



Model-informed identification of optimised dosing strategies for meropenem in critically ill patients receiving SLEDD: an observational study

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Abstract

Purpose An increasing number of critically ill patients receive slow extended daily dialysis (SLEDD) due to their pathophysiology while suffering from sepsis, necessitating effective and safe antibiotic therapy. Although SLEDD reduces meropenem exposure and increases treatment failure risk, effective and safe dosing regimens are unclear. We aimed to identify optimised meropenem dosing strategies for critically ill SLEDD patients through population pharmacokinetic (PK) modelling and PK/pharmacodynamic (PD)-based probability of target attainment (PTA) analysis.

Methods Clinical data from a prospective study involving critically ill SLEDD patients receiving meropenem were monitored through routine therapeutic drug monitoring. A total of 178 blood samples from 13 patients (median 14 samples per patient) were analysed. A PK model was developed and utilised to evaluate 24 clinically relevant dosing regimens during SLEDD therapy (7-h on-SLEDD periods $q24h$) in PTA analyses. The PK/PD target window of minimum meropenem concentration between 8 mg/L (*P. aeruginosa*; R-breakpoint) and 44.45 mg/L (toxicity threshold) was used.

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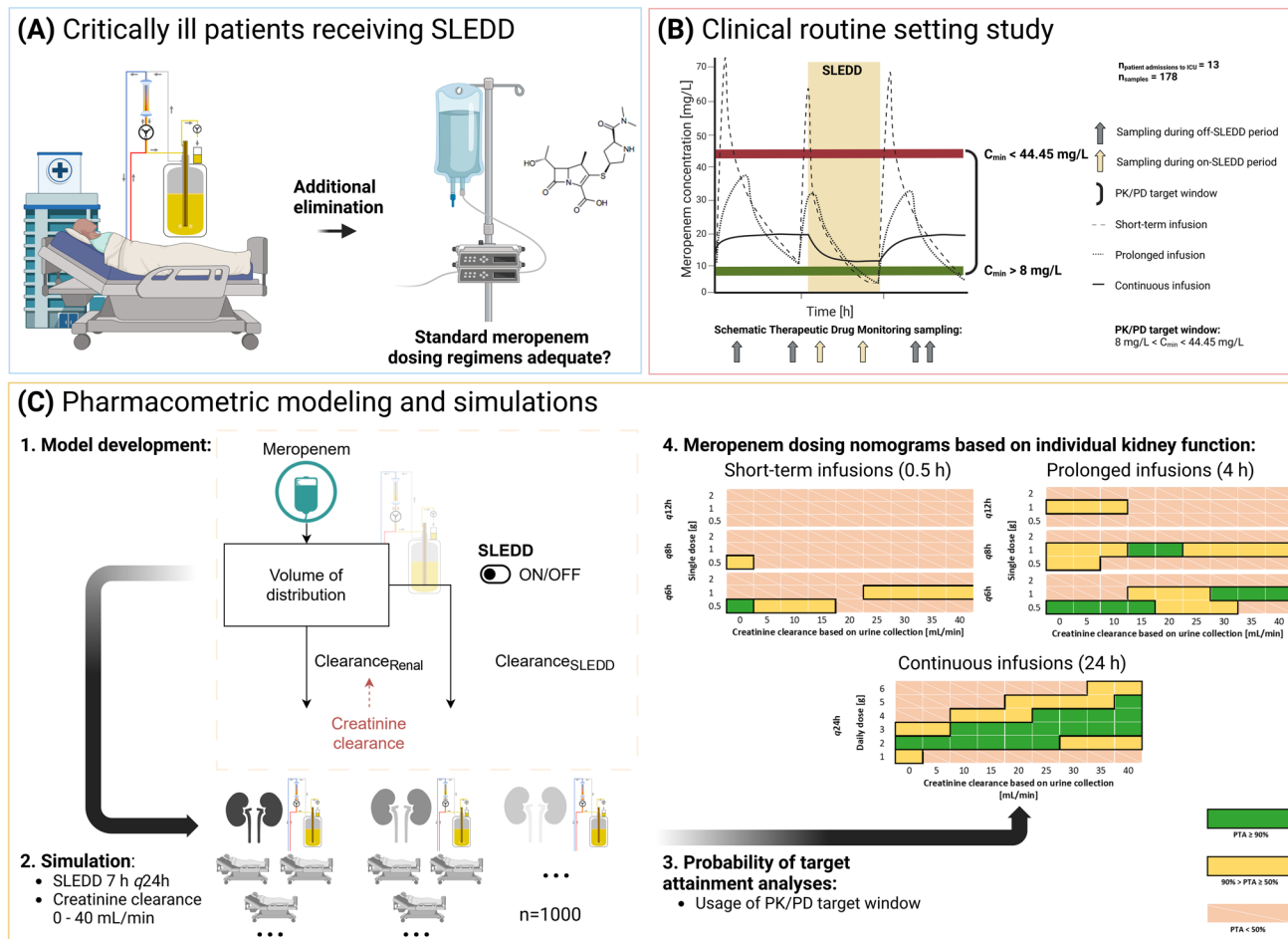
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Results A one-compartment PK model with linear elimination and total clearance (CL) split into renal (CL_{REN} ; 45%) and SLEDD-associated (55%) CL well characterised the SLEDD data. Creatinine clearance (urine-collected; $CLCR_{urine}$) was identified as significant factor on CL_{REN} . Continuous infusions, specifically 2 g $q24h$ for $CLCR_{urine}$ 0–25 mL/min and 3 g $q24h$ for $CLCR_{urine}$ 25–40 mL/min, showed the highest PTA being effective and safe during SLEDD therapy. A comprehensive dosing nomogram was developed.

Conclusion Our easy-to-use dosing nomogram presents a promising tool in optimising meropenem dosing regimens for critically ill SLEDD patients considering their kidney function in clinical practice.

Trial registration Clinicaltrials.gov NCT03985605. Registered 14 June 2019. <https://classic.clinicaltrials.gov/ct2/show/study/NCT03985605>

Graphical abstract



Keywords Meropenem · SLEDD · Critically ill · Pharmacokinetics · Clinical PK/PD target attainment

Abbreviations

AKI	Acute kidney injury
CI	Confidence interval
CKRT	Continuous kidney replacement therapy
CLCR	Creatinine clearance
$CLCR_{urine}$	Creatinine clearance based on urine collection
CL_{REN}	Renal clearance

CL_{SLEDD}	SLEDD clearance
C_{min}	Minimum serum concentration
CV	Coefficient of variation
eGFR	Estimated glomerular filtration rate
$fT_{>MIC}$	Time period of unbound antibiotic concentration exceeding MIC
GFR	Glomerular filtration rate
ICU	Intensive care unit

