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ORIGINAL ARTICLE

Physiologically based pharmacokinetic evaluation of cefuroxime in perioperative antibiotic prophylaxis

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Aims: Adequate plasma concentrations of antibiotics during surgery are essential for the prevention of surgical site infections. We examined the pharmacokinetics of 1.5 g cefuroxime administered during induction of anaesthesia with follow-up doses every 2.5 hours until the end of surgery. We built a physiologically based pharmacokinetic model with the aim to ensure adequate antibiotic plasma concentrations in a heterogeneous population.

Methods: A physiologically based pharmacokinetic model (PK-Sim®/MoBi®) was developed to investigate unbound plasma concentrations of cefuroxime. Blood samples from 25 thoracic surgical patients were analysed with high-performance liquid chromatography. To evaluate optimized dosing regimens, physiologically based pharmacokinetic model simulations were conducted.

Results: Dosing simulations revealed that a standard dosing regimen of 1.5 g every 2.5 hours reached the pharmacokinetic/pharmacodynamic target for *Staphylococcus aureus*. However, for *Escherichia coli*, >50% of the study participants did not reach predefined targets. Effectiveness of cefuroxime against *E. coli* can be improved by administering a 1.5 g bolus immediately followed by a continuous infusion of 3 g cefuroxime over 3 hours.

Conclusion: The use of cefuroxime for perioperative antibiotic prophylaxis to prevent staphylococcal surgical site infections appears to be effective with standard dosing of 1.5 g preoperatively and follow-up doses every 2.5 hours. In contrast, if *E. coli* is relevant in surgeries, this dosing regimen appears insufficient. With our derived dose recommendations, we provide a solution for this issue.

KEYWORDS

pharmacokinetics, pharmacokinetic–pharmacodynamic < pharmacodynamics < pharmacodynamics, antibiotics < infectious diseases

PI statement: The authors confirm that the Principal Investigator for this paper is Christian Lanckohr and that he had direct clinical responsibility for patients.

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1 | INTRODUCTION

Surgical site infections (SSI) are among the most common hospital-acquired infections, causing increased patient morbidity and mortality, as well as increased cost for healthcare systems.[1] Therefore, the prevention of SSIs is of paramount importance in the management of surgical patients. Contemporary strategies for the reduction of SSI-rates typically combine several different approaches into prevention *bundles*, e.g. aspects of skin preparation, disinfection, perioperative homeostasis and anti-infectives.[2-5] The perioperative application of parenteral antibiotics is a cornerstone in the reduction of postoperative infections and the efficacy of perioperative antibiotic prophylaxis (PAP) is well established in a wide range of surgical procedures. Various guidelines provide recommendations on the application of PAP.[6] Besides the choice of antibiotic to cover skin flora and the flora of the operative field, several pharmacological aspects must be considered to ensure adequacy of PAP. Typically, the antibiotic should be infused within approximately 60 minutes before skin incision, with repeated doses given after approximately 2 half-lives of the respective drug, if the surgery continues.[6-8] This practice recommendation reflects the tenet that concentrations of antibiotic in the operative field must be high enough to ensure eradication of pathogens that enter tissues because of the incision. As β-lactam antibiotics are the mainstay of PAP, the relevant pharmacokinetic (PK)/pharmacodynamic (PD) parameter is the fraction of time of the dosing interval (ƒT) that the free unbound antibiotic concentration remains higher than the minimal inhibitory concentration (MIC) of bacteria (ƒT > MIC) at the focus of infection.[9] In the absence of a widespread availability of therapeutic drug monitoring of antibiotic concentrations in plasma or tissues, dosing strategies of antibiotic therapies and prophylaxis are empirical, assuming efficacy for a wide range of different patients with standard doses.

Cefuroxime is a second-generation cephalosporin with widespread use in PAP. The half-life of cefuroxime is approximately 1.17 hours (70 min) in patients with normal renal function (glomerular filtration rate [GFR] 90–130 mL/min).[10] After initial doses of 1.5 g preoperatively, guidelines recommend a follow-up dose after 3–4 hours if the surgery continues beyond this period.[6,9] This recommendation is somewhat peculiar, as 2 half-lives of cefuroxime would rather mean a repetition after 2.5 hours and the span of 3–4 hours appears arbitrary. In addition, a considerable interindividual variation in the disposition of cefuroxime has been described.[10] In unfavourable circumstances (e.g. augmented renal clearance, increased blood loss), a reduction in cefuroxime concentration below the MIC of relevant pathogens might result in insufficient protection against SSI.

For cefuroxime, no relevant active distribution (e.g. P-glycoprotein transporter) or metabolism (e.g. cytochrome P-system) is known. A single dose of cefuroxime is excreted unchanged in the urine within 24 hours.[11,12] Superposition of literature concentration–time (CT) curves and the observed proportionality between area under the CT curve (AUC) and dosage[10] suggest linearity in the renal elimination. Application of probenecid as co-medication causes a significant decrease of cefuroxime clearance.[13-15] Cephalosporins have similar affinities for OAT-1 and -3 while the role of OAT-4, P-glycoprotein, MRP2/4 and NPT1 for renal absorption and excretion is at least questionable.[16,17] To gain insight into PK properties of cefuroxime used as PAP, we collected perioperative blood samples in patients undergoing thoracic surgical procedures. Cefuroxime concentrations were measured and used for building a physiologically based PK (PBPK) model with the aim to ensure adequate antibiotic protection in a heterogeneous population.

What is already known about this subject

- Cefuroxime is 1 of the standard drugs used in the field of perioperative antibiotic prophylaxis.
- Current guidelines recommend to administer cefuroxime 1.5 g intravenously before the start of surgery. Follow-up doses are recommended after approximately 2 half-lives.

What this study adds

- During surgery, a timely follow-up dose of 1.5 g cefuroxime after 2.5 hours is warranted to reach minimal inhibitory concentration targets of common pathogens of surgical site infection (e.g. *Staphylococcus aureus*).
- In case of pathogens with higher minimal inhibitory concentrations than *S. aureus* (e.g. *Escherichia coli*), a change in the dosing strategy with a prolonged infusion of cefuroxime should be considered.
- We provide simulated dosing regimens which should enable physicians to individualize perioperative antibiotic prophylaxis.

2 | METHODS

2.1 | Patient population

This study was conducted prospectively at the University Hospital Muenster after approval of the study protocol by the local ethics committee (Study Code 02-AnIT-12) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from 25 competent adult patients scheduled for routine thoracic surgery with intercostal thoracotomy. Exclusion criteria were an allergy to cephalosporine, end-stage renal failure and preoperative application of any antibiotic within 7 days. Patients were recruited on the day before surgery. Age, height, weight and sex were recorded during the preoperative visit. Laboratory measurements of creatinine, urea, albumin and protein were performed on the day of surgery from blood samples drawn at incision.

2.2 | Administration of cefuroxime

During intravenous induction of anaesthesia (followed by inhalational maintenance), a dose of 1.5 g cefuroxime (Fresenius Kabi, Germany) was administered intravenously over 10–15 minutes. A follow-up dose of 1.5 g cefuroxime was given every 2.5 hours (150 min) until wound closure (standard dosing regimen at the University Hospital Muenster). No postoperative applications of antibiotic were prescribed in accordance with local standards.

