eGFR of 104 mL min^{-1} (IQR 78–119 mL min^{-1}) in patients not attaining target compared to 49 mL min^{-1} (IQR 26–89 mL min^{-1}) in patients who reached target.

The effect of the albumin concentration is more difficult to interpret, as cefotaxime exhibits relatively low protein binding. This implies that clearance is less dependent on changes in free concentrations compared to what can be expected for drugs that have a high protein binding (>90%). In the latter, this correlation would be the other way around: a decrease in albumin concentrations can lead to an increase in free concentration available to be eliminated from the body and therefore an increased clearance.[33] In terminally ill patients, it has been proposed that hypoalbuminemia can be an expression of inflammation, which can decrease CYP3A activity, subsequently increasing drug clearance.[34] Cefotaxime, however, is predominantly cleared renally and to a lesser extent metabolized by acetylation and not by oxidation, ruling out a significant involvement of CYP3A. Hypoalbuminaemia may be the result of several disease driven physiological changes apart from inflammation, such as trans capillary escape in sepsis, malnutrition, downregulation of synthesis by stress response and malignancies.[33] Possibly, in our study, higher albumin concentrations might be indicative of less severe illness and, overall, fewer physiological changes that can influence PK. However, SOFA and APACHE score did not influence clearance significantly, showing no change and an increase in objective function in the forward covariate analysis, respectively. In the elderly, a similar effect of albumin was seen in a study by Urien *et al*.[35] However, a previous study by Aardema *et al*., comparing 1q4h intermittent dosing of cefotaxime to continuous infusion of 4 g 24 h^{-1} in critically ill patients did not find albumin concentration to be of influence.[11]

Comparison of PTA results is difficult due to the heterogeneity of critically ill patients. Aardema *et al*. showed that 96,4% of patients reached and maintained target attainment 100% *f*T>MIC for continuous infusion of 4 g 24 h^{-1}, while intermittent dosing of 1 g q6h resulted in 71.4% PTA for an MIC of 1 mg L^{-1}.[11] In our population we find that, when using the same methods as described by Aardema *et al*., 77.6% of patients in the 1 g q6h group reached target, which is in a similar range. Extrapolating our simulated data to the median conditions used in this study, continuous infusion would result in 100%

PTA. In the CI group of Aardema *et al*., a quarter of patients had an eGFR above 107 mL min^{-1}, which in our simulations decreases PTA. This might explain the difference in PTA between the 2 studies. The higher PTA reached in continuous administration is obvious, though.

Furthermore, different targets for β-lactam antibiotics are used in literature for PTA and can be discussed. In children and neonates targets ranged from 75 to 100%.[36] In adults, targets of 100% of total or free concentration above or 4–5 times above the (actual measured) MIC have also been used in the critically ill.[11,27,37,38] In concordance with Aardema *et al*. we used 100% *f*T> MIC_{ECOFF}. The MIC_{ECOFF} was used to account for variability in MIC testing and natural variability within isolates.[39] The use of the MIC_{ECOFF} instead of *measured* MIC compensates also partly for the factor 4–5 used in other studies. While 40–60% *f*T>MIC should be reached to treat infections with cephalosporins and targets for prophylactic use have not been well established, we chose 100% *f*T>MIC due to the severity of illness in this specific population.

One of the limitations in our study is that we did not measure the desacetylcefotaxime metabolite. However, desacetylcefotaxime concentrations are low compared to cefotaxime concentrations and activity is considered negligible compared to cefotaxime.[11,21,22,24] In continuous infusion, total concentrations of desacetylcefotaxime were 40% of total cefotaxime concentrations.[11] Taking into account an antimicrobial activity of approximately 12%, the contribution of desacetylcefotaxime would therefore be 5% of the antimicrobial activity of cefotaxime. However, practically, this limitation has no clinical impact since EUCAST based clinical breakpoints for the dosing regimens on the parent drug only.

Furthermore, in our study we simulated continuous infusion based on a model built on intermittent dosing. However, we do not expect PK parameters of cefotaxime to change depending on dosing strategy. We expect that the heterogeneity of critically ill patients is of much more influence on PK parameters and possible differences in results between studies.