IQR	Interquartile range
ID	Individual patient defined by admission to one of the study ICUs
IHD	Intermittent haemodialysis
IIV	Interindividual variability
IOV	Interoccasion variability
i.v.	Intravenous
KRT	Kidney replacement therapy
MIC	Minimum inhibitory concentration
No.	Number
off-SLEDD	SLEDD-free interval within SLEDD therapy
on-SLEDD	SLEDD interval within SLEDD therapy
P	Percentile
PD	Pharmacodynamics
PK	Pharmacokinetics
PTA	Probability of target attainment
q	Every (e.g. $q8h$ indicates new infusion every 8 h, i.e., thrice daily)
RSE	Relative standard error
RUV	Residual unexplained variability
SAPS II	Simplified acute physiology score
SIR	Sampling importance resampling
SLEDD	Slow extended daily dialysis
SOFA	Sequential organ failure assessment score
TDM	Therapeutic drug monitoring
V	Volume of distribution

Introduction

Critically ill patients suffer from multiple pathophysiological conditions, such as altered fluid balance, capillary leak syndrome and organ dysfunction, often requiring supportive extracorporeal therapies. Up to 25% of these patients receive kidney replacement therapy (KRT) during their intensive care unit (ICU) stay [1, 2]. Associated pathophysiological conditions have been shown to alter the pharmacokinetics (PK) of antibiotics, resulting in high inter- and intraindividual exposure variability in this patient population [3]. Additionally, especially for drugs that are mainly eliminated via renal pathways, renal dysfunction and KRT each contribute significantly to the uncertainty of the expected individual drug/antibiotic exposure [3]. An increasingly common KRT modality for acute kidney injury (AKI) treatment is slow extended daily dialysis (SLEDD), also referred to as sustained low efficiency dialysis. SLEDD utilises conventional haemodialysis machines for prolonged KRT amalgamating benefits from intermittent haemodialysis (IHD) and continuous kidney replacement therapy (CKRT); with blood and dialysate flow rates of 100–300 mL/min (equivalent to 6–18 L/h), which were high in comparison to CKRT but resulted in moderate overall elimination efficiency due to the limited treatment duration of 6–12 h [4].

Over 35% of ICU patients develop sepsis or septic shock, experiencing a 5.7-fold higher ICU mortality rate than non-ICU patients [5–7]. Their treatment primarily involves timely and adequate antibiotic therapy, being the only causal treatment option in most cases [8, 9]. Meropenem, a beta-lactam antibiotic, mainly eliminated renally via glomerular filtration and tubular secretion, with a broad spectrum and good tolerability, is commonly used empirically in these patients [10, 11]. However, high exposure to meropenem can lead to nephrotoxic and neurotoxic adverse drug reactions [12]. Meropenem is effective against gram-negative and gram-positive pathogens, including commonly less susceptible pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. [13]. Generally, meropenem's efficacy depends on maintaining unbound antibiotic concentrations above the pathogen's minimum inhibitory concentration (MIC) for the entire dosing interval (i.e. $100\%fT_{>MIC}$) in critically ill patients [14]. Additionally, therapeutic drug monitoring (TDM) is advised to optimise treatment [9, 14].

Previous studies indicated that SLEDD affects meropenem therapy by additionally removing it due to its low volume of distribution (V) of 21 L, low molecular mass and minimal protein binding of 2% (98% unbound) [11, 15–17]. SLEDD therapy may cause fluctuating drug concentrations, potentially too low during periods in which the SLEDD device is switched on (on-SLEDD), risking reduced efficacy, and too high when switched off (off-SLEDD), increasing the toxicity risk.

Standard dosing regimens include 0.5 g or 1 g $q8h/q12h$ [18]. However, published studies on optimal antibiotic dosing in critically ill SLEDD patients with AKI are limited and inconsistent in their recommendations [8, 17, 19]. These ambiguities complicate meropenem therapy during SLEDD therapy in clinical practice. Model-informed precision dosing instruments, taking into account PK/PD models and patient, pathogen, dosing and TDM data, can guide clinical dosing practices for improved PK/PD target attainment [20]. Hence, this study aimed to: (1) quantify meropenem exposure during SLEDD therapy in critically ill patients using a nonlinear mixed-effects PK model approach with routine TDM data, (2) identify patient subgroups at risk for decreased PK/PD target attainment, (3) derive simulation-based clinical dosing recommendations, and (4) translate the findings to a clinically usable nomogram supporting therapeutic decision-making.

Methods

Clinical study data

The clinical patient, meropenem dosing, laboratory and SLEDD data analysed were collected within a prospective

monocentric observational study approved by the local institutional review board and registered at clinicaltrials.gov (registration number: 18-578, NCT03985605) and performed at two ICUs of the University Hospital Munich, LMU (Ludwig Maximilian University) [15]. Written informed consent was obtained from the patients or their legal representatives before their inclusion in the study, in accordance with the Declaration of Helsinki and all applicable local regulations. The patients in this study represented a critically ill patient population with a median Sequential Organ Failure Assessment (SOFA) score of 11 (IQR: 10, 14) and a Simplified Acute Physiology Score (SAPS) II of 53 (44, 84). Diagnosis and further demographic characteristics are summarised in Table 1. All laboratory measurements were performed as part of the routine clinical care within the local TDM program. TDM was performed before, during and after the on-SLEDD periods (Fig. 1, Fig. S1). SLEDD therapy, including the machine settings and timing of treatment, as well as the initiation of meropenem therapy and the administration of specific dosing regimens, were prescribed at the discretion of the treating physician. SLEDD was performed with a Genius batch system (Fresenius Medical Care, Germany) using a GENIUS® sleddFlux (surface area: 0.7 m², Fresenius Medical Care, Germany). Within the Genius system, a 1:1 tubing was used during 98% of the meropenem TDM measurements (57 of 58 TDM samples taken during on-SLEDD periods), with identical blood and dialysate flow rates. In one patient and during one TDM measurement, a 2:1 tubing configuration was applied during a single on-SLEDD period, with a blood flow rate of 150 mL/min and a dialysate flow rate of 75 mL/min, which was considered negligible for further analysis. Serum samples were analysed for meropenem using a validated high-performance liquid chromatography-tandem mass spectrometry analysis [21]. Blood flow rates, dialysate flow rates, ultrafiltration rates, blood volumes, i.e. the total volume of extracorporeal blood processed during an on-SLEDD period, and times (start and stop) were documented for all on-SLEDD periods. Within the study bioanalysis, total meropenem concentrations were assessed. The meropenem dose and administration details, blood sampling time points and demographic data, including age, sex, body weight, height, creatinine clearance (CLCR), residual diuresis, and serum creatinine and albumin concentrations, were collected for each patient from the electronic hospital information system. CLCR was determined based on 8 h urine collection (CLCR_{urine}) (Table 1) calculated via Eq. 1 with the creatinine concentration in urine (C_{Urine creatinine}), the total urine volume collected (V_{Urine}), creatinine concentration in serum (C_{Serum creatinine}) and the urine collection duration (T_{Collection}) of 8 h [22, 23].