2.3 | Blood sampling for cefuroxime measurement

Blood samples were exclusively drawn from an arterial line into ethylenediaminetetraacetic acid-containing tubes (S-Monovette 2.7 mL K3E, Sarstedt, Nuembrecht, Germany) at the following time points: 10 minutes after the initial dose, at incision, shortly before each successive dose of cefuroxime, 10 minutes after every repetition dose and at skin closure. These acquisition points represent peak and trough concentrations of cefuroxime with samples at incision and wound closure providing additional information between these instances. In several patients, supplementary blood samples were collected during the operation. Cefuroxime concentrations of these extra blood samples were included into the PK analyses.

2.4 | Cefuroxime assay

For sample preparation the blood was centrifuged (10 min, 2500 *g*) and 200 µL plasma were transferred; 4 µL internal standard solution (cefazolin 1 mg/mL in water) and 500 µL acetonitrile were added and vortex-mixed (15 s) followed by centrifugation at 12 000 *g* for 3 minutes. The supernatant was transferred and extracted with 500 µL chloroform; 50 µL of the upper phase was injected into the high-performance liquid chromatograph. For separation and detection of cefuroxime a reversed-phase column (XTerra RP18, 3.5 µm, 150 × 4.6 mm, Waters GmbH, Eschborn, Germany) on a 125 liquid chromatograph (Beckman Coulter GmbH, Krefeld, Germany) interfaced with a model 168 diode array detector was used. As mobile phase an acetonitrile/50 mM sodium hydrogen phosphate buffer pH 2.4, 25:75 (v/v) and an isocratic flow of 1 mL/min was applied. Inter-assay and intra-assay coefficients of variation were <10% for each quality control samples. Linearity was observed in the validated concentration range of 1 to 300 mg/L (r^2 = 0.99). The lower limit of quantification was 1 mg/L.

3 | PK ANALYSES

3.1 | Software

PBPK models were built using PK-Sim® and MoBi® version 7.0.0, which are part of the Open Systems Pharmacology software package (http://www.open-systems-pharmacology.org/). Parameter identifications were conducted with the MoBi Toolbox for MATLAB® version 8.0.0, release 2012b (The MathWorks, Inc., Natick, MA, USA; http://www.mathworks.de/products/matlab/). A more detailed insight into software PK-Sim® is given by Eissing *et al.*[18] and Willmann *et al.*[19,20] The software R (version 3.4.0, R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) was used for PK-analyses, statistical analyses and graphics creation. The software SigmaPlot® version 12.5 (© 2011 Systat Software, Inc) for 2 ANOVA testing.

3.2 | Model building—evaluation

Each step in the model building process was evaluated by comparing simulation results with observed in vivo PK data taken from the literature or measured in the study, considering the European Medicines Agency guideline on the qualification and reporting of PBPK modelling and simulation.[21] For each step in the workflow, the model predictions were visually inspected against the observed data using visual predictive checks, goodness of fit (GOF) and relative-residuals-*vs*-observed-concentrations plots.[22] Percentage error (PE) and absolute PE (APE) were calculated for every concentration point according to Equations (1 and 2):

$$PE\ [\%] = \frac{(C_{pred} - C_{obs})}{C_{obs}} \times 100 \quad (1)$$

$$APE\ [\%] = \frac{|C_{pred} - C_{obs}|}{C_{obs}} \times 100 \quad (2)$$

where C_{pred} is the PBPK-simulated plasma concentration of cefuroxime and C_{obs} is the actual concentration of cefuroxime. Additionally, mean PE (MPE) to quantify the bias and mean APE (MAPE) were calculated to quantify the precision.[23] PK parameters such as AUC and maximum plasma concentration (C_{max}) were also used for model evaluation by comparison with published AUC values extrapolated to infinity (AUC_{inf}) or calculated to the last simulated time point in the respective study. The relative changes in AUC and C_{max} were calculated on the basis of Equation 1.

3.3 | Model building—healthy adults

For model building we used a generally accepted procedure.[24] Based on a literature search, the physicochemical properties, the (absorption), distribution, metabolism, excretion behaviour of cefuroxime in healthy adults as well as their physiological anthropometric values were matched together (Figure 1). First, an initial PBPK model was developed for healthy adults receiving various dosing regimens of cefuroxime. Virtual twins (a virtual twin is an in silico generated counterpart based on given physiological factors) matched the anthropometric measures of the patient group in the comparison studies (Table S1). As GFR, either GFR from the literature or estimated GFR (eGFR) values calculated by CKD-EPI [25] were used. If no GFR or serum creatinine values were available, we assumed 120 mL/min/1.73m^2 for healthy adults. In both cases we considered body surface area, using

