Population pharmacokinetics and probability of target attainment in patients with sepsis under renal replacement therapy receiving continuous infusion of meropenem: Sustained low-efficiency dialysis and continuous veno-venous haemodialysis

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Aims: To describe the population pharmacokinetics (PK) and probability of target attainment (PTA) of continuous infusion (CI) of meropenem in septic patients receiving renal replacement therapy (RRT).

Methods: Fifteen patients without RRT, 13 patients receiving sustained low-efficiency dialysis and 12 patients receiving continuous veno-venous haemodialysis were included. Population PK analysis with Monte Carlo simulations for different dosing regimens was performed. For minimum inhibitory concentration 2 mg/L was chosen. The target was set as 50% time ≥4× minimum inhibitory concentration.

Results: The PK of meropenem was best described by a 1-compartment model with linear elimination. Serum creatinine, residual diuresis and time on RRT, with no difference between sustained low-efficiency dialysis and continuous veno-venous haemodialysis, were found to be significant covariates affecting clearance, explaining >20% of the clearance between subject variability. PTA analysis showed that in patients with RRT, 2 g/24 h, meropenem CI achieved a PTA of 95%. In patients without RRT, the target was achieved with 3 g/24 h CI or prolonged infusion of 1 g meropenem over 8 hours but not with bolus application of 1 g meropenem for 8 hours. Only 2 patients (both without RRT) had meropenem concentrations below the target level. However, approximately half of the patients with RRT receiving CI 3 g/24 h meropenem had toxic concentrations.

Conclusion: We found relevant PK variability for meropenem CI in septic patients with or without RRT, leading to a substantial risk for overdosing in patients with RRT. This finding highlights the strong demand for personalized dosing in critically ill patients.
1 | INTRODUCTION

Meropenem is an intravenous broad-spectrum β-lactam carbapenem antibiotic with a wide spectrum of activity, including Gram-positive, Gram-negative and anaerobic microorganisms. Due to its high degree of activity, tolerability and low incidence of toxicity, it is frequently used to treat severe bacterial infections, such as severe pneumonia, complicated intra-abdominal infections, complicated urinary tract infections or sepsis, in critically ill patients. For these indications, the approved standard dosing regimen for adults with normal renal function is 500 or 1000 mg administered as short-term infusions every 8 hours; for acute bacterial meningitis, a dose of 2000 mg every 8 hours is recommended. Meropenem is a hydrophilic, small molecule with a low volume of distribution (0.3 L/kg) and linear pharmacokinetics (PK). Meropenem exhibits minimal protein binding (2%) and an elimination half-life of approximately 1 hour in healthy volunteers. In healthy adults, meropenem is largely excreted renally with 54–79% excreted unchanged in the urine and 19–27% excreted as an inactive metabolite. Similar to other β-lactam antibiotics, meropenem displays time-dependent bacterial killing features. Its efficacy depends on the percentage of the time interval (T) between which the plasma concentration of the unbound drug fraction (f) exceeds the minimal inhibitory concentration (MIC) for the causative pathogen (% f T>MIC) rather than peak concentrations. Meropenem exhibits bacteriostatic activity at 20% f T>MIC and the f T>MIC required for optimal bactericidal activity has been reported to be 40%. Regarding clinical efficacy, a PK/pharmacodynamic (PD) target of 50–100% f T>MIC has been proposed. However, previous studies have shown that the standard meropenem dosing regimen appeared to result in insufficient meropenem exposure in a considerable fraction of critically ill patients. Reasons for inappropriate antimicrobial exposure include pathophysiological changes associated with critical illness and/or a reduced antibiotic susceptibility of causative pathogens. These pathophysiological alterations can lead to both an increase in the apparent volume of distribution of an antibiotic (due to capillary leakage and/or aggressive volume therapy) and increased clearance (e.g. augmented renal clearance in the hyperdynamic phase of sepsis). Thus, sepsis syndrome bears the potential to lead to subtherapeutic antimicrobial concentrations at the site of infection, treatment failure and the development of antibiotic resistance. One possibility to improve antimicrobial exposure involves the use of alternative dosing strategies, e.g. use of prolonged or even continuous infusion for β-lactam antibiotics. Continuous infusion (CI) has been demonstrated to improve PK/PD target attainment in various studies of time-dependent antibiotics. Furthermore, a recent meta-analysis found decreased hospital mortality in patients treated with CI of β-lactams, including meropenem.