One patient had very low creatinine concentrations resulting in an eGFR of > 300 mL min^{-1}. Limiting the eGFR of this patient to 141 mL min^{-1}, the second highest eGFR in our study, showed no marked effect on the estimates.

In our study CRRT was not found to be a significant covariate. CRRT was only registered at baseline CRRT was included as a binary covariate as data on duration and continuation of CRRT during sampling were not present. Excluding the 5 patients on CRRT from the analysis did not markedly influence the PK estimates. The exact effect of CRRT on the PK of cefotaxime needs to be further investigated.

Overall, we described the PK of cefotaxime in a clinically relevant and heterogeneous population, the critically ill patient, using a dense sampling schedule. Our model can be used for initial dose estimation based on eGFR and albumin concentration, if necessary, followed by therapeutic drug monitoring in the individual critically ill patient with a high risk of target nonattainment (high eGFR and albumin concentration), Total concentrations can be used as protein binding is sufficiently constant among ICU patients.[11]

We found that eGFR and albumin concentration significantly influence clearance of cefotaxime and target attainment. To optimize treatment in the heterogeneous population of critically ill patients, we recommend further research to investigate the PK and target attainment in subpopulations, such as patients on CRRT and septic patients in which other bacteria, besides those primarily targeted by SDD, for instance *S. pneumoniae*, also need to be covered.

In conclusion, in the 92 critically ill adult patients in this study, cefotaxime PK is best described by a 2-compartment model with the eGFR and the albumin concentration as covariates influencing clearance. For the treatment of Enterobacterales, 1 g q8h or CI of 4 g 24 h^{-1} is adequate at all combinations of eGFR and albumin concentration. If treatment for *S. aureus* is also indicated, the use of CI of 6 g 24 h^{-1} would be preferred if eGFR and albumin concentration exceed 80 mL min^{-1} and 40 g L^{-1} respectively.

ACKNOWLEDGEMENTS

The authors are much obliged to Prof. Dr Johan W. Mouton for all his work. The authors would like to thank all the participants, the ICU teams, and the pharmacy laboratory of the Erasmus University Medical Center in Rotterdam.

An abstract with part of the results has been presented at ECCMID and IATDMCT congress. The EXPAT study was supported by the Erasmus Medical Center; no specific funding was received.

COMPETING INTEREST

There are no competing interests to declare.

TRANSPARENCY

None to declare.

CONTRIBUTORS

A.A., N.G.M.H., and B.C.P.K. were involved in the concept and design of the study. A.A. and A.D. were involved in recruitment and screening of trial participants. E.E.R., A.E.M. and B.C.M.d.W. performed data analysis. All authors contributed to interpretation of the data. E.E.R. wrote the first draft of the manuscript and all authors contributed to subsequent drafts and gave final approval of the version to be published.

COMPLIANCE WITH ETHICAL STANDARDS

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines. Approval for the study protocol was obtained from the Erasmus MC Medical Ethics Committee (MEC-2015-502/NL53551.078.15) and the study was registered in the Netherlands Trial Registry (EXPAT trial, NTR 5632). Informed consent was obtained from the patients or their legal representative.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Eveline E. Roelofsen https://orcid.org/0000-0001-6508-0898