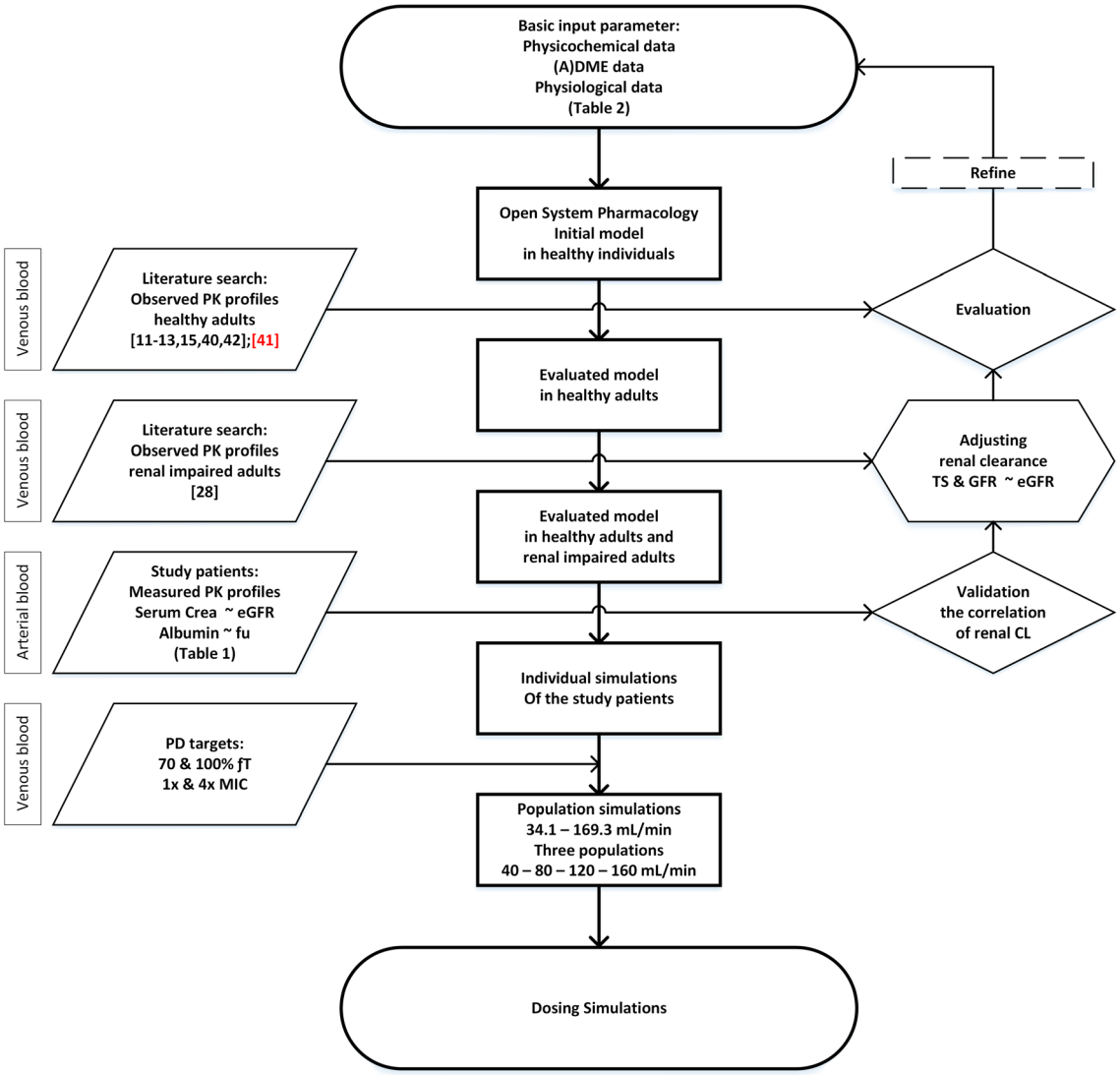

FIGURE 1 Schematic workflow of the cefuroxime physiologically based pharmacokinetic model development and verification. Each step of the model development follows the arrows top down starting with basic input parameters from the literature. The final model input parameters are given in Table 2. The left parallelograms visualize which pharmacokinetic profiles were used to evaluate the respective step in the model development. The red reference represent the study used for an internal validation of the model. The pharmacodynamic targets are the respective time interval above the minimal inhibitory concentrations. Right side: each step was evaluated with the help of goodness of fit plots and calculated prediction errors. Refinements of the basic input parameter were only done if necessary and physiologically plausible. The adjustment of the individualized renal clearance in relation to the estimated glomerular filtration could be confirmed with the study patients' pharmacokinetic profiles. Final dosing simulations were performed on the basis of the three renal clearance groups. (A)DME, (absorption), distribution, metabolism and excretion; CL, clearance; eGFR, estimated glomerular filtration rate (CKD-EPI); ƒT, fraction of time of the dosing interval; fu, fraction unbound; GFR, glomerular filtration rate (model input parameter); MIC, minimal inhibitory concentration; TS, tubular secretion (model input parameter)

the equation described by Dubois and Dubois,[26] to correct the standardized eGFR.

The standard GFR of the virtual twin ($sGFR_{v\text{-}twin}$) can be calculated using PK-Sim® specific values for the GFR ($GFR_{specific}$) and the kidney volume of the virtual twin ($V_{k\text{-}v\text{-}twin}$) Equation (3):

$$sGFR_{v-twin}\left[\frac{mL}{min}\right] = GFR_{specific}\left[26.6\,\frac{mL}{min \times 100g\ organ}\right] \times V_{k-v-twin}\,[dL] \tag{3}$$

The $sGFR_{v\text{-}twin}$ calculated by PK-Sim® was corrected using the fraction of the eGFR ($GFR_{fraction}$) and $sGFR_{v\text{-}twin}$ to achieve the same passive renal elimination in silico, as in the literature or later in our study patients Equation (4):

$$GFR_{fraction} = \frac{eGFR\ [mL/min]}{sGFR_{v-twin}} \tag{4}$$

The remaining tubular secretion via OAT-transporter (integrated as tubular secretion) was fitted via parameter identification using the integrated Monte-Carlo algorithm within PK-Sim® for all studies. The obtained mean value for healthy adults was used for simulations.

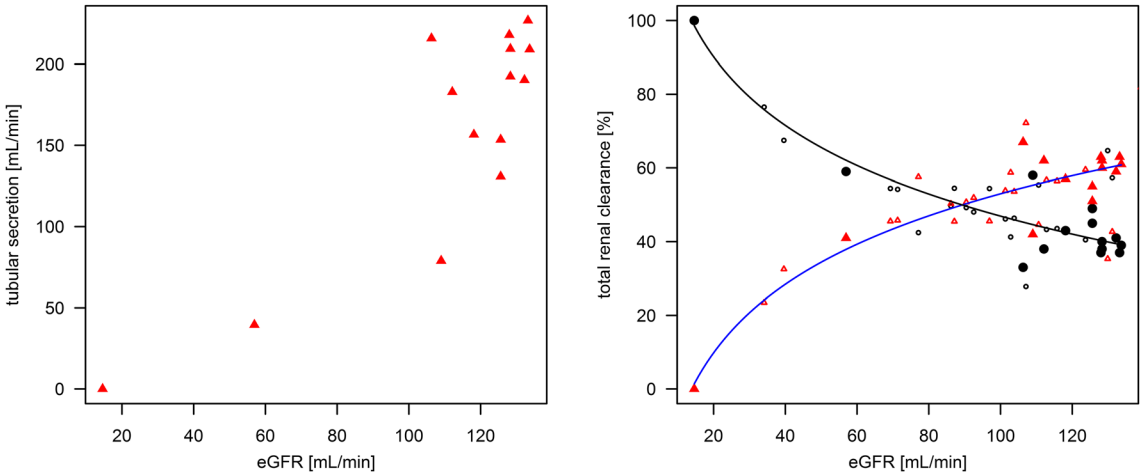

FIGURE 2 Calculation of the total renal clearance as a function of the estimated glomerular filtration. Left side: fitted tubular secretion plotted against the described estimated glomerular filtration (eGFR). Right side: percentage of the glomerular filtration and tubular secretion in relation to the total renal clearance plotted against their estimated glomerular filtration values. The blue regression line was used for calculation of the renal clearance (equations 5, 6). Filled circles represent eGFR taken from the literature, filled triangles represent the remaining renal clearance described as tubular secretion fitted against literature concentration-time profiles (literature values are described in Table 3), open triangles symbolize the estimated glomerular filtration obtained from the study population, open circles visualize the fitted tubular secretion obtained from the study population, blue and black line: ratio between glomerular filtration and tubular secretion as a function of the eGFR

3.4 | Model building—renally impaired adults

The model was then scaled to renally impaired individuals. Drug-specific parameters (e.g. molecular weight and lipophilicity) were not changed. With a deteriorating kidney function of 50 mL/min or less, cefuroxime is completely eliminated by glomerular filtration,[27] indicating that tubular secretion does not contribute to the renal elimination in case of renal impairment. To describe the decreasing function of the OAT-systems in renal impairment, the tubular excretion was implemented according to available literature values.[28,29] In Figure 2a, the fitted tubular secretion is plotted against the described eGFR. In Figure 2b, the percentage of the GFR and tubular secretion (TS [%]) in relation to the total renal clearance are plotted against their eGFR values.

A log-regression function (blue line) yields the best coefficient of determination (R^2 = 0.8662). The obtained equation describes the TS [%] in relation to the total renal elimination, as a function of the corresponding eGFR value (Equation 5):

$$TS\ [\%] = 26.8^{*}\ln(eGFR[mL/min]) - 70.6 \quad (5)$$

The TS in [mL/min] can be calculated using the eGFR [mL/min] and considering the ratio between TS [%] and eGFR [%].

To adjust the calculated TS [mL/min] from the literature or study patients and the virtual twin ($TS\ [mL/min]_{v\text{-}twin}$), the ratio of the standard kidney volume (V_{ks} = 0.44 L; a PK-Sim® specific value) and the $V_{k\text{-}v\text{-}twin}$ was considered as follows Equation (6):

$$TS\ [mL/min]_{v-twin} = TS\ [mL/min]^{*}\frac{V_{ks}[dL]}{V_{k-v-twin}[dL]} \quad (6)$$

The correlation of renal clearance (Equation 5) obtained through regression analyses is lacking, especially at lower kidney functions. We used our study population to confirm this equation using the above described procedure. The open symbols in Figure 2b present the optimal clearance values derived via parameter identification using the integrated Monte-Carlo algorithm within PK-Sim®.