Table 1 Patient characteristics, laboratory measurements and SLEDD settings

Characteristics	Frequency (%) or median (P _{0.05} , P _{0.95})
Patients	
No. of patients ^a	13 (100)
No. of female patients	3 (23)
Total body weight (kg)	78 (50.5, 98.0)
Age (years)	66 (23.3, 78.6)
Diagnosis at admission	
Pneumonia	4 (31)
Sepsis	2 (15)
Lung transplantation	2 (15)
Liver transplantation	1 (8)
Polytrauma	1 (8)
Ruptured abdominal aortic aneurysm	1 (8)
Cerebral haemorrhage	1 (8)
Pulmonary artery embolism	1 (8)
Laboratory measurements	
Serum albumin concentration (g/dL) ^b	2.60 (1.90, 3.00)
Creatinine clearance (mL/min) ^c	1.00 (0.00, 56.0)
Serum creatinine concentration (mg/dL) ^b	2.60 (1.07, 4.77)
Residual diuresis (mL/d) ^d	325 (0, 3263)
Dialysis setting	
No. of patients with SLEDD therapy	13 (100)
No. of on-SLEDD periods	28 (–)
No. of SLEDD periods per patient	2 (1, 4.4)
On-SLEDD period duration (h) ^e	6.75 (3.57, 12.4)
Blood flow (mL/min) ^e	165 (131, 240)
Dialysate flow (mL/min) ^e	165 (120, 240)
Ultrafiltration rate (mL/h) ^e	305 (107, 565)
Blood volume (L) ^e	75 (26.8, 109)
Meropenem TDM samples	
No. of meropenem samples (total serum)	178 (–)
No. of meropenem samples per patient	14 (4.6, 25.2)
No. of meropenem samples on-SLEDD	58 (32.6)
Meropenem concentration ^f (mg/L)	24.9 (7.73, 59.9)
Meropenem concentrations off-SLEDD ^f (mg/L)	24.9 (7.60, 61.8)
Meropenem concentrations on-SLEDD ^f (mg/L)	25.1 (8.16, 52.0)

TDM therapeutic drug monitoring, SLEDD slow extended daily dialysis, No. number, P percentile, on-SLEDD during SLEDD period within SLEDD therapy, off-SLEDD not during SLEDD period within SLEDD therapy

^aDefined by admission to one of the study ICUs

^bMedian value calculated from 102 laboratory measurements across all individuals

^cBased on urine collection calculated for 8 h and median value calculated from 101 CLCR_{urine} values across all individuals

^dMedian value calculated from 111 collected residual diuresis measurements across all individuals

^eMedian of 28 on-SLEDD periods

^fCollected at various time points across the dosing interval

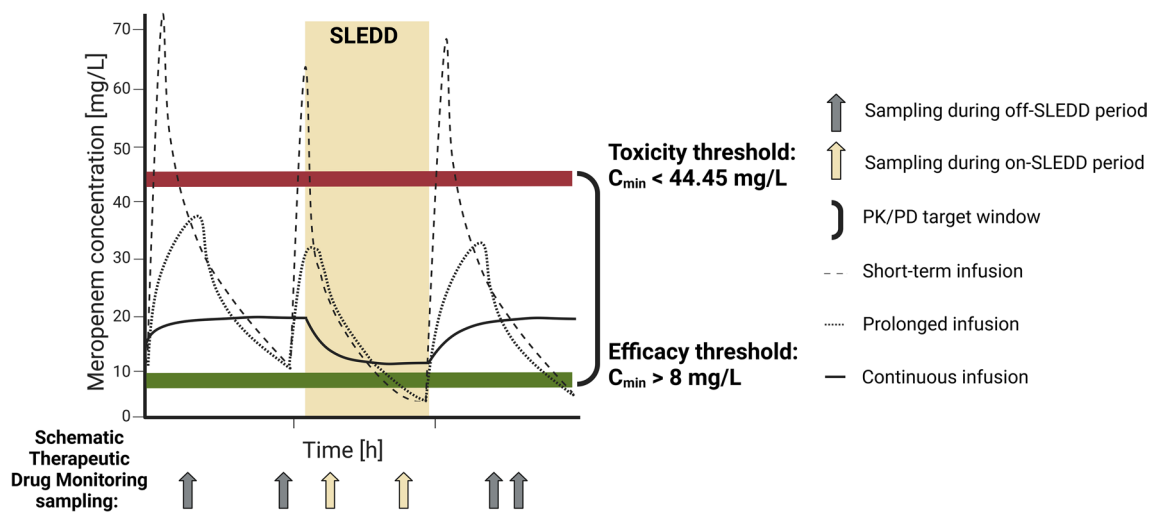


Fig. 1 Schematic meropenem concentration versus time plot for short-term, prolonged and continuous infusions in critically ill patients on slow extended daily dialysis (SLEDD) therapy in the clinical routine setting of this study. Therapeutic Drug Monitoring was performed before (white), during (beige) and after (white) on-SLEDD periods with schematic sampling schedule. The pharmacokinetic/

pharmacokinetic (PK/PD) target window included an efficacy threshold, i.e. $C_{\min} > 8$ mg/L (*Pseudomonas aeruginosa* R-breakpoint, green horizontal line), and a toxicity threshold, i.e. $C_{\min} < 44.45$ mg/L ([12], red horizontal line). A summary of dosing regimens utilised and sampling times is provided in the Supplementary material Section 1 (Table S1)

$$CLCR_{\text{urine}} = \frac{C_{\text{urine creatinine}} * V_{\text{urine}}}{C_{\text{serum creatinine}} * T_{\text{collection}}} \quad (1)$$

Urine was collected daily from 9 pm to 5 am of the following day and serum creatinine was determined as single measurements every morning. Accordingly, $CLCR_{\text{urine}}$ was recalculated with the new measurements every 24 h.

Thanks to the observational character of the study reflecting clinical routine practice, various dosing regimens were used and changed within patients: 54% (96) of the samples were taken within or after a short-term infusion (duration: < 2 h), 9% (16) within or after a prolonged infusion (duration: 2–8 h) and 37% (66) within or after a continuous infusion (duration: > 8 h). The meropenem individual dose per infusion ranged from 0.5 to 2 g for short-term and prolonged infusions. For continuous infusions, 2 g/24 h to 6 g/24 h were administered. A summary of dosing regimens utilised and sampling times is provided in the Supplementary material Section 1 (Table S1).

Characterisation of meropenem population pharmacokinetics during SLEDD therapy

To characterise intravenous (i.v.) meropenem PK, one-, two- and three-compartment PK models with zero-order input and first-order distribution and elimination processes were investigated. Interindividual variability (IIV) and interoccasion variability (IOV) were investigated using exponential models and residual unexplained variability (RUV) using additive, proportional, and combined variability models.

Impact of body weight on PK parameters was tested (allometric scaling: exponent of 0.75 for CL and 1 for V parameters). Moreover, candidate covariates for the PK parameters CL and V were preselected based on graphical evaluation and prior publications and tested with stepwise covariate modelling in Perl-speaks-NONMEM. To investigate the impact of on-SLEDD and off-SLEDD periods on CL within SLEDD therapy the elimination was dissected into renal (CL_{REN}) and nonrenal (CL_{SLEDD}) pathways. Final covariate selection was based on statistical and clinical significance, IIV reduction, covariate effect impact and precision, and plausibility. The developed PK model was extensively evaluated regarding parameter precision and accuracy obtained by sampling importance resampling (SIR) and predictive performance using prediction-corrected visual predictive checks ($n = 1000$) [24].