What is already known about this subject

- Critically ill individuals develop pathophysiological changes that alter meropenem pharmacokinetics (PK), which affects drug exposure.
- These changes increase the likelihood of therapeutic failures, bacterial resistance and toxicity.
- Little is known about the population PK and probability of target attainment of continuous infusion of meropenem in septic patients receiving renal replacement therapy.

What this study adds

- We found relevant PK variability for meropenem continuous infusion in septic patients with or without renal replacement therapy, leading to a substantial risk for overdosing in patients with renal replacement therapy.
- This finding highlights the strong demand for personalized dosing in the treatment of critically ill patients.

In addition, the use of supportive extracorporeal therapies, such as continuous renal replacement therapy, further complicates the PK behaviour of antibiotics. In addition to continuous renal replacement therapy (CRRT), sustained low-efficiency dialysis (SLED) is used as a renal replacement modality in critically ill patients with acute kidney injury. SLED in which conventional haemodialysis machines are used to provide extended duration RRT of 8–12 hours vs. 3–4 hours with classic intermittent haemodialysis, are considered to be a conceptual and technical hybrid of CRRT and intermittent haemodialysis. Due to its PK (e.g. volume of distribution) and physicochemical properties (e.g. hydrophilicity, low protein binding, low molecular weight), meropenem is efficiently removed during renal replacement therapy (RRT). Meropenem clearance (CL) varies in patients with RRT. Under continuous veno-venous haemofiltration (CVVHF) and continuous veno-venous haemodiafiltration, clearance attributed to extracorporeal routes was previously estimated around 4 L/h. For SLED, the mean clearance was estimated at 7.9 L/h in addition to non-SLED clearance, which is depending on residual diuresis. Still, clearance in Renally impaired populations is substantially lower than the clearance noted in healthy subjects (15.5 L/h).

To date, studies on the PK of meropenem in critically ill patients with sepsis, undergoing different modes of RRT, have
enrolled only patients receiving intermittent bolus administration of meropenem\textsuperscript{15,18} or for continuous infusion, only patients receiving CVVHF.\textsuperscript{17} The aim of this study was to describe the population PK (PopPK) of meropenem in critically ill septic patients receiving continuous administration of meropenem and undergoing SLED or continuous veno-venous haemodialysis (CVVHD) in comparison to critically ill septic patients without acute kidney injury. With the final model, the probability of target attainment (PTA) for meropenem dosing scenarios in the respective subpopulations was analysed.

2 | METHODS

2.1 | Study design, study population and setting

The study was performed at the Department of Anesthesiology and Intensive Care Therapy at Jena University Hospital. Patients aged ≥18 years with sepsis treated with meropenem were eligible for study enrolment. Sepsis was defined according to Sepsis-2 criteria.\textsuperscript{20} Fifteen patients without RRT, 13 patients receiving SLED and 12 patients receiving CVVHD were enrolled (Table 1). The trial was approved by the local ethics committee (3782–05/13) and registered at the German Clinical Trials Register (DRKS0004778). Written informed consent was obtained from all patients or their legal representative. To summarize the characteristics of patients, we provide absolute and relative frequencies and the mean ± standard deviation. We applied the \(\chi^2\) test or, if indicated, Fisher's exact test and the Mann–Whitney \(U\)-test to assess differences between patients.

2.2 | Meropenem administration

The decision for treatment with meropenem was made at the discretion of the treating physician. All patients received meropenem as CI