In the ESM (electronic supplementary material), an example calculation for a theoretical 30-year-old person with a kidney function of 115 mL/min is given.

3.5 | Model building—study patients' individual simulation

In a next step, the evaluated model for healthy and renal impaired adults was used to simulate the study patients. The low albumin concentrations in our study population leads to a possible change in protein binding compared to a healthy adult population.

Serum protein binding of cefuroxime is described as a fraction unbound (fu) of 0.67[12,14] with reported values ranging from 0.5 to 0.91. [30-33]These discrepancies may result from different *in vivo* or *in vitro* testing systems or different populations with altered albumin concentrations.

To calculate the individual fu (fu_i) for each patient, we used an approach described by Radke *et al.* [22]and Dallmann *et al.* [34]Individual albumin ($[Albumin]_i$) concentrations and the modified equation described by McNamara *et al.*[35] with the average fraction unbound (fu_a) of 0.67[12] and 4.5 mg/dL being the average albumin concentration ($[Albumin]_a$) in healthy adults [35]were used Equation (7):

$$fu_i = \frac{1}{1 + \frac{[Albumin]_i}{[Albumin]_a} * \frac{(1 - fu_a)}{fu_a}} \quad (7)$$

The plasma unbound concentration of cefuroxime was calculated with the aid of the generated fu_i and the measured total plasma concentrations.

3.6 | Model building—study patients' population simulation

In a last step, a population with 5000 individuals was built corresponding to the study patients' characteristics. For final dose recommendations, this population was split into three groups with defined ranges of GFR: mild renal impairment (40–<80 mL/min) = low, no renal impairment (80–<120 mL/min) = normal and increased clearance (120–160 mL/min) = increased. To calculate the renal clearance, PK-Sim correlates a defined average clearance with the kidney volume (Equations 3 and 6). Each of the populations contain individuals with kidney volumes resulting in GFR and TS values within the predefined ranges. Each built population finally compromises >2000 individuals (low = 4564; normal = 3796 and increased = 3189).

3.7 | PD target of cefuroxime as a β-lactam antibiotic

We chose *Staphylococcus aureus* and *Escherichia coli* as model organisms for the definition of MIC-ranges as they represent common pathogens of SSI in various types of surgeries.[6,36] *S. aureus* is particularly relevant in *clean* surgical procedures, while *E. coli* is a concern in *clean–contaminated* procedures where the alimentary tract is opened during surgery. The respective MIC values were taken from EUCAST Clinical Breakpoint Tables.[37]

The recommended PD target for time-dependent antibiotics is the ƒT of the dosing interval for the free unbound drug above the MIC.

We chose 2 and 8 mg/L as the simple MIC (1 × MIC), as well as 8 and 32 mg/L as 4 times the MIC (4 × MIC) representing *S. aureus* and *E. coli* infections, respectively. For the ƒT above the MIC, we chose only bactericidal criteria of 70 and 100%. Six targets were evaluated (70% ƒT > 2 mg/L, 70% ƒT > 8 mg/L, 70% ƒT > 32 mg/L, 100% ƒT > 2 mg/L, 100% ƒT > 8 mg/L and 100% ƒT > 32 mg/L).

3.8 | Dosing strategies

We tested different dosing regimens (bolus *vs* prolonged infusion), for three different kidney populations matching the anthropometric characteristics of our study population (see Model building):

Bolus	Prolonged infusion	Bolus + prolonged infusion
1 g every 1 h	3 g over 3 h	0.5-g bolus + 3 g over 3 h
1.5 g every 2.5 h	4.5 g over 3 h	1-g bolus + 3 g over 3 h
4.5 g at start of surgery		1.5-g bolus + 3 g over 3 h

Furthermore, we set an upper limit of 3 × 1.5 g cefuroxime over 7.5 hours, as this was the maximum amount of antibiotic used and the longest duration of surgery observed in this study population.

3.9 | Sensitivity analyses

Sensitivity analyses were performed on the cefuroxime model to investigate the impact of single model parameters on the predicted AUC_{inf} and C_{max} at the first dose interval given a 1.5-g dose. Parameters were included into the analysis if they have been optimized, if they could have a strong influence on the PK due to their use in calculation of permeabilities or partition coefficients (e.g. fraction unbound). Sensitivity is calculated as the ratio of the relative change of the simulated AUC_{inf} according to Equation 8:

$$S = \frac{\Delta AUC}{AUC} \tag{8}$$

where S is the sensitivity of the AUC to the tested model parameter, ΔAUC is the change of the AUC, and AUC is calculated with the original model parameter value. Sensitivity analyses were performed using a relative perturbation of ±100%. For body weight and height, a relative perturbation of ±10% and for logP and pKa the corresponding values were changed with ±1. This means a 10-fold change due to the octanol:water ratio or the concentration of the oxonium ion!

4 | RESULTS

4.1 | Patient demographics

In total, 25 surgical patients treated with cefuroxime were enrolled yielding a total of 135 blood samples. No measured concentration fell below the lower limit of quantification. Twenty-two patients received a second follow-up dose. Detailed demographic data and patient characteristics are summarized in Table 1.

4.2 | Evaluation of the model

The relevant input parameters for the PBPK-model are given in Table 2. The final model was able to accurately describe cefuroxime exposure after bolus and extended infusions for the literature CT curves. Only C_{max} values were slightly underestimated by the model,

TABLE 1 Patient characteristics

Parameters	Median (range)
Age [y]	59 (18–77)
Actual body weight [kg]	80 (53–120)
Height [cm]	176 (160–193)
Male [%]	68
Albumin [g/dL]	3.6 (3.1–4.2)
eGFR [mL/min][a]	103.8 (34.1–169.3)
fu_i[b]	0.72 (0.69–0.75)
Administered dose [g]	1.5
Infusion duration [h]	i.v. bolus
Repetition every [h]	2.5
Time of application of cefuroxime to incision [h]	0.8 (0.2–2)
Time from incision to skin closure [h]	3.6 (0.92–6.55)

N = 25 with overall 135 plasma concentrations

[a]eGFR calculated according to CKD-EPI and Dubois–Dubois

[b]Fraction unbound calculated for each individual

TABLE 2 Summary of input parameters for the physiologically based pharmacokinetic model of cefuroxime

Parameters	Value	References
Model settings	Standard model for small molecules	
Model parameters: Partition coefficient	PK-Sim standard	
Model parameters: Cellular permeabilities	PK-Sim standard	
Molecular weight [g/Mol]	424.4	[38]
Lipophilicity [log units]	−0.9	[39]
fu_i	0.71[a]	[12,35]
pK_a	3.15	[39]
eGFR [mL/min]	34.1–169.3	[25]
Tubular secretion [mL/min]	10–339	According to[29] calculation equations 5, 6

fu_i mean fraction unbound individual, GFR glomerular filtration rate, pK_a negative decadic logarithm of acid dissociation constant,

[a]for population simulations only the mean fraction unbound was used and not the range as described in Table 1, due to a native variance of albumin concentrations in population simulations

especially concerning low dosages. The more clinically relevant subpopulation with three different levels of kidney function leads to a good visual representation as well as MPE and MAPE values of 2.8% and 28.4%, respectively. A summary for the quality of prediction for literature and study patients is presented in Table 3.