Evaluation of standard and alternative dosing regimens

To predict PK/PD target attainment of different dosing regimens, the developed PK model was used to perform stochastic dosing simulations in 1000 virtual patients ($CLCR_{\text{urine}}$ [creatinine clearance based on urine collection] range: 0–40 mL/min) receiving short-term (0.5 h), prolonged (4 h), or continuous (24 h) infusions, followed by a probability of target attainment (PTA) analysis. Doses ranged from 0.5 to 2 g for short-term and prolonged infusions, and 1 to 6 g for continuous infusions. Dosing intervals for intermittent infusions were 6 h, 8 h, 12 h, or 24 h (in total: 24 regimens).

To consider both treatment efficacy and safety in the analysed renally impaired patient population, a PK/PD target window was defined: the *Pseudomonas aeruginosa* meropenem breakpoint (EUCAST R-breakpoint of 8 mg/L) was used as the MIC value for the target $fT_{>MIC} = 100\%$ [25] combined with the nephrotoxicity threshold of the meropenem minimum concentration (C_{min}) < 44.45 mg/L proposed in [12], resulting in a final PK/PD target window of $8 \text{ mg/L} < C_{min} < 44.45 \text{ mg/L}$ (Fig. 1). In the utilised PK/PD target window, efficacy and toxicity thresholds were equally weighted. A SLEDD regimen of 7 h q24h, representing the typical regimen in the study, was used [15]. Per dosing regimen, 1000 simulations were assessed to calculate the PTA for the PK/PD target window with assumed steady-state (i.e., 48 h after the start of dosing). A mean PTA of $\geq 90\%$ for all calculated PTA values was considered therapeutically adequate [26]. Total meropenem concentrations were considered due to its low protein binding (2%) [11].

Results

Characterisation of meropenem population pharmacokinetics during SLEDD therapy

The i.v. infusion PK of meropenem in critically ill SLEDD patients was best characterised by a one-compartment model with zero-order infusion, first-order elimination, and total clearance (CL) divided into renal CL (CL_{REN}) and SLEDD-associated CL (CL_{SLEDD}) based on the exploratory graphical analysis (Fig. S2). From the total CL of 6.36 L/h, 45%

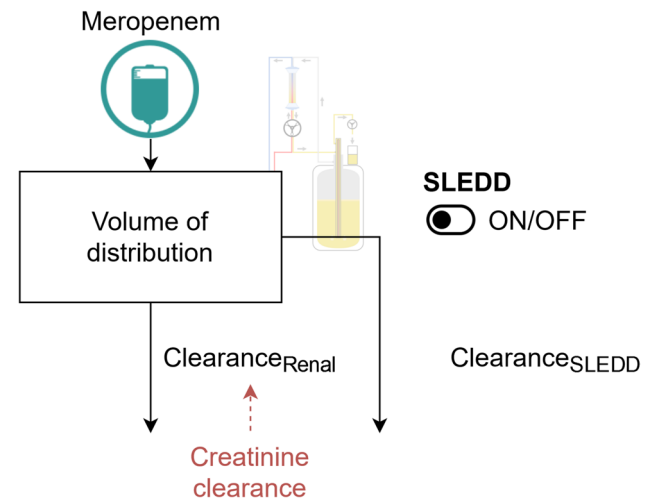


Fig. 2 Illustration of the developed pharmacokinetic model for meropenem in critically ill patients receiving slow extended daily dialysis (SLEDD) with clearance (CL) split into renal and SLEDD-associated CL and a covariate relationship between creatinine clearance based on urine collection and renal CL:

$$CL_{REN_i} = CL_{REN} \times \left(\frac{TBW_i}{70}\right)^{0.75} \times (1 + (CLCR_{urine} \text{ covariate effect on } CL_{REN}))$$

$\times (CLCR_{urine,i} - CLCR_{urine,m})$ and $V: V_i = V \times \left(\frac{TBW_i}{70}\right)$. CL_{REN} : renal meropenem clearance, i : individual, TBW : total body weight, $CLCR_{urine}$: Creatinine clearance based on urine collection $CLCR_{urine,m}$: Median of the individual-level weighted mean values of $CLCR_{urine}$, i.e. $CLCR_{urine,m} = 4.13 \text{ mL/min}$ (see Supplementary Section 3 “Characterisation of population pharmacokinetics during SLEDD therapy”), V volume of distribution

(2.87 L/h) was attributed to CL_{REN} , and 55% (3.49 L/h) to CL_{SLEDD} . Furthermore, IIV on CL_{REN} (21.1%CV), IOV

Table 2 Parameter estimates and confidence intervals of the developed population pharmacokinetic model of meropenem in critically ill patients receiving SLEDD

Parameter	Estimate (RSE, %)	95% CI (SIR)
CL_{REN} (L/h) ^a	2.87 (10)	2.49–3.33
V (L) ^b	33.8 (17.8)	28.1–42.9
CL_{SLEDD} (L/h)	3.49 (39.8)	2.06–5.18
Covariate effect of $CLCR_{urine}$ on CL_{REN} ^c	0.0251 (44.2)	0.0125–0.0391
Interindividual variability on CL_{REN} , %CV	21.1 (34.1)	14.5–32.5
Interoccasion variability on CL_{SLEDD} ^d , %CV	109 (40.4)	51.9–185
Residual variability (proportional), %CV	34.2 (16.3)	30.9–39.3

CI confidence interval, CL_{REN} renal clearance for 70 kg patient, CL_{SLEDD} SLEDD clearance, $CLCR_{urine}$ creatinine clearance based on urine collection, *CV* coefficient of variation, *RSE* relative standard error, *SIR* sampling importance resampling, *SLEDD* slow extended daily dialysis, V volume of distribution for 70 kg patient

^aFor a $CLCR_{urine}$ of 4.13 mL/min and body weight of 70 kg (allometrically scaled with exponent 0.75)

^bFor a body weight of 70 kg (allometrically scaled with exponent 1)

^c $CL_{REN_i} = CL_{REN} \times (1 + (\text{Covariate effect of } CLCR_{urine} \text{ on } CL_{REN}) \times (CLCR_{urine,i} - CLCR_{urine,m}))$, where the index i represents the individual $CLCR_{urine}$ and m the median of the individual-level weighted mean values, i.e. $CLCR_{urine,m} = 4.13 \text{ mL/min}$ (see Supplementary Sect. 3 “Calculation of median covariate values”)

^dOccasion defined as start of respective on-SLEDD period

on CL_{SLEDD} (109%CV) and a proportional RUV model (34.2%CV) were integrated. Allometric scaling of total body weight was included on the CL_{REN} and V (Table 2, Fig. 2).