| Variable | No RRT (n = 15) | SLED (n = 13) | CVVHD (n = 12) | \(P\) |
|----------|----------------|--------------|---------------|------|
| Age (y)  | 59 ± 12        | 69 ± 17      | 69 ± 10       |      |
| Male, n (%) | 10 (66.7)       | 12 (92.3)    | 7 (58.3)      |      |
| Height (cm) | 172.8 ± 10.2   | 174.7 ± 5.9  | 168.8 ± 7.8   |      |
| Weight (kg) | 82.3 ± 16.1    | 83.1 ± 12.6  | 82.7 ± 12.8   |      |
| Sepsis, n (%) | 10 (66.7)       | 12 (92.3)    | 7 (58.3)      |      |
| Septic shock, n (%) | 5 (33.3)         | 1 (7.7)      | 5 (41.7)      |      |
| Mechanical ventilation on sampling day, n (%) | 7 (46.7)           | 8 (61.5)     | 7 (58.3)      |      |
| Use of vasopressor on sampling day, n (%) | 7 (46.7)           | 5 (38.5)     | 9 (75.0)      |      |
| Length of ICU stay, d (range) | 25 (5–64)        | 27 (5–92)    | 22 (8–38)     |      |
| Hospital mortality, n (%) | 2 (13.3)          | 1 (7.7)      | 4 (33.3)      |      |
| Serum creatinine \([\text{\mu mol/l}]^a\) on sampling day 1 | 75.7 ± 21.5       | 265.8 ± 114.3 | 257.7 ± 103.4 | <.001\(^c\) |
| Serum albumin \([\text{g/L}]\) on sampling day 1 | 17.5 ± 4.0        | 17.9 ± 3.7   | 19.0 ± 4.4    |      |
| Ultrafiltration rate \([\text{mL/h}]\) on sampling day 1 | Na                | 187 (0–1163) | 155 (22–200)  |      |
| Blood flow \([\text{mL/min}]\) | Na                | 150 (90–210) | 130 (100–180) |      |
| Creatinine clearance \([\text{mL/min}]^b\) | 82.8 ± 44.8       | 29.5 ± 13.3  | 30.7 ± 12.1   | <.01\(^c\) |
| Residual diuresis \([\text{mL/d}]^d\) | 2441 ± 4,0        | 330 ± 399    | 113 ± 191     | <.01\(^c\) |
| Time between stop of previous RRT session and T\(_0\), (h) | Na                | 12.5 (12–144) | 12.0 (12–41)  |      |

\(^a\)Data of the first day of inclusion in study, possibly affected by previous SLED or CVVHD sessions.  
\(^b\)Cockroft–Gault equation, data affected by RRT.  
\(^c\)Level of significance for RRT vs. no-RRT.  
\(^d\)Number of patients with anuria (<100 mL/24 h); oliguria (<500 mL/24 h); no RRT: 00, SLED: 5:5, CVVHD: 8:3.  
\(^e\)Level of significance for both CVVHD vs. no-RRT and SLED vs. no-RRT, (\(t_0\)) immediately before initiation of RRT (respectively in patients without RRT during routine blood sampling in the morning) and 1 hour (\(t_1\)), 5 hours (\(t_5\)) and 9 hours (\(t_9\)) thereafter. In patients with a full SLED session, 1 additional sample was taken 1 hour after the session ended (\(t_9\)). RRT: renal replacement therapy; SLED: sustained low-efficiency dialysis; CVVHD: continuous veno-venous haemodialysis; ICU: intensive care unit.
based on the following dosing protocol: immediately after administration of a loading dose of 1 g meropenem over 30 minutes, a CI of 3 g meropenem over 24 hours was initiated in all patients. To guarantee stability, meropenem was prepared every 8 hours by diluting 1 g of meropenem in 50 mL of 0.9% sodium chloride. All patients received a total dose of meropenem of 4 g/d on day 1 and 3 g/d thereafter.

2.3 Sample collection and measurements

PK sampling was performed on the third day of meropenem therapy. In patients without RRT, samples for PK analysis were obtained as part of routine blood sampling from the arterial catheter in the morning (t₀) and 1 hour (t₁), 5 hours (t₅) and 9 hours (t₉) thereafter. In patients with RRT, first blood samples (t₀) were obtained immediately before initiation of RRT and 1 hour (t₁), 5 hours (t₅) and 9 hours (t₉) thereafter. In patients with SLED, 1 additional sample was obtained 60 minutes after termination of the SLED (t₉). The first blood sample (t₀) was taken at least 12 hours after the previous RRT session ended, if applicable. Blood samples were centrifuged within 15 minutes at 14.065 g for 10 minutes at 20°C. The serum supernant was either analysed immediately or stored at −30°C for a maximum of 48 hours until analysis. Samples were analysed by liquid chromatography-tandem mass spectrometry. The method was validated and conducted in accordance with the guidelines of the US Food and Drug Administration’s guidance for industry on bioanalysis. The coefficients of variation for the intraday precision were 9.0, 9.2 and 10.8% for meropenem concentrations of 15, 60 and 125 mg/L, respectively. The interday precision coefficients of variation were 13.9, 9.2 and 10.8% for 15, 60 and 125 mg/L, respectively. The accuracy was between −4.3 and −2.2% for the aforementioned concentration levels. The lower limit of quantification (LLOQ) of the assay was 10 mg/L.