Alan Abdulla https://orcid.org/0000-0002-2158-6376

REFERENCES

1. Ridley S, Burchett K, Gunning K, et al. Heterogeneity in intensive care units: fact or fiction? *Anaesthesia*. 1997;52(6):531-537. doi:10.1111/j.1365-2222.1997.109-az0109.x
2. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014;58(8):1072-1083. doi:10.1093/cid/ciu027
3. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. *Intensive Care Med*. 2014;40(3):380-387. doi:10.1007/s00134-013-3187-2
4. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med*. 2013;39(12):2070-2082. doi:10.1007/s00134-013-3088-4
5. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. *Ann Intensive Care*. 2012;2(1):35. Published 2012 Jul 28. doi:10.1186/2110-5820-2-35
6. Kuti JL, Nightingale CH, Nicolau DP. Optimizing pharmacodynamic target attainment using the MYSTIC antibiogram: data collected in North America in 2002. *Antimicrob Agents Chemother*. 2004;48(7):2464-2470. doi:10.1128/AAC.48.7.2464-2470.2004
7. Thomas JK, Forrest A, Bhavnani SM, et al. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother*. 1998;42(3):521-527. doi:10.1128/AAC.42.3.521
8. Abdulla A, Rogouti O, Hunfeld NGM, et al. Population pharmacokinetics and target attainment of ciprofloxacin in critically ill patients. *Eur J Clin Pharmacol*. 2020;76(7):957-967. doi:10.1007/s00228-020-02873-5
9. Roberts JA, Kumar A, Lipman J. Right Dose, Right Now: Customized Drug Dosing in the Critically Ill. *Crit Care Med*. 2017;45(2):331-336. doi:10.1097/CCM.0000000000002210
10. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. *Intensive Care Med*. 2020;46(6):1127-1153. doi:10.1007/s00134-020-06050-1
11. Aardema H, Bult W, van Hateren K, et al. Continuous versus intermittent infusion of cefotaxime in critically ill patients: a randomized controlled trial comparing plasma concentrations. *J Antimicrob Chemother*. 2020;75(2):441-448. doi:10.1093/jac/dkz463
12. Sinnollareddy MG, Roberts MS, Lipman J, Roberts JA. β-lactam pharmacokinetics and pharmacodynamics in critically ill patients and strategies for dose optimization: a structured review. *Clin Exp Pharmacol Physiol*. 2012;39(6):489-496. doi:10.1111/j.1440-1681.2012.05715.x
13. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. *Crit Care*. 2018;22(1):233. Published 2018 Sep 24. doi:10.1186/s13054-018-2155-1
14. Abdulla A, Dijkstra A, Hunfeld NGM, et al. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: a two-center prospective study (EXPAT). *Crit Care*. 2020;24(1):558. Published 2020 Sep 15 doi:10.1186/s13054-020-03272-z
15. Reeves DS, White LO, Holt HA, Bahari D, Bywater MJ, Bax RP. Human metabolism of cefotaxime. *J Antimicrob Chemother*. 1980;6(Suppl A):93-101. doi:10.1093/jac/6.suppl_a.93
16. Lüthy R, Münch R, Blaser J, Bhend H, Siegenthaler W. Human pharmacology of cefotaxime (HR 756), a new cephalosporin. *Antimicrob Agents Chemother*. 1979;16(2):127-133. doi:10.1128/AAC.16.2.127
17. Esmieu F, Guibert J, Rosenkilde HC, Ho I, Le Go A. Pharmacokinetics of cefotaxime in normal human volunteers. *J Antimicrob Chemother*. 1980;6(Suppl A):83-92. doi:10.1093/jac/6.suppl_a.83
18. Lüthy R, Blaser J, Bonetti A, Simmen H, Wise R, Siegenthaler W. Comparative multiple-dose pharmacokinetics of cefotaxime, moxalactam, and ceftazidime. *Antimicrob Agents Chemother*. 1981;20(5):567-575. doi:10.1128/AAC.20.5.567
19. Fillastre JP, Leroy A, Humbert G, Godin M. Pharmacokinetics of cefotaxime in subjects with normal and impaired renal function. *J Antimicrob Chemother*. 1980;6(Suppl A):103-111. doi:10.1093/jac/6.suppl_a.103
20. Ings RM, Reeves DS, White LO, Bax RP, Bywater MJ, Holt HA. The human pharmacokinetics of cefotaxime and its metabolites and the role of renal tubular secretion on their elimination. *J Pharmacokinet Biopharm*. 1985;13(2):121-142. doi:10.1007/BF01059394
21. Ko RJ, Sattler FR, Nichols S, et al. Pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with liver disease. *Antimicrob Agents Chemother*. 1991;35(7):1376-1380. doi:10.1128/AAC.35.7.1376
22. Wise R, Wright N, Wills PJ. Pharmacology of cefotaxime and its desacetyl metabolite in renal and hepatic disease. *Antimicrob Agents Chemother*. 1981;19(4):526-531. doi:10.1128/AAC.19.4.526
23. Chamberlain J, Coombes JD, Dell D, et al. Metabolism of cefotaxime in animals and man. *J Antimicrob Chemother*. 1980;6(Suppl A):69-78. doi:10.1093/jac/6.suppl_a.69
24. Limbert M, Seibert G, Schrinner E. The cooperation of cefotaxime and desacetyl-cefotaxime with respect to antibacterial activity and beta-lactamase stability. *Infection*. 1982;10(2):97-100. doi:10.1007/BF01816732
25. Harding SM, Monro AJ, Thornton JE, Ayrton J, Hogg MI. The comparative pharmacokinetics of ceftazidime and cefotaxime in healthy volunteers. *J Antimicrob Chemother*. 1981;8(Suppl B):263-272. doi:10.1093/jac/8.suppl_b.263
26. Patel KB, Nicolau DP, Nightingale CH, Quintiliani R. Pharmacokinetics of cefotaxime in healthy volunteers and patients. *Diagn Microbiol Infect Dis*. 1995;22(1–2):49-55. doi:10.1016/0732-8893(95)00072-i
27. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. *Br J Clin Pharmacol*. 2007;63(1):100-109. doi:10.1111/j.1365-2125.2006.02730.x
28. Abdulla A, Bahmany S, Wijma RA, van der Nagel BCH, Koch BCP. Simultaneous determination of nine β-lactam antibiotics in human plasma by an ultrafast hydrophilic-interaction chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2017;1060:138-143. doi:10.1016/j.jchromb.2017.06.014
29. (FDA) USFaDA. Guidance for industry: bioanalytical method validation 2013. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf
30. Karlsson MO, Savic RM. Diagnosing model diagnostics. *Clin Pharmacol Ther*. 2007;82(1):17-20. doi:10.1038/sj.clpt.6100241
31. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Dosages_v_11.0_Breakpoint_Tables.pdf March 2021
32. Swartling M, Smekal AK, Furebring M, Lipcsey M, Jönsson S, Nielsen EI. Population pharmacokinetics of cefotaxime in intensive care patients. *Eur J Clin Pharmacol*. 2022;78(2):251-258. doi:10.1007/s00228-021-03218-6

33. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin Pharmacokinet*. 2011;50(2):99-110. doi:10.2165/11539220-000000000-00000
34. Franken LG, Masman AD, de Winter BCM, et al. Hypoalbuminaemia and decreased midazolam clearance in terminally ill adult patients, an inflammatory effect? *Br J Clin Pharmacol*. 2017;83(8):1701-1712. doi:10.1111/bcp.13259
35. Urien S, Laurent N, Barre J, Druguet M, Bouvier D'yvoire M, Maire P. Pharmacokinetic modelling of cefotaxime and desacetylcefotaxime--a population study in 25 elderly patients. *Eur J Clin Pharmacol*. 2004;60(1):11-16. doi:10.1007/s00228-003-0725-9
36. Marsot A. Population pharmacokinetic models of first choice beta-lactam antibiotics for severe infections treatment: What antibiotic regimen to prescribe in children? *J Pharm Pharm Sci*. 2020;23:470-485. doi:10.18433/jpps30927
37. Koedijk JB, Valk-Swinkels CG, Rijpstra TA, et al. Pilot Study of the Pharmacokinetics of Cefotaxime in Critically Ill Patients with Acute Kidney Injury Treated with Continuous Renal Replacement Therapy. *Antimicrob Agents Chemother*. 2016;60(6):3587-3590. Published 2016 May 23. doi:10.1128/AAC.02888-15
38. Woksepp H, Hällgren A, Borgström S, et al. High target attainment for β-lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied. *Eur J Clin Microbiol Infect Dis*. 2017;36(3):553-563. doi:10.1007/s10096-016-2832-4
39. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. *J Antimicrob Chemother*. 2018;73(3):564-568. doi:10.1093/jac/dkx427

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Roelofsen EE, Abdulla A, Muller AE, et al. Dose optimization of cefotaxime as pre-emptive treatment in critically ill adult patients: A population pharmacokinetic study. *Br J Clin Pharmacol*. 2022;1-9. doi:10.1111/bcp.15487