The GOF plots for literature, individual and population simulations are depicted in Figure 3 (Figure S3 represent the GOF plots for the urine fractions). In contrast to the literature, the individual simulations of our study collective show a slight over prediction due to lower plasma concentrations. About 97.2% of all literature, 87.4% of all individual and 86.7% of all population predictions lie within the ±50% error range of the observed plasma concentrations. In total 99.3% of all literature, 96.3% of all individual and 94.8% of all population predictions are located in the ±100% error range (calculation in accordance to Equation 1). The results of sensitivity analyses (Figure S1) and literature-simulated CT curves vs observed CT points (Figure S6) are given in the ESM.

4.3 | Simulations of the study population

The final PBPK model provides good individual predictions with a MPE of −1.1% between predicted and observed concentrations. The MAPE of 27.8% illustrates the large heterogeneity of our study population and quantifies the precision of the model. Using one population representing all levels of kidney function leads to an adequate visual prediction (Figure 4a, b). As a result, most of the measured plasma concentrations are located in the shaded area. No measured concentration fell below the MIC of 2 mg/L. Three of 135 plasma unbound samples fall short of the MIC of 8 mg/L, while 49 samples fell below the MIC of 32 mg/L (Figure 4c). Considering different PK targets for *E. coli*, 10.1% (100% ƒT > MIC), 90.3% (70% ƒT > 4 × MIC) and 97.4% (100% ƒT > 4 × MIC) of the simulated population does not fulfil criteria for bactericidicity during the first dosing interval (yellow, green and orange vertical line in Figure 4c). Protection against *S. aureus* is considerably better, with only 10.1% of the population not reaching bactericidicity targets for the strictest requirements (100% ƒT > 4 × MIC; Figure S4 linear y-axes ESM).

4.4 | Simulated dosing regimes

A dosing regimen of 1.5-g bolus immediately followed by a 3 hours extended infusion of 3 g cefuroxime and the standard application scheme (Figure 5) showed the longest protection times.

TABLE 3 Bias and precision for the final physiologically based pharmacokinetic model and comparison between literature and simulated pharmacokinetic parameters

	Dose [mg]	Administration	MPE [range] [%] Plasma	MPE [range] [%] Urine	MAPE [%] Plasma	MAPE [%] Urine	Relative error [%] AUC	Relative error [%] C_{max}	Source
Literature	250	i.v. bolus	−14.7 [−52.4–1.1]	−16.4; [−17.9 – −14.1]	15.0	16.4	−20.2	−51.0	[12]
	500	i.v. bolus	1.7 [−44.4–26.3]	6.6 [2.6–9]	15.8	9.0	−6.1	−26.2	[11,12]
	750	i.v. bolus	2.9 [−55.6–49.3]	−6.2 [−26.9–13.1]	14.4	7.7	0.6	−19.6	[11,28,40,41]
	1000	i.v. bolus	7.9 [−25.8–104.7]	−2.5 [−3.9 – −0.8]	16.5	2.5	6.9	−21.7	[12,41]
	1500	i.v. bolus	0.9 [−34.1–41.7]	-	18.1	-	6.1	−8.7	[40,41]
	664	i.v. 240 min	−5.1 [−46.3–33.1]	-	17.9	-	-	6.1	[41]
	750	i.v. 20–30 min	5.3 [−52.4–42.5]	-	20.4	-	−2.4	−15.7	[13,42]
	1500	i.v. 20–30 min	12.8 [−36.5–57.2]	-	21.9	-	6.8	−0.6	[13,15]
	Weighted average		2.8	−3.5	16.7	8.7	0.3	−17.2	
Patients	3 × 1500	i.v. bolus	−1.1 [−52.2–103.8]	-	27.8	-	-	-	Individual
	3 × 1500	i.v. bolus	11.0 [−71.5–359.2]	-	38.7	-	-	-	One-population
	3 × 1500	i.v. bolus	2.8 [−60.6–149.1]	-	28.4	-	-	-	Split-population

MAPE, mean absolute prediction error; MPE, mean prediction error; One-population, kidney level ranging from 40–160 mL/min; Split-population, 3 different kidney levels ranging from 40–<80, 80–<120 and 120–160 mL/min; area under the concentration–time curve (AUC) calculated to last simulated time point for the respective study with the exception of AUC to infinity for Kågedal *et al.*[15] C_{max}, maximum plasma concentration