2.4 RRT

The type of RRT was prescribed at the discretion of the treating physician. CVVHDF was performed using a Multifiltrate system (Fresenius Medical Care, Germany). Ultraflux-type haemofilters with a surface area of 1.8 m² (AV 1000S, Fresenius Medical Care, Germany) were used. The blood flow rate was 100–200 mL/min, and the dialysate flow rate was 2000–3000 mL/min. Net fluid removal was between 50–200 mL/h depending on the clinical circumstance. The circuit was anticoagulated with heparin. SLED was performed with the Genius batch system (Fresenius Medical Care, Germany) using a Genius sleddFlux filter (surface area 0.7 m², Fresenius Medical Care, Germany). The blood flow rate was 100–200 mL/min, and the dialysate flow rate was 1:1. Net fluid removal was 50–200 mL/h depending on the clinical circumstances. All machine settings in RRT were at the discretion of the attending physician.

2.5 PopPK modelling

Data preanalyis and graphical output were created in R (version 3.6.1; R foundation for statistical computing, Vienna, Austria). Model building was performed using NONMEM (Version 7.4; ICON Development Solutions, Ellicott City, MD, USA) with the differential equation solver (ADVAN 6 subroutine) and the FOCE+I estimation method. Visual predictive checks (VPCs) were performed with the Pearl speaks Nonmem module (PsN, Version 4.8.1). Graphical output was created with additional use of the Xpose package (version 4.6.1). The basic structural model was tested with the following compositions: 1 and 2 compartments with linear clearance, nonlinear (Michaelis–Menten) clearance and a combination of both. There was no covariate inclusion before the basic structural model was defined. For nested models, the difference in the −2 log likelihood via calculation of the objective function value was considered the best parameter to quantify model improvement. Reductions in χ² distributed objective function value of 3.84 and 6.63 corresponding to 5% for forward inclusion and 1% backward elimination level of significance, respectively, were considered an adequate model improvement for model changes with 1 degree of freedom. Nonhierarchical models were compared using the Akaike information criterion in combination with goodness of fit plots. Demographic and clinical characteristics, which were considered biologically plausible for affecting meropenem PK, such as serum creatinine and Cockcroft–Gault derived creatinine clearance, residual diuresis and dialysis parameters, were tested for inclusion as covariates. Covariate testing was performed using stepwise covariate modelling with a 5% forward inclusion and 1% backward elimination level of significance criterion. Model performance was evaluated by creating goodness of fit plots including individual predictions and population predictions vs. the observed values and plots for conditional weighted residuals vs. time, time after start of dialysis and population model predictions. VPCs based on 1000 simulations were performed to test the predictive performance of the model.

2.6 Probability of target attainment

The primary PK/PD target was set to 50% T >4 × MIC. For MIC, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cut-off value for Pseudomonas aeruginosa, i.e. 2 mg/L, was chosen. This cut-off value is equal to the clinical susceptibility breakpoint for P. aeruginosa as published by the EUCAST. Monte Carlo simulations using 40 dummy patients and 100 repetitions based on the observed patients included in this study were performed to determine the PTA with and without RRT, resulting in 4000 simulated individual profiles for evaluation. We simulated treatment regimens with different total daily doses of meropenem (2 g up to 6 g) and different application schemes (continuous infusion, prolonged infusion [4 h] and intermittent bolus infusion [IB, 30 min]). Simulations were conducted to mimic the initial study setup. The first 24 hours after start of therapy were simulated without RRT. At 24 hours, the
respective treatment was started using the parameters from the respective patient on which the simulation dummy was based on. The 24-hour window after the start of RRT was used for PTA evaluations. PTA was evaluated through graphical exploration of the fraction of time greater than the designated MIC target.

3 | RESULTS

3.1 | Data preanalysis

A total of 166 serum samples were obtained from 40 patients. Meropenem plasma concentrations were explored by an initial analysis of the raw data. A wide range of plasma concentrations was detected (Figure 1 and Figure S1). In 4 patients, clotting of the dialysis system led to a premature ending of the dialysis session. Of those, in 3 patients, the SLED session was stopped after 2 hours in each case; in 1 patient, the CVVHD session was stopped after 4 hours. Patients with RRT had significantly higher meropenem concentrations than patients without RRT at all measured time points (Table 1). When categorized by type of renal replacement therapy, time-dependent differences in meropenem plasma concentrations were observed across the respective sampling time points in the renal replacement subgroups (Figure 1). Based on the individual meropenem concentration at each time point, only 2 patients had at least 1 meropenem concentration measured below the proposed target. The first patient had normal renal function (GFR 75 mL/min, diuresis 2400 mL/24 hr), and a meropenem concentration of 5.5 mg/L was measured on T9. The second patient had augmented renal clearance (GFR 141 mL/min, diuresis 1600 mL/24 hr) and a meropenem concentration below the proposed target at 2 timepoints (T5 4.5 mg/L and T9 5.5 mg/L). In contrast, 30.8% (4/13) of patients with SLED had at least 1 timepoint a concentration >44.4 mg/L, and 15.4% (2/13) of patients had a concentration >64.2 mg/L. These thresholds have recently been associated with meropenem-associated neurotoxicity (Cmin > 64.2 mg/L) and nephrotoxicity (Cmin > 44.4 mg/L). In patients with CVVHD, the number was even greater with 58.3% (7/12) of patients having a concentration >44.4 mg/L and 16.7% (2/12) of patients having a concentration >64.2 mg/L. No patient without RRT had a meropenem concentration above these thresholds at any timepoint.