The developed model included residual renal function, represented as $CLCR_{urine}$, as an impactful covariate on CL_{REN} in a linear relationship showing a 25.1% reduction in CL_{REN} for every 10 mL/min decrease in $CLCR_{urine}$ (Table 2, Fig. 3, Fig. S3, Eq. S1). This covariate inclusion explained 39% of the IIV on CL_{REN} of the base model (Table 2, Table S2). All SLEDD parameters such as blood flow rate, dialysate flow rate, ultrafiltration rate, blood volume, and time on SLEDD were evaluated as potential covariates on CL_{SLEDD} (Figs. S4–S5) but were excluded from the final model due to their statistically insignificant effects in the

forward inclusion (no reduction in objective function value more than ≥ 3.84 , for more details see Supplementary Section “3. Pharmacokinetic Modelling”).

The developed model displayed no systematic bias according to individual and population goodness-of-fit plots (Fig. 4, Figs. S6–S7). Although a minor tendency towards underprediction at lower concentrations (≤ 10 mg/L) was noted in population predictions during on-SLEDD periods, this was no longer observed in individual predictions. Model evaluation demonstrated high parameter accuracy, precision as well as model robustness and predictive performance (Fig. S8).

Fig. 3 Total meropenem serum concentrations normalised by a representative 3 g daily dose versus creatinine clearance based on urine collection on a log–log scale including regression equation, R^2 , Pearson r correlation coefficient and the respective p values (Pearson correlation test). Only meropenem samples during off-SLEDD periods (n = 120) were taken into account. Meropenem sampling was performed across the entire dosing interval. Colours represent dosing regimens: blue = short-term [duration: < 2 h], green = prolonged [duration: 2–8 h], orange = continuous infusions [duration: > 8 h]

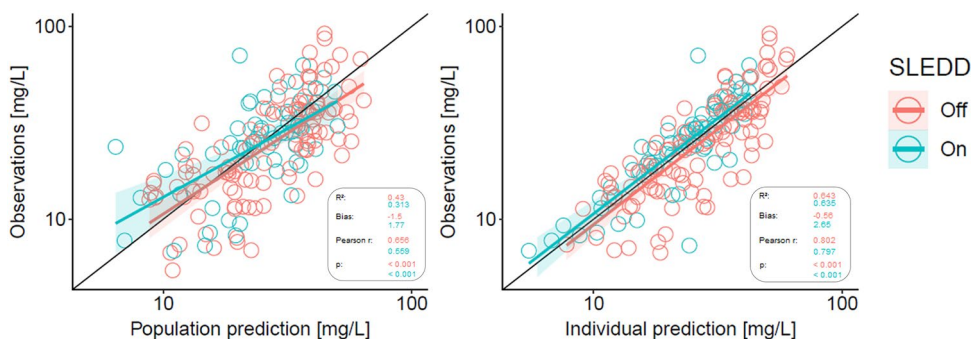
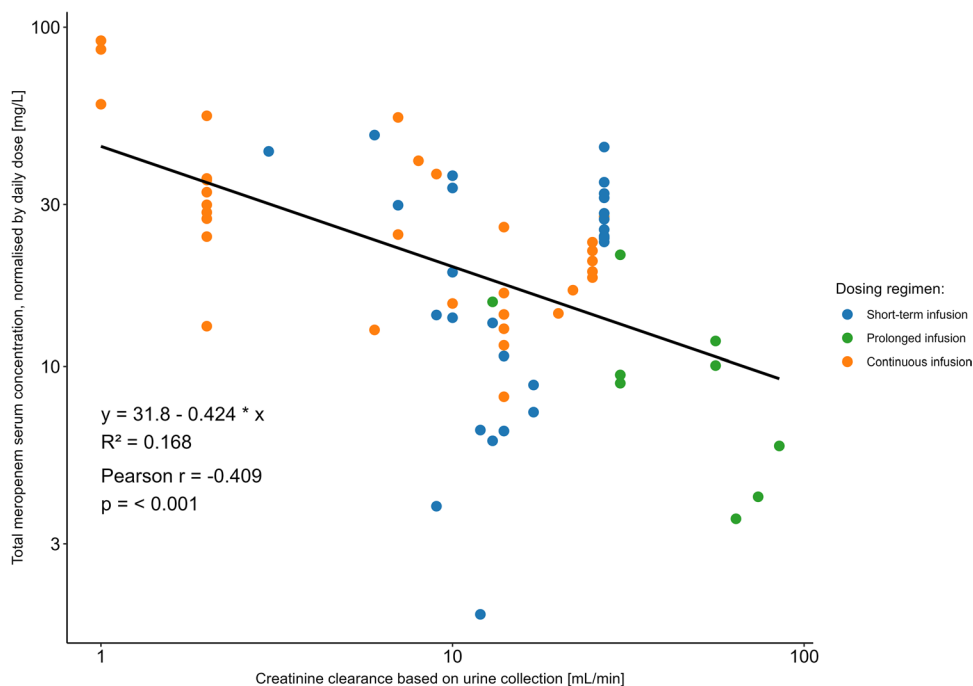


Fig. 4 Goodness-of-fit plots of the developed population PK model for meropenem in critically ill including R^2 , bias, Pearson r correlation coefficient and the respective p values (Pearson correlation test). Circles in red indicate observed meropenem measurements taken during off slow extended daily dialysis (SLEDD) and in turquoise during

on-SLEDD. Coloured lines represent linear regression line with confidence intervals. Black line: unity line. Observed versus population-predicted concentrations (left) and versus individually predicted concentrations (right)