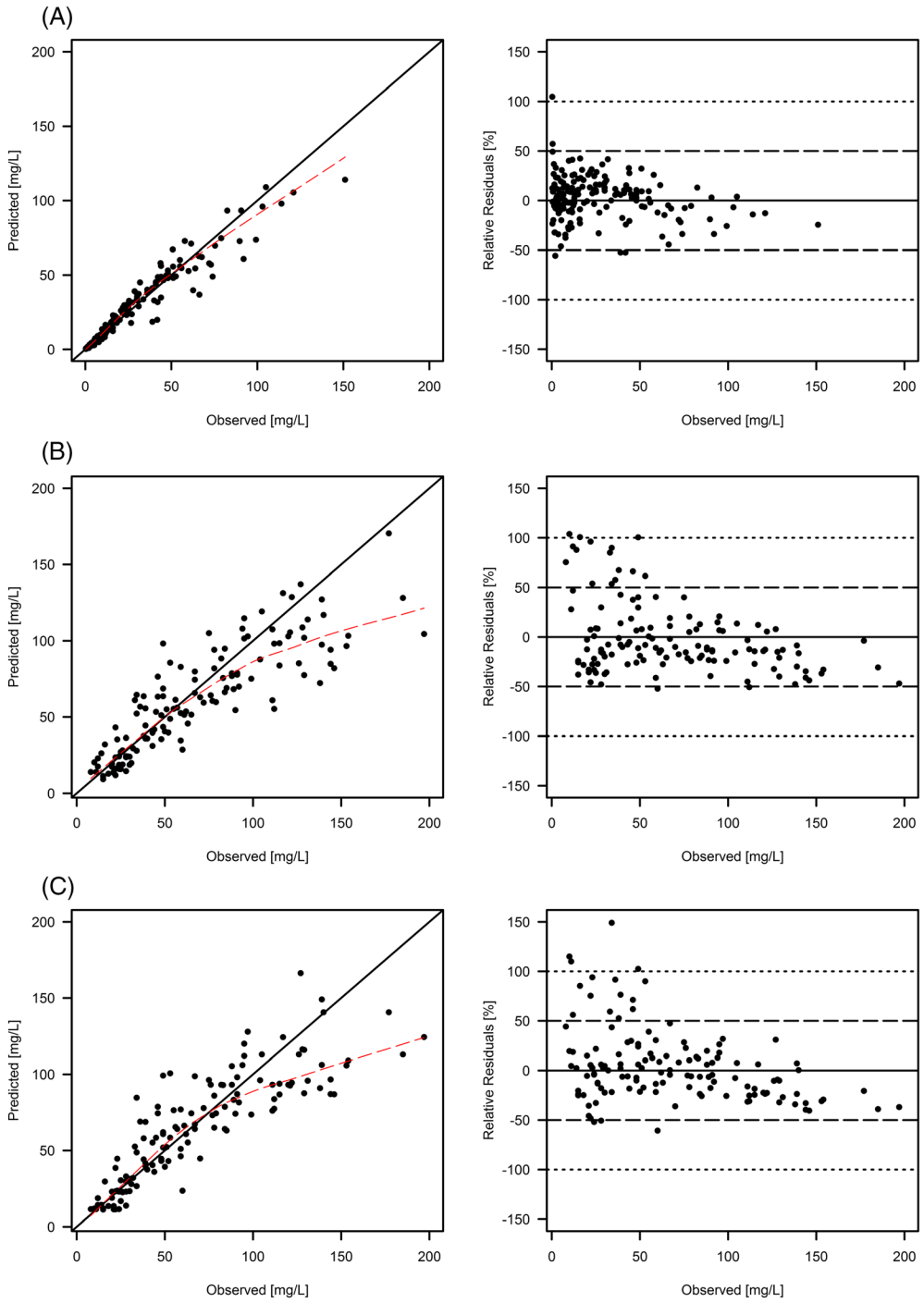

FIGURE 3 Goodness of fit plots and relative residuals *vs* concentration plots for cefuroxime plasma concentrations used for model evaluation. (A) literature concentration–time curves (venous compartment); (B) individual simulations from the study patients (arterial compartment); (C) population simulations (3 subgroups of 40–<80, 80–<120, 120–160 mL/min estimated glomerular filtration) for the study population (arterial compartment); goodness-of-fit legend: black line: Line of identity, red line: Trendline indicating a possible trend, relative residuals-legend: The solid black line indicates the line of identity, dashed lines indicate ±50% range, dotted lines indicate ±100% range, filled circles (A) literature concentration time points, or (B, C) measured plasma concentrations

For *S. aureus* coverage, bolus application provides protection for more than 4.5 hours, considering the lowest target conditions (70% ƒT > MIC) irrespective of kidney function. A higher MIC target (70% ƒT > 4 × MIC) decreases protection time to 2.6 hours. Prolonging the ƒT above the MIC to 100% of the dosing interval, bolus dosing leads to a protection of 3.2 hours when considering standard MIC-values (100% ƒT > MIC). Considering the strictest requirements (100% ƒT > 4 × MIC), protection is decreased to 1.8 hours in the highest clearance group (Table 4). A continuous infusion of cefuroxime does not significantly improve target

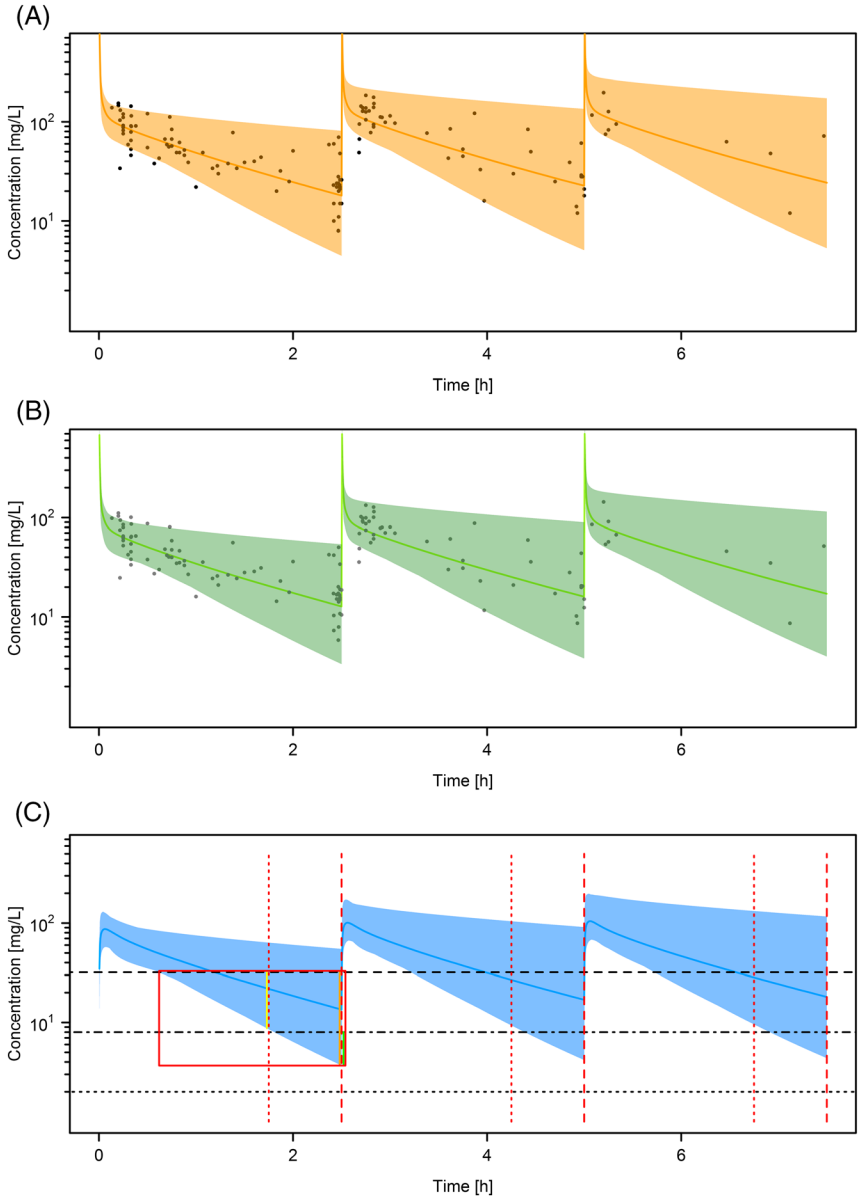

FIGURE 4 Simulated cefuroxime plasma concentration–time profiles of the physiologically based pharmacokinetic model. (A) Arterial plasma concentrations after intravenous administration of 1.5 g every 2.5 hours; (B) unbound arterial plasma concentrations after intravenous administration of 1.5 g every 2.5 hours; (C) unbound venous plasma concentrations after intravenous administration of 1.5 g every 2.5 hours. Black points: measured plasma concentrations; grey points: individual calculated plasma unbound values according to individual albumin levels; orange, green and blue solid lines: population median; orange, green and blue area: range of the kidney levels (34.1–169.3 mL/min), red dotted lines: 70% ƒT, red dashed lines: 100% ƒT, black dotted line: minimal inhibitory concentration (MIC) at 2 mg/L, black dotted/dashed line: MIC at 8 mg/L, black dashed line: MIC at 32 mg/L, red box: The potentially underdosed population—yellow vertical line: underdosed proportion of the population for 70% ƒT > 4 × MIC; green vertical line: underdosed proportion of the population for 100% ƒT > MIC; orange vertical line: underdosed proportion of the population for 100% ƒT > 4 × MIC target

attainment in these circumstances, as a timely repetition after 2.5 hours will be sufficient in the majority of patients.

When taking PK targets for *E. coli*, the standard dosing regimen appears to be insufficient (Table 4). In the lowest target conditions (70% ƒT > MIC), a bolus only strategy provides protection for >2.6 hours, even in patients with increased kidney function. Protection time is markedly shorter when assuming increased ƒT over MIC (100% ƒT > MIC) or increased MIC targets (70% ƒT > 4 × MIC and 100% ƒT > 4 × MIC). Even decreased kidney function does not extend target attainment to acceptable levels.