3.2 | Model building

The PK of meropenem when administered as continuous infusion were best described by a 1-compartment model with linear elimination. Accounting for between-subject variability significantly improved the model’s performance on the clearance part. Allowing for variability in the volume of the distribution term did not result in a significant improvement. Residual errors were best explained by a combined additive and proportional error model. Concentrations below the LLOQ were included by integrating the density function from minus infinity to the limit of detection to yield a probability of the data being below the LLOQ (M3 Method). Given that renal function and dialysis status were previously detected as an influence in the data preanalysis, covariate testing was first performed on renal parameters. The inclusion of serum creatinine as a covariate on clearance significantly ($P < .001$) improved the model (Equation 1). The influence of creatinine clearance calculated by the Cockroft–Gault equation was also tested but showed a less significant impact. Including 24-h residual diuresis prior to the start of dialysis and thus prior to the start of sampling further explained the residual variability in clearance (Equation 2). Separating both RRT types, i.e. SLED and CVVHD, in the covariate analysis, did not improve the models’ performance and yielded similar parameter results. Thus, the model was further tested by grouping RRT and non-RRT patients. A time-dependent change in steady-state meropenem concentrations during RRT was previously detected in the data preanalysis. Even after inclusion of covariates, conditional weighted residuals from the current model correlated with the duration of the dialysis session for both RRT types (Figure 2, Figure S2). Thus, the time on RRT was included as an effect on clearance through a sigmoidal function, which allowed for the clearance to contribute to dialysis reaching a plateau after the start of dialysis (Equation 3).

**FIGURE 1** Meropenem concentrations with and without renal replacement therapy (RRT) at different sampling time points. SLED: sustained low-efficiency dialysis; CVVHD: continuous venovenous haemodialysis.
CREATININE EFFECT ON CLEARANCE: \( \theta_{CL} \), population estimate for clearance; \( \theta_{CLi} \), individual clearance; \( C_{\text{crea}} \), individual creatinine [\( \mu \text{mol/L} \)]; \( C_{\text{creaMedian}} \), median population creatinine value (191 \( \mu \text{mol/L} \)). \( \theta_{\text{crea}} \), estimated creatinine covariate effect

\[
\theta_{CLi} = \theta_{CL} \left( \frac{C_{\text{crea}}}{C_{\text{creaMedian}}} \right)^{\theta_{\text{crea}}}
\]  

Impact of residual diuresis prior to the start of dialysis on clearance. The covariate effect was centred on a population median of 4.3

\[
\theta_{\text{diuresis}}
\]

Estimated covariate effect. \( \theta_{CL} \), population estimate for clearance.

\[
\theta_{CLi} = \theta_{CL} \times \left( 1 + (\text{diuresis} \times [4.30] - 4.30) \times \theta_{\text{diuresis}} \right)
\]

Time-dependent increase in clearance after the start of dialysis. \( t_{\text{Dial}} \), time on dialysis in hours; \( D_{50} \), time frame in which a 50% clearance increase occurs.

More than 20% of the clearance between-subject variability was explained by the inclusion of these 3 covariate relationships. All other tested covariate relationships did not improve the model significantly and were either not eligible for inclusion in the model during the forward covariate search or failed the 1% level of significance cut off for the backward elimination step. Parameter estimates of the final model together with the results of a bootstrap analysis are presented in Table 2. A VPC was created, showing adequate predictivity for patients with and without renal replacement therapy (Figure 3).