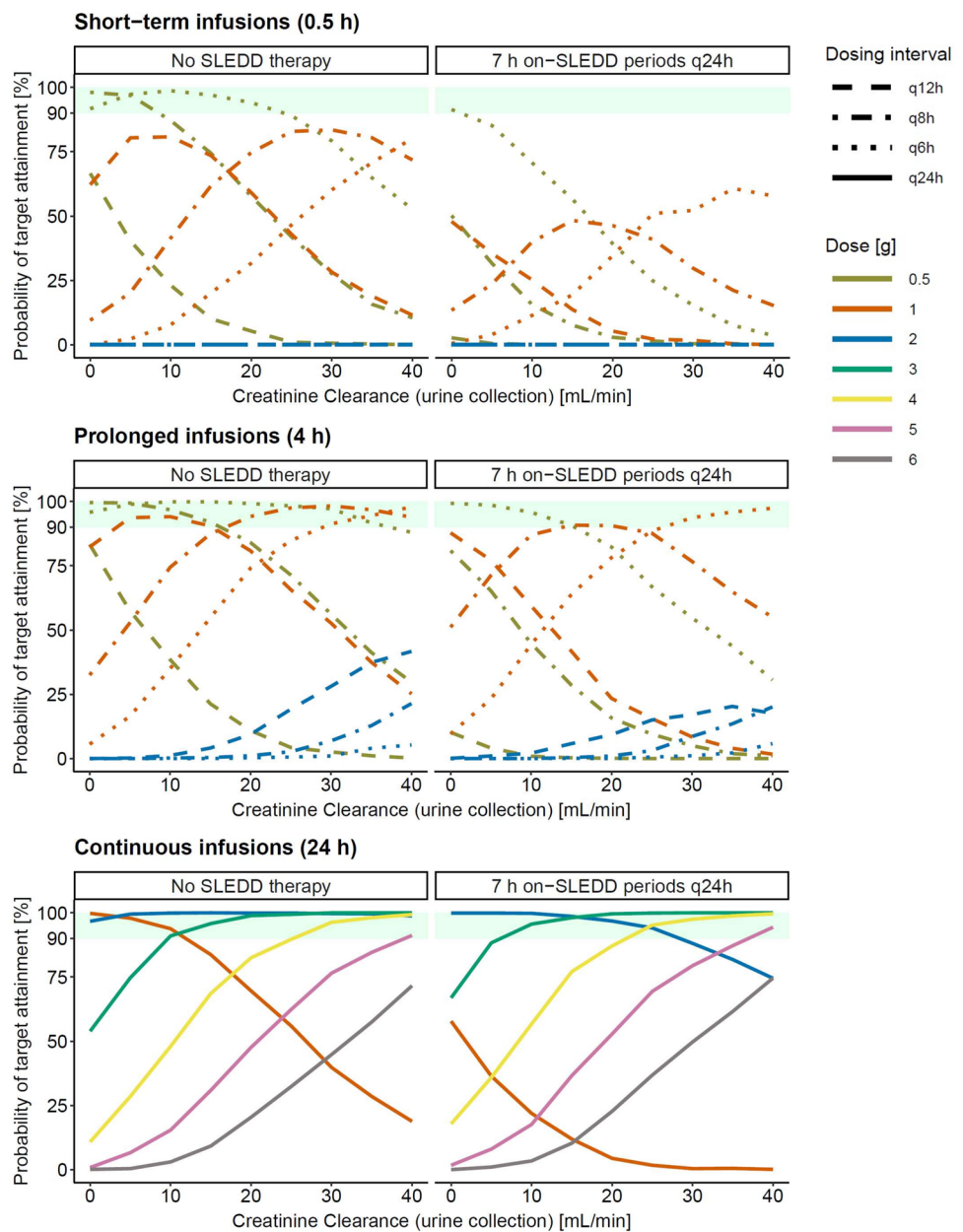
Evaluation of standard and alternative dosing regimens

Based on the PTA analysis with the 24 investigated dosing regimens, an overall risk of not reaching the PK/PD target window for the underlying patient population was found, observable in both patients with and without SLEDD therapy (Fig. 5). A separate PTA analysis for the efficacy and toxicity targets showed the importance of considering both; as regimens with a high probability of effective treatment had an increased probability of exceeding the toxicity threshold (e.g. 2 g *q*6h prolonged; Fig. S9-10) and vice versa safe regimens did not necessarily show a high probability of being effective (e.g. 1 g *q*12h prolonged, Fig. S9-10). In addition,

SLEDD affected the probability of achieving effective and safe concentrations. Concerning safety, SLEDD showed a moderate protective effect in terms of an increased probability of not exceeding the toxicity threshold (Fig. S10). Continuous infusions of 2 g or 3 g *q*24h showed the highest probability of reaching both the efficacy target as well as the toxicity target. (Supplementary Section 4).

For attaining the PK/PD target window, continuous infusions consistently showed the highest probability across all $CLCR_{urine}$ values and among all dosing regimens. For SLEDD patients with $CLCR_{urine}$ between 30–40 mL/min, continuous infusions of 3 g or 4 g, or prolonged infusions of 1 g *q*6h, reached a PTA $\geq 90\%$. For $CLCR_{urine}$ values between 15–30 mL/min, continuous infusions of 2 g

Fig. 5 Probability of PK/PD target attainment for meropenem not during SLEDD therapy (left) and during SLEDD therapy with 7 h on-SLEDD periods every 24 h (*q*24h; right) versus renal function (determined as creatinine clearance via urine collection) for 24 different dosing regimens (all investigated dosing regimens incl. seven different doses between 0.5 and 6 g as well as *q*6h, *q*8h, *q*12h and *q*24h), top: short-term infusions (0.5 h), middle: prolonged infusions (4 h), bottom: continuous infusion (24 h), green area: 90–100% probability of target attainment for PK/PD target: $8 \text{ mg/L} < C_{min} < 44.45 \text{ mg/L}$; C_{min} minimum concentration, PK/PD pharmacokinetic/pharmacodynamic, SLEDD Slow extended daily dialysis



or 3 g *q*24h, or prolonged infusions of 1 g *q*8h achieved PTAs $\geq 90\%$ (Fig. 5). For $CLCR_{urine}$ values < 15 mL/min, only continuous infusions of 2 g *q*24h or prolonged infusions of 0.5 g *q*6h attained the target window (Fig. 5). In general, the differences between non-SLEDD and SLEDD therapy were identified to be the lowest for continuous infusions compared to prolonged and short-term infusions.

For high clinical utility, the simulation and PTA analysis results with the joint PK/PD target window for efficacy and toxicity from Fig. 5 were translated and summarised in a dosing nomogram for each type of infusion, dose and interval (Fig. 6). For each $CLCR_{urine}$ value from 0 to 40 mL/min in increments of 5 mL/min, dosing regimens that achieved PTAs of $\geq 90\%$ were labelled green, those between 50 and 90% yellow and those $< 50\%$ red.

Discussion

In critically ill SLEDD patients, continuous infusion dosing regimens were the most suitable type of infusion to maximise PK/PD target attainment, taking into account efficacy and toxicity thresholds. Leveraging data reflecting the real-world situation in ICUs, the identification of the most suitable dosing regimens was achieved by successfully developing a population PK model for meropenem in critically ill patients receiving SLEDD and evaluating PK/PD target attainment in this population across a wide range of clinically relevant dosing regimens. The associated simulation results were translated into a clinically usable dosing nomogram.

Splitting elimination into two distinct processes, i.e. the extracorporeal elimination and remaining renal pathway, was successful. CL_{SLEDD} contributed to more than half (55%) of the total meropenem CL of 6.4 L/h. While not directly quantified through dialysate and pre-/post-filter measurements, the assessment of TDM data during clinical routine on-SLEDD and off-SLEDD periods allowed for a differentiation between and quantification of CL_{SLEDD} and CL_{REN} . Overall, all PK model parameters were plausible compared to previously reported parameters. Our dialysis-associated CL of 3.49 L/h corresponded well with previously reported values of 1.2 L/h and 4.8 L/h for intermittent KRT [27, 28]. Using significantly higher ultrafiltration rates (500 mL/h, our study: 280 mL/h) and blood/dialysate flows (250 mL/min, our study: 180 mL/min), a higher SLEDD-associated CL of 7.9 L/h was reported in [8]. Another study including renally impaired patients reported a lower total CL of 3.52 L/h without dissection into a dialysis-associated CL and a renal CL [19], yet the PK analysis was based on a population receiving SLEDD, the less efficient CKRT or KRT (each group about one third).

In terms of V, Mouton et al. [29] reported 21 L in healthy non-continuous kidney replacement volunteers.