Much longer times of protection for all targets can be reached with a prolonged infusion of cefuroxime (Figure 5). To exceed the MIC rapidly, a 1.5-g bolus injection (*loading dose*) is necessary before initiation of prolonged infusion. Table 4 shows that the desired time of protection can be reached with this administration protocol. Due to a negligible time of crossing the MIC targets after bolus infusion, the coverage until the end of infusion is about 3 hours shorter. A remaining protection of 0.2 hours shows the necessity of a further 1 g/h until the surgery ends in the highest clearance group with the strictest targets for *E. coli*. For the other kidney function groups accumulation processes should be considered. Lower MIC targets (70% ƒT > 4 × MIC or 100% ƒT > MIC in *S. aureus* coverage) do not necessitate a prolonged infusion and redosing every 2.5 hours appears adequate (Figure S5 linear y-axes ESM).

5 | DISCUSSION

The prevention of SSI is an important component of perioperative medicine. The application of antibiotics as PAP is part of a multifactorial prevention bundle and should be performed in an optimal fashion.

To better characterize the PK properties of cefuroxime in PAP, we used literature data on various aspects of cefuroxime disposition and excretion to build a PBPK model of cefuroxime. The PBPK model was able to accurately describe and predict the PK of cefuroxime. In

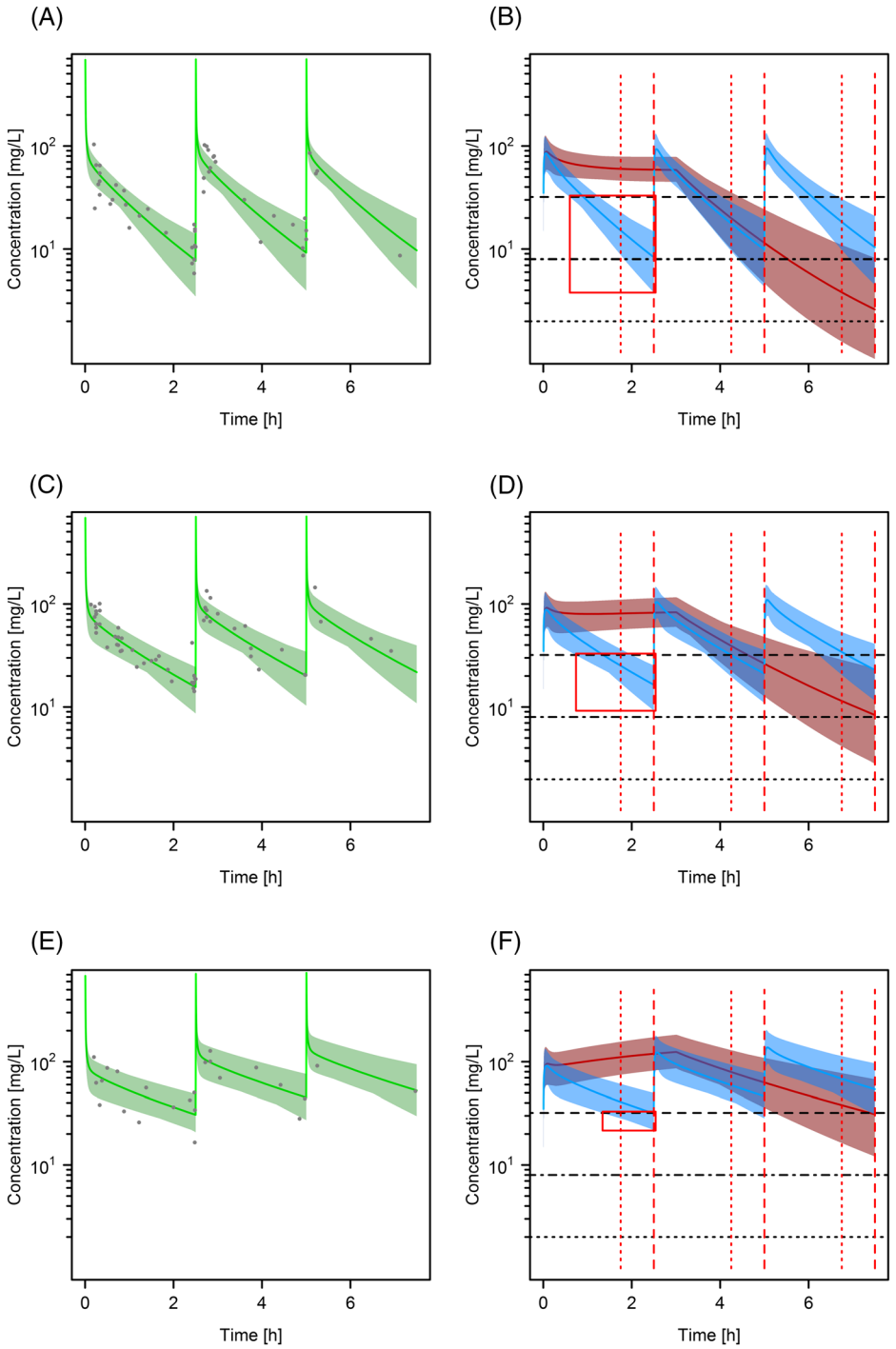

FIGURE 5 Simulated cefuroxime plasma concentration–time profiles on the basis of the 3 populations defined by estimated glomerular filtration rate (40–<80, 80–<120, 120–160 mL/min). In (A), (C) and (E) simulated cefuroxime arterial plasma unbound concentrations after intravenous administration of 1.5 g every 2.5 hours are visualized. In (B), (D) and (F) simulated cefuroxime venous plasma unbound concentration after intravenous administration of 1.5-g bolus every 2.5 hours and 1.5-g bolus immediately followed by a continuous infusion of 3 g cefuroxime over 3 hours are given. Grey points: individual calculated plasma unbound values; green, red and blue solid lines: population median; green, blue and red areas: range of the defined kidney levels ([A, B] 120–160 mL/min, [C, D] 80–<120 mL/min, [E, F] 40–<80 mL/min); red dotted lines: 70% ƒT; red dashed lines: 100% ƒT; black dotted lines: minimal inhibitory concentration (MIC) at 2 mg/L; black dotted/dashed lines: MIC at 8 mg/L; black dashed lines: MIC at 32 mg/L; red box: possible underdosed part of the population

contrast to previously published cefuroxime models,[14,34] we were able to describe a large range of renal clearances in our study group using Equations 3–6. With the help of these equations, we integrated the changing ratio between GFR and TS in a physiological way. A possible explanation for the slight underprediction of our study patients compared to healthy individuals from the literature could be that factors linked to the surgery itself influencing the distribution and clearance (e.g. infusions of crystalloid fluids) are not fully considered in the model.