### Table 2 Parameter estimates of the final model together with results of a bootstrap analysis

| Parameter | Parameter estimate [RSE] | Bootstrap 90% CI |
|-----------|--------------------------|------------------|
| \( \theta_{CL} \) [L/h] | 3.52 [6%] | 3.2 – 3.8 |
| \( V \) [L] | 11.3 [83%] | 3.1 – 33.0 |
| \( \theta_{\text{Crea}} \) | -0.45 [25%] | -0.6 to -0.3 |
| \( \theta_{D50} \) | 11.6 [53%] | 2.9 – 18.7 |
| \( \theta_{\text{diuresis}} \) | 0.02 [24%] | 0.01 – 0.04 |
| IIV CL | 32.6 [10%] | 24.4 – 25.5 |
| Prop err [%] | 11.8 [21%] | 9.1 – 13.7 |
| Add err [mg/L] | 2.47 [28%] | 1.1 – 3.5 |

RSE: relative standard error; CI: confidence interval; CL: clearance; V: volume of distribution; Crea: estimate for power function of effect of creatine on clearance; D50: time on dialysis for half maximal increase in time-dependent clearance; diuresis: effect of residual diuresis on clearance; IIV CL: unexplained interindividual variability; Prop Err: proportional error term; Add err: additive error term in residual error model.

### 3.3 Probability of target attainment

Different regimens for meropenem application, i.e. continuous infusion after an initial bolus of 1 g meropenem, prolonged infusion (4 h, 8 h) and bolus infusion (30 min, 8 h), were simulated, and the renal function of the patients were compared. Plasma concentration-time
curves for the simulated regimen are presented in the supplement (Figures S3 and S4). From the simulations, the PTA %T$_{\geq\text{MIC}}$ was assessed at 36 hours for non-RRT (Figure 4) and RRT (Figure 5) patients. The results of the simulation show that in patients with RRT, a CI of 2 g meropenem or prolonged infusion (PI) of 1 g meropenem 8 hours achieved a PTA of >95% (Figure 4). In patients without RRT, the target was achieved in 95% of the simulated population with a CI of at least 3 g meropenem or PI of at least 1 g meropenem for 8 hours but not with bolus application of 1 g and 2 g meropenem for 8 hours, which reached the designated target in only 80 and 90%, respectively.

4 | DISCUSSION

To the best of our knowledge, this is the first report of a popPK analysis on CI meropenem therapy in patients undergoing commonly used types of RRT, including CVVHD and SLED, in the intensive care setting compared to patients without RRT. In our study, the PK properties of meropenem were adequately described by a 1-compartment model. Overall, we were able to explain 22% of the individual variability in our population by introducing the serum creatinine effect on clearance as well as the impact of residual diuresis prior to dialysis and duration of RRT, reducing overall interindividual variability from 54 to 32%. These observations are consistent with the results of various meropenem PopPK models studying the critically ill population, showing creatinine clearance or serum creatinine as the most commonly detected covariates of meropenem clearance. The most studied type of RRT in the critical care setting is CRRT. Most models have incorporated the RRT effect via a sieving coefficient, linearly increasing the clearance in relation to the dialysate flow rate. When modelling a single RRT type and comparing the clearance to non-RRT patients with a sparse sampling setup during dialysis, this is the most
feasible method of incorporating this effect. Overall, PK parameter estimates derived from these models are consistent with our findings. A recent population PK study also displayed the effect of SLED therapy on meropenem PK. In contrast to our modelling approach, a nonparametric approach was used. Nevertheless, the reported median estimates are in good agreement with our population means. The authors detected SLED as a covariate on clearance by differentiating the clearance term to an extra equation when SLED was applied. Furthermore, residual diuresis was associated with meropenem clearance when SLED was not used and improved the model significantly. In a study by Deshpande et al. involving 10 intensive care unit (ICU) patients receiving SLED, the mean reduction of plasma meropenem concentration was 79.1 ± 7.3%, and the mean half-life was 3.6 ± 0.8 hours during the 8-hour SLED session. Significantly more meropenem was removed in the first 4 hours of SLED compared with the rest of the sessions. In a recently published PK study by Donnellan et al. in 6 stable patients with chronic kidney disease the authors could also demonstrate that significant quantities of meropenem are removed during a SLED-HDF session. Meropenem total and SLED-HDF clearance ranged from 141 to 180 mL/min and 126–205 mL/min, respectively.