In comparison, Chung et al. reported 14.3 L for V of the central and 17.7 L for V of the peripheral compartment in CKRT patients, which is similar to the V of 33.8 L observed in our study [30]. One- and two-compartment disposition models have been previously described in the literature for meropenem, which supports the identification of a one-compartment model in this study to characterise the PK of meropenem in critically ill patients [31–33].

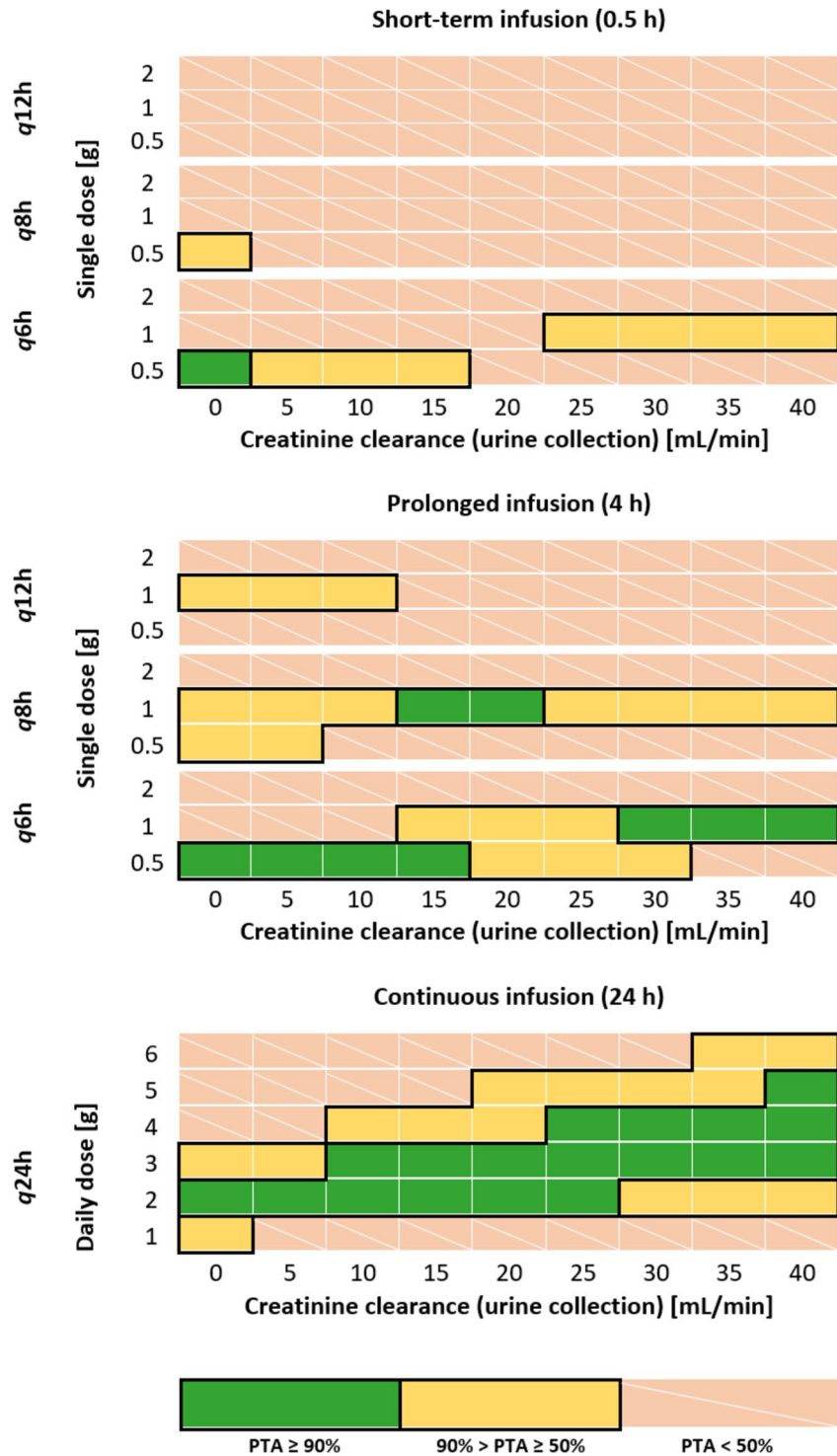
The meropenem CL of healthy volunteers has been shown to range from 11–14 L/h [27, 28]. Since our study population suffered from severe renal impairment (Table 1), we expected our estimated CL_{REN} value to be substantially lower: the estimated value of 2.87 L/h corresponded to a glomerular filtration rate of 4.13 mL/min ($CLCR_{urine}$). Thus, at $CLCR$ values of healthy individuals, e.g. 120 mL/min, CL_{REN} reached the expected range for healthy volunteers at 11.2 L/h, highlighting the plausibility of the estimated effect size in our covariate model, namely a 25% decrease in CL_{REN} for a 10 mL/min deterioration in glomerular filtration. The identification and quantification of $CLCR_{urine}$ as a time-varying covariate influencing CL_{REN} , considered potential changes in renal CL of meropenem in individual patients over the course of therapy. This covariate–parameter relationship aligned with previously developed non-dialysis meropenem models in which kidney function has been shown to significantly influence meropenem CL [32]. The residual meropenem CL of 2.87 may be attributable to a reported increase in active tubular secretion and proportion of non-renal elimination and/or metabolism of meropenem in renally impaired critically ill patients [27, 34].

For the first time, this study quantified the variability of meropenem CL_{SLEDD} , most likely due to machine setting changes, within the different on-SLEDD periods of a critically ill patient implemented as IOV. This was only possible due to the availability of a larger number of data points from multiple on-SLEDD periods per patient. In previously developed population PK models of meropenem therapy in critically ill SLEDD patients this aspect was not considered [8, 19]. The high variability between the on-SLEDD periods (109%CV) underlined the probable impact of distinct SLEDD settings (e.g. duration, interval, dialysate flow rates, blood flow rates, ultrafiltration rate, and dialyser type) on the SLEDD-associated CL of meropenem. However, similar to Braune et al. [8], none of those settings or other factors were identified as significant covariates on CL_{SLEDD} , despite weak correlation trends in the graphical analysis between CL_{SLEDD} , the dialysate flow rate, and the ultrafiltration rate, respectively (Fig. S5). That we could not identify this relationship as statistically significant might also be likely due to a rather small variation in different SLEDD settings and the variable but sparse sampling scheme. Nevertheless, IOV could be associated with the SLEDD elimination of

Fig. 6 Dosing nomogram for meropenem in critically ill patients for short-term infusions (top), prolonged infusions (middle) and continuous infusion (bottom) during slow extended daily dialysis (SLEDD) therapy (7 h on-SLEDD periods $q24h$). PK/PD target window: $8 \text{ mg/L} < C_{\min} < 44.45 \text{ mg/L}$. PTA: probability of target window attainment (colour-coded as green for $\geq 90\%$ PTA, yellow for $90\% > \text{PTA} \geq 50\%$ and red for $< 50\%$ PTA), q : every (e.g. $q8h$ indicates a new infusion every 8 h, i.e. thrice daily), PK/PD pharmacokinetic/pharmacodynamic

Dosing nomogram for critically ill SLEDD patients

Only for SLEDD regimen: 7 h on-SLEDD periods every 24 h



Disclaimer: This dosing nomogram has not yet been prospectively validated. Use should be conducted with caution.

meropenem, reducing RUV by 13%. The additional inclusion of IIV on CL_{SLEDD} did not result in an improvement of the model.