TABLE 4 Time of protection depending on the kidney status

		1.5 g bolus		1.5 g bolus +3 h infusion 3 g	
Kidney function		Duration of protection [h]			
		70% ƒT	100% ƒT	70% ƒT	100% ƒT
Increased	MIC 32 mg/L	0.8	0.6	4.6	3.2
	MIC 8 mg/L	2.6	1.8	6.4	4.5
	MIC 2 mg/L	4.5	3.2	8.6	6.0
Normal	MIC 32 mg/L	1.0	0.7	5.4	3.8
	MIC 8 mg/L	3.8	2.7	8.1	5.7
	MIC 2 mg/L	6.8	4.7	11.9	8.3
Low	MIC 32 mg/L	1.9	1.4	7.5	5.2
	MIC 8 mg/L	6.5	4.6	12.3	8.6
	MIC 2 mg/L	11.8	8.3	20.3	14.2

MIC, minimal inhibitory concentration: 8 and 32 mg/L against *E. coli*; 2 and 8 mg/L against *S. aureus*; 70% ƒT and 100% ƒT required percentage time of the dosing interval above the MIC; increased = eGFR 120–160 mL/min, normal = eGFR 80–<120 mL/min, low = eGFR 40–<80 mL/min; red numbers, potentially difficult times of coverage

Furthermore, we found kidney function to be the most relevant individual factor influencing cefuroxime concentrations. Sex and patient weight do not have a clinically relevant influence on plasma concentrations during the time of PD targets (see ESM: Evaluation of factors influencing the PK; Figure S2). Similar results were obtained through the sensitivity analyses (see ESM: Sensitivity analysis). Here, also the logP (a surrogate for the lipophilicity) showed an effect on the model performance.

In a next step, the model was used to examine the PK adequacy of 1.5 g cefuroxime given preoperatively with strict repetition every 2.5 hours. We considered *S. aureus* and *E. coli* with their respective MICs as two relevant pathogens associated with surgical site infections. Furthermore, we choose bactericidicity as the PD target. For a bactericidal effect, the concentration of the free drug in the targeted tissue should exceed the pathogens' MIC for approximately 60–70% of the dosing interval (70% ƒT > MIC). It is also recommended that blood concentrations should exceed the MIC by a factor of 4–6 (4 × MIC) in order to reach the maximum rate-of-killing effect.[43,44] Recent clinical studies were able to demonstrate that the translation of these in vitro suggestions to clinical scenarios leads to better outcomes, especially for patients with Gram-negative infections.[45-48] In fact, longer durations above the MIC up to 100% ƒT > MIC are correlated with higher rates of survival and significantly greater clinical cure.[49-51] Some of these studies also demonstrated that 2.1 or 4.3 × MIC leads to better microbiological success and lower risk of clinical failure.[45,46] Accordingly, Heffernan *et al*. suggested that for optimal outcomes and the avoidance of resistance induction 100% ƒT > 2–5 × MIC is required.[48]

Considering these PD-assumptions for β-lactam drugs, we found that the standard application scheme for cefuroxime generates bactericidal plasma concentrations for *S. aureus* in all patients over a wide range of kidney functions. Guidelines recommend a redosing after approximately 2 half-lives.[6] As cefuroxime half-life is approximately 70 min, redosing after 2.5 hours thus seems adequate to protect against *S. aureus* infection.

A different outcome was found when taking MIC values of *E. coli* into account. A considerable proportion of patients fail to reach bactericidicity criteria for *E. coli*. This finding is particularly pronounced during the first dosing interval, while an accumulation of cefuroxime elevates drug concentrations after the second and third application of cefuroxime. Our finding of insufficient exposure of cefuroxime with regard to the MIC of *E. coli* raises the question of adequacy of this antibiotic in a setting where this pathogen poses a risk. Surgical site infection in clean thoracic surgery targeting lung tissue is not often associated with this Gram-negative enterobacterium.[6] However, surgeries concerning the gastrointestinal tract are associated with a high local inoculum and carry a considerable risk of perioperative infections with *E. coli*. Therefore, standard dosing schemes of cefuroxime appear unsuitable in this setting especially if follow-up doses are delayed or forgotten or other factors lowering cefuroxime concentrations occur (e.g. blood loss, infusion of large volumes of fluid, augmented renal clearance).

Besides a timely repetition of PAP, an application scheme considering PK properties of cefuroxime as a β-lactam might be helpful to reduce the number of patients at risk of underdosing. As a time-dependent antibiotic, a bolus directly followed by continuous application during surgery might offer advantages. Using our model, we could show an improvement of *E. coli* coverage by using a 1.5-g bolus of cefuroxime directly followed by a continuous infusion of 3 g cefuroxime over 3 hours. In long-lasting surgeries, an extension of the continuous infusion appears pragmatic and feasible. The beneficial effects of prolonged or continuous infusion of β-lactam antibiotics have recently been demonstrated.[52] In any inoculum, pathogens occur with elevated MICs beyond clinical breakpoints for *sensitive*. In this case, a prolonged infusion might be beneficial in order to provide extended coverage above necessary thresholds.[53] Clones with higher MICs carry the risk of further mutations (mutation selection window) and a β-lactam concentration of >6 × MIC is assumed to suppress resistance.[48] Considering the low probability of adverse effects of increased doses of cefuroxime (and most other β-lactam antibiotics), we would thus favour an aggressive dosing scheme aiming at higher pharmacologic targets (100% ƒT > 4 × MIC). Only renal function and the duration of surgery should be individually considered for dose selection.

List of assumptions (limitations) made during PBPK model development

Assumption	Justification	Implication
ICRP 2002 (integrated within PK-Sim) and 1975	As a common approach, missing anthropometric data like age, weight and height were extrapolated with the ICRP data. It has to be considered, that the described healthy volunteers are often a small group of individuals. The possibility that the anthropometric characteristics differ from the average in the ICRP is high. To take into account mean changes of height and weight related to the different decades of the studies, we used the best matching ICRP report for each study (ESM Table S1). The possible bias was tested with a sensitivity analyses (ESM).	The sensitivity analyses showed no relevant impact for cefuroxime
Range of the population	For simulations of the dose recommendations, the populations were built on basis of the anthropometric values taken from the study collective (age: 18–77 y; weight: 53–120 kg; height 160–193 cm)	Predictions for extreme small or obese person should be made carefully. This also needs to be considered for certain age groups (≥78 and ≤17 y)
Model is validated with venous data	Although a dedicated arterial compartment is not validated, an extrapolation is a strength of PBPK. Both venous and arterial compartment simulations were evaluated, showing minimal differences (MPE arterial = − 1.1% and venous = 5.4%).	No significant effect
Calculation of fraction unbound	Measured f_u concentrations of cefuroxime were not available in this study. To consider intra- and interindividual differences, we chose an approach by taking the individual albumin concentrations into account. This approach was evaluated and validated before.[22,34]	Small possible effect, due to the large effect of f_u in the sensitivity analysis
eGFR range validated from 34.1–169.3 mL/min	The correlation between eGFR and TS is built and validated on sparse data. For severe renal injury, extrarenal clearance pathways described by Walstad *et al*.[54] obtain a more important role. Without describing the extrarenal pathways in severe renal impairment and other relevant parameters (e.g. loss of albumin, changes in haematocrit, extra space fluids etc.), the distribution and excretion cannot be described adequately.	The model, the equation and the findings should only be used in eGFR levels greater than 30–40 mL/min

6 | CONCLUSION

Our PBPK-model predicts achievable concentrations of cefuroxime in our patient population. The use of cefuroxime for PAP to prevent *S. aureus* SSI, seems to be reasonable and recommendable. However, the protection against *E. coli* using the actual standard dosing regimen appears to be insufficient. With our dose recommendations, we provide a potential solution for this issue.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

C.R., C.L., D.H., B.E., R.K. and G.H. conceived the study. C.L., C.A., K.W. and B.R. recruited patients and collected clinical specimens. C.A., D.H. and M.F. performed high-performance liquid chromatography analyses. All authors contributed to data analysis and writing of the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

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