Here, we describe a method of modelling 2 RRT types in parallel that use very different flow rates but seem to have a similar impact on meropenem clearance. In general, the dialysate flow rate is lower in CVVHD (20–40 mL/min) compared with SLED (100–300 mL/min). Given that all flow rates were documented and sampling was conducted at several time points during the RRT sessions, we were able to test the effect of the different RRT setups on meropenem clearance. However, rather than implementing a sieving coefficient depending on the dialysis flow rate, we detected a time-dependent increase in meropenem clearance for both types of RRT. By using the linear sieving coefficient approach, which was described in the literature previously, less significant improvements for our population model were obtained compared with the sigmoidal effect of dialysis duration with a half-maximal increase in meropenem clearance estimated at 11.6 hours after starting RRT. The tight sampling strategy at meropenem steady-state concentrations and during ongoing dialysis enabled the detection and quantification of this time-varying change in meropenem clearance attributed to ongoing dialysis.

Recently, Roberts et al. described the variability in RRT techniques and antibiotic dosing in critically ill patients receiving RRT in a multinational PK study. The overall median estimated total renal clearance was 50 mL/min (interquartile range 35–65) which translates to a range of 2–4 L/h, comparable to our clearance estimate of 3.5 L/h. Higher estimated total renal clearance was associated with lower trough concentrations for all antibiotics (P < .05). The median (interquartile range) trough concentration for meropenem was 12.1 mg/L (7.9–18.8) for Roberts et al. where all patients received bolus administration of meropenem with daily doses ranging from 1 g to 12 g. This was substantially lower than that noted in our patients with RRT and continuous administration. This is in line with results of Jamal et al. who studied the PK of continuous meropenem administration in patients with RRT. They randomly assigned patients with CVVHF therapy to 3 g meropenem CI (n = 8) or IB dosing 1 g every 8 hours (n = 8). Here, CI produced a significantly higher steady-state concentration (25.9 (24.5–41.6) compared to the Cmin observed with IB administration (17.0 [15.7–19.8] mg/L; P < .01) when samples were drawn between days 1–3 of therapy. Compared to our observations, the steady-state concentration measured in our CVVHD patients was slightly higher, e.g. 38 mg/L after 9 hours. Total clearance calculated with non-compartmental methods by Jamal et al. is comparable to our results with 0.96 mL/kg/min translating to 4 L/h in a standard

**FIGURE 5** Probability of target attainment for patients without renal replacement therapy and different regimens for meropenem application, i.e. prolonged infusion (4 h, 8 h), continuous infusion (24 h) and bolus infusion (30 min, 8 h), and dosing (2–6 g total daily dose). Each line represents a percentile of the simulated population. At the solid line, i.e. 95th percentile, 95% of the simulated population was above the respective T > MIC target. MIC: minimal inhibitory concentration
70-kg adult. According to this study, half of the clearance can be accounted for by CVVH; however, this is calculated from the total 8-hour ultrafiltrate collection interval, rather than through time dependent analysis. In conclusion, the study of Jamal et al. showed that lower doses overall of meropenem could be used in patients with continuous infusion undergoing RRT. This finding is consistent with the observations and results of the Monte Carlo simulations in our study that demonstrate meropenem exposure greater than the target is achieved with CI of 3 g/24 h meropenem in patients with RRT. In the Monte Carlo simulations, we evaluated several CI and IB dosing scenarios through simulations with the created model. Our PTA assessment was guided by a PTA of 50% T ≥4x MIC to cover the EUCAST epidemiological cut-off value for _P. aeruginosa_, i.e. 2 mg/L. The plots of target attainment, however, show the entire range of 0–100% T > MIC across a wide range of common MICs to guide therapy in different settings. Our steady-state simulations of different types of application and total daily meropenem doses showed that a CI of 2 g/24 h meropenem or PI of 1 g meropenem 8 hours in patients with RRT and a CI of 3 g/24 hours or PI of 1 g meropenem 8 hours in patients without RRT resulted in an adequate PTA for 95% of the simulated population. This finding was supported by the observation that in our study, only 2 patients without RRT missed the therapeutic target at 1 and 2 time points, separately. One of the patients had augmented renal clearance, a known leading cause for β-lactam subexposure and higher rates of clinical failure. In our simulation, the application via prolonged infusion is more favourable than a single bolus administration, although this finding is more dominant in patients without RRT. In the RRT group, the application of a 1 g bolus for 8 hours resulted in an adequate PTA, whereas this dosing regimen was adequate in only 80% of patients without RRT. However, as the simulations were performed using a 1-compartment model that was established under continuous infusion settings, the interpretation of the results of the Monte Carlo simulations for bolus administration is limited. Nonetheless, our results are consistent with the results of a recently published study showing that 56% of critically ill ICU patients receiving bolus application of 1 g meropenem for 8 hours did not achieve the target of 50% T ≥ 8 mg/L.6 These results highlight the fact that the mode of administration is of utmost importance for β-lactam antibiotics in critically ill patients with and without RRT.