Critically ill patients are at high risk of excessive meropenem serum concentrations, quickly reaching nephrotoxic ($C_{min} > 44.45$ mg/L) or neurotoxic levels ($C_{min} > 64.2$ mg/L), which can be prevented via a dosing strategy guided by the defined PK/PD target window [12, 35]. The toxicity threshold proposed by Imani et al. was selected because the analysed patient population is urgently dependent on their remaining kidney function. The applied target window offers practical and clinically oriented assistance based on the latest guidelines [9, 14].

Within the simulation plots, the bell-shaped curves per dosing regimen in Fig. 5 resulted from the relationship between $CLCR_{urine}$ and meropenem exposure: lower $CLCR_{urine}$ led to higher meropenem concentrations, increasing the probability of exceeding the toxicity threshold (i.e. 44.45 mg/L), whereas higher $CLCR_{urine}$ resulted in lower meropenem exposure, reducing the probability of exceeding the efficacy threshold (i.e. 8 mg/L). The dosing simulation analyses for a clinically relevant range of $CLCR_{urine}$ values between 0 to 40 mL/min revealed that continuous infusions of 2 g or 3 g had the highest PTA values compared to short-term and prolonged infusion regimens. Our results are consistent with those of Westermann et al., who reported that patients with KRT and 2 g/24 h continuous meropenem infusion achieved a PTA of 95% [19].

This study focused on meropenem dosing regimens in the rare population of highly vulnerable critically ill patients undergoing SLEDD, resulting in a small total number of included patients. However, the extensive data collected per patient (median of 14 samples, from on-SLEDD as well as off-SLEDD periods) facilitated the robust estimation of PK parameters. Our developed dosing nomogram allows clinicians to determine the most suitable dosing regimen for patients undergoing SLEDD, aligning with the conditions of our study, yet commonly applied (7 h on-SLEDD periods $q24h$, blood flow 131–240 mL/min, dialysate flow 120–240 mL/min, ultrafiltration rate 107–565 mL/h and blood volume 26.8–109 L). Based on our analyses, we advise not to use estimated glomerular filtration rate formulas with our nomogram, only $CLCR_{urine}$. In clinical scenarios with patients exhibiting no residual diuresis and thus $CLCR_{urine}$ cannot be calculated, the dosing recommendations from the first column of the dosing nomogram (i.e. $CLCR_{urine} = 0$ mL/min), can still be employed. Before our developed model and dosing nomogram can be used more broadly in clinical practice, a prospective clinical validation with external data must be performed.

In the clinical study, no individual pathogen or MIC determinations were acquired [15] which could in a next step further optimise meropenem exposure during SLEDD

therapy. In order to apply the finding to other SLEDD settings than in this clinical trial, future studies should focus on broader ranges of durations, intervals, and flow rates to identify influential parameters on the SLEDD-associated elimination of meropenem.

Overall, our developed PK model for SLEDD therapy in critically ill patients has the potential to be integrated into easy-to-use model-informed precision dosing instruments [20] after completion of the prospective validation. Thereby, our model can enable healthcare professionals to decide on dosing adjustments when SLEDD therapy is applied directly at the patient's bedside. By integrating TDM data, Bayesian data analysis approaches could be combined with our model to enhance the precision of meropenem exposure predictions, facilitating more accurate and tailored dosing recommendations [20, 36–39].

Conclusion

Continuous meropenem infusion regimens (2 g for $CLCR_{urine}$ of 0–25 mL/min, 3 g for $CLCR_{urine}$ of 25–40 mL/min $q24h$) demonstrated the highest probability of achieving adequate antibiotic exposure and avoiding potentially nephro- and neurotoxic concentrations in the highly vulnerable population of critically ill SLEDD patients. The availability of TDM and accurate early $CLCR_{urine}$ measurements is essential for optimal individual dosing. Our dosing nomogram represents an easy-to-use model-informed precision dosing instrument for clinicians and antimicrobial stewardship teams for selecting the best meropenem dosing regimen for SLEDD patients where conditions align with our study.

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Author contributions CS, UL, MZ, and MV designed the clinical study. UL and CS conducted the clinical study. MP and KH performed the bioanalysis. FWb, UL, FWe, and CK designed the data analysis. FWb conducted the data analysis, RM, LA, GM mentored, and CK supervised. FWb, FWe, LA, RM, GM, WH, UL, and CK discussed the results. FWb drafted the manuscript. All authors reviewed and approved the manuscript. All authors meet key authorship requirements and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials The clinical data and model is available from the corresponding author upon reasonable request due to privacy/ethical restrictions.

Declarations

Conflict of interest Franz Weber (FWb): no competing interest. Christina Scharf (CS): CS received speaker honoraria from CytoSorbents Europe GmbH. Linda Brita Sofia Aulin (LA): no competing interest. Ferdinand Weinelt (FWe): no competing interest. Michael Paal (MP): no competing interest. Gerd Mikus (GM): no competing interest. Michael Vogeser (MV): no competing interest. Katharina Habler (KH): no competing interest. Wilhelm Huisinga (WH): WH received research grants from an industry consortium (AbbVie Deutschland GmbH & Co. K.G., AstraZeneca, Boehringer Ingelheim Pharma GmbH & Co. KG., F. Hoffmann-La Roche Ltd., Merck KGaA, Novo Nordisk A/S and Sanofi) for the graduate research training program PharMetriX. Michael Zoller (MZ): MZ received research support from CytoSorbents Europe GmbH, consulting fees from Gilead and speaker honoraria from MSD. Robin Michelet (RM): no competing interest. Charlotte Kloft (CK): CK received research grants from an industry consortium (AbbVie Deutschland GmbH & Co. K.G., AstraZeneca, Boehringer Ingelheim Pharma GmbH & Co. KG., F. Hoffmann-La Roche Ltd., Merck KGaA, Novo Nordisk A/S and Sanofi) for the graduate research training program PharMetriX, from the Innovative Medicines Initiative-Joint Undertaking (“DDMoRe”), from H2020-EU.3.1.3 (“FAIR”), Diurnal Ltd. and the Federal Ministry of Education and Research within the Joint Programming Initiative on Antimicrobial Resistance Initiative (“JPIAMR”), all outside the submitted work. Uwe Liebchen (UL): UL received consulting honoraria from CytoSorbents Europe GmbH and Medows Särl, and was part of an advisory board of Roche Diagnostics International Ltd.

Ethics approval Ethics approval and consent were obtained from the Institutional Review Board of the Medical Faculty of the Ludwig-Maximilians-University Munich, Germany (registration number 18-578).

Consent for publication Not applicable.

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