In addition to the fear of underdosing, there is increasing concern of antibiotic-induced toxicity, mainly neurotoxicity, with meropenem exposures that far exceed recommended levels. Imani et al. proposed threshold concentrations for which there is a 50% risk of developing neurotoxicity (C_{min} > 64.2 mg/L) or nephrotoxicity (C_{min} > 44.4 mg/L) events. In our cohort of patients, no patient without RRT had a meropenem concentration above these thresholds at any timepoint. In contrast, 4 out of 13 patients with SLED had a concentration of >44.4 mg/L, and 2 patients had a concentration >64.2 mg/L. In patients with CVVHD, the number was even higher with 7 out of 12 patients >44.4 mg/L and 2 out of 12 patients >64.2 mg/L. However, we did not observe any signs of clinical neurotoxicity.

### 4.1 Limitations

There are several limitations in the current study. Most importantly, given that the study only included patients who received continuous infusion of meropenem and concentrations were measured at steady state, the volume of distribution was not estimated precisely, and interindividual variability was noted. Sampling was conducted at meropenem steady-state concentrations during CI. The start of CI occurred a median of 41.3 hours (range 31.2–64.8) before the first sample was obtained. The meropenem distribution phase was therefore difficult to quantify, and only a 1-compartment model was thought suitable for this study setting with the central volume of distribution being estimated at rather low precision. Previous publications have detected a distribution into a deeper compartment using a 2-compartment model on data more closely collected after the first meropenem application. Moreover, a recently published meta-analysis model by Dhaese et al. evaluating the agreement between concentrations predicted by 8 different PopPK models in critically ill patients receiving CI meropenem, suggests that a 1-compartment model is sufficient for describing meropenem PK. Interindividual variability was only estimated for the clearance term. However, there is no doubt that the manifold processes occurring in the studied special population will also have an impact on the compartments to which meropenem is thought to be distributed, but these effects are not detectable at the equilibrium state. Due to the different types of dialysis studied, we did not choose to fix interindividual variability of the volume of distribution to a value published in a different population but rather only modelled the population estimate of the volume of distribution. In addition, the LLOQ was set rather high in our study (10 mg/L). However, only 3 measured values were below the LLOQ, and the Laplacian M3 approach was additionally used to model uncertainty for values detected below this value. Moreover, given that the creatinine clearance calculated by the Cockcroft–Gault formula is influenced by a variety of confounders in critically ill patients, creatinine clearance might be inaccurate. This limitation was overcome by choosing the more robust covariate creatinine to distinguish the patients’ renal function prior to the start of dialysis. Finally, as we did not measure the pre- and postfilter plasma concentrations as well as the dialysate concentrations, we cannot conclude about the clearance of the RRT and fractional removal by RRT.

### 5 Conclusions

In this study, we observed relevant PK variability for meropenem in critically ill patients undergoing RRT. Serum creatinine, residual diuresis and time on RRT were found to be significant covariates affecting meropenem clearance, explaining >20% of the between-subject variability in clearance. In addition, we observed a time-dependent increase in meropenem clearance in the RRT cohort after the start of dialysis. Further studies are required to validate and investigate this finding. In addition, our study shows that in patients with RRT and
continuous infusion, lower doses of meropenem are needed to achieve the PK/PD target compared to healthy adults, avoiding unnecessarily high concentrations that might simultaneously provoke toxicity. However, in patients without RRT, even with continuous infusion of 3 g meropenem in 24 hours, the PK/PD target is not safely achieved for every patient. Given the high variability of meropenem PK in critically ill patients and bacterial susceptibility, optimizing application modalities and therapeutic drug monitoring may help to optimize individual meropenem dosing to improve target attainment and avoid toxicity.

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COMPETING INTERESTS
Upon manuscript submission, all authors declare they have no competing interests.

CONTRIBUTORS
I.W., F.B., M.P. and S.H. made substantial contributions to the conception, study design, data collection and interpretation of data and drafting of the manuscript and approved the final version to be published. S.G. and C.M. made substantial contributions to data analysis, interpretation of data and drafting the manuscript and approved the final version to be published. R.W. and F.R. made substantial contributions to the sample analysis and drafting of the manuscript and approved the final version to be published.

DATA AVAILABILITY STATEMENT
Data are available on request due to privacy/ethical restrictions.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Ethics approval was obtained from the local ethics committee. Written informed consent was obtained either from the patient or their appointed legal guardian.

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