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Effect of renal clearance and continuous renal replacement therapy on appropriateness of recommended meropenem dosing regimens in critically ill patients with susceptible life-threatening infections

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Background: Meropenem plasma concentration above a pathogen's MIC over the whole dosing interval (100% $fT_{>MIC}$) is a determinant of outcome in severe infections. Significant variability of meropenem pharmacokinetics is reported in ICU patients.

Objectives: To characterize meropenem pharmacokinetics in variable CL_{CR} or renal replacement therapy and assess the appropriateness of recommended regimens for MIC coverage.

Methods: A pharmacokinetic analysis (NONMEM) was conducted with external model validation. Patient characteristics were tested on meropenem clearance estimates, differentiated according to the presence/absence of continuous renal replacement therapy (CRRT, CL_{CRRT} or $CL_{no\text{-}CRRT}$). Simulations evaluated the appropriateness of recommended dosing for achieving 100% $fT_{>MIC}$ in 90% of patients.

Results: A total of 101 patients were studied: median 63 years (range 49–70), 56% male, SAPS II 38 (27–48). 32% had a CL_{CR} >60 mL/min, 49% underwent CRRT and 32% presented severe sepsis or septic shock. A total of 127 pathogens were documented: 76% Gram-negatives, 24% Gram-positives (meropenem MIC_{90} 2 mg/L, corresponding to EUCAST susceptibility breakpoint). Three hundred and eighty plasma and 129 filtrate–dialysate meropenem concentrations were analysed: two-compartment modelling best described the data. Predicted meropenem $CL_{no\text{-}CRRT}$ was 59% lower in impaired (CL_{CR} 30 mL/min) compared to normal (CL_{CR} 100 mL/min) renal function. Simulations showed that recommended regimens appropriately cover MIC_{90} in patients with CL_{CR} <60 mL/min. Patients with CL_{CR} of 60 to <90 mL/min need 6 g/day to achieve appropriate coverage. In patients with CL_{CR} ≥90 mL/min, appropriate exposure is achieved with increased dose, frequency of administration and infusion duration, or continuous infusion.

Conclusions: Recommended meropenem regimens are suboptimal in ICU patients with normal or augmented renal clearance. Modified dosing or infusion modalities achieve appropriate MIC coverage for optimized antibacterial efficacy in meropenem-susceptible life-threatening infections.

Introduction

Sepsis is a leading cause of death in critically ill patients despite prompt administration of an appropriate antimicrobial therapy at recommended dosing regimens.[1–4] Standard drug dosing may not be suited to the specific pharmacokinetic (PK) characteristics of this patient population.[5–8] Altered fluid status, microvascular failure and rapid changes in renal and hepatic function significantly modify drug PK. Insufficient antibiotic exposure, particularly for

microorganisms with reduced susceptibility, may be associated with treatment failure.[9]

Meropenem is a broad-spectrum β-lactam antibiotic of the carbapenem class. Unlike imipenem, meropenem is relatively stable in plasma, and does not require combination with a dehydropeptidase-1 inhibitor; however, meropenem has a short half-life of ∼1 h. Two percent of the drug is bound to plasma proteins and 98% is free circulating as microbiologically active fraction. Elimination is mainly renal through glomerular filtration and tubular secretion, with 60%–80% of the dose being recovered unaltered in the urine, 2% in the faeces and the remaining fraction being eliminated as inactive metabolite.[10–12] In renal failure, the half-life of meropenem is increased up to 10-fold. In continuous renal replacement therapy (CRRT), the half-life is ∼4.5 h, drug clearance being determined by the volume of filtrate produced and the dialysate flow rate.[13,14]

The best pharmacodynamic (PD) predictor of microbiological efficacy of β-lactam antibiotics is the percentage of the time interval (*T*) between two administrations during which the plasma concentration of the unbound drug fraction (*f*) exceeds the MIC for the causative pathogen (% $fT_{>MIC}$). *In vitro* and animal studies have shown a maximum killing rate at 40% $fT_{>MIC}$ for carbapenems, whereas 60%–70% and 50% are required for penicillins and cephalosporins, respectively.[15,16] Clinical studies suggest that a higher exposure is required for efficacy, in particular in patients with severe infections.[17,18] Recently, an association between favourable clinical outcome and 100% $fT_{>MIC}$ was reported in critically ill patients.[9] Additionally, a more aggressive target of 100% $fT_{>4\times MIC}$ has been proposed to suppress the emergence of resistance, with uncertain impact on individual clinical outcomes.[19] Whether these targets can be achieved with recommended meropenem dosing regimens remains uncertain, particularly in patients with infections due to pathogens with higher MICs such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. In critically ill patients with sepsis, burns or poly-trauma, augmented renal clearance (ARC) predicted subtherapeutic β-lactam concentrations.[7,19–23] Whereas dose adjustment is routinely recommended in patients with impaired renal function, the dose increase in patients with ARC is not standard practice.[24]

We performed a population PK analysis to characterize the PK profile of meropenem in critically ill patients in variable renal function or renal replacement therapy and assessed the appropriateness of recommended dosing regimens for MIC coverage in ICU patients with life-threatening infections through simulations.

Materials and methods

Study design and population

This study was performed in a 35-bed tertiary medico-surgical ICU at the Lausanne University Hospital. Ethics approval was obtained from the institutional ethics committee on human research (protocol no. 109/08).

Eighty-six adult patients admitted to the ICU from October 2010 to March 2013 and receiving meropenem treatment were either prospectively enrolled in a therapeutic drug monitoring (TDM) study, which aimed to assess the clinical utility of measuring antibiotic blood concentrations ($n = 30$) or were included in the institutional TDM programme, which aimed to individualize drug dosing according to blood concentrations and clinical plus microbiological characteristics ($n = 56$). In both settings, clinical, laboratory and pharmacological data were collected from the electronic health records. In addition, data from 15 patients enrolled in a previous study by Robatel *et al.*[14] on continuous veno-venous haemodiafiltration (CVVHDF) with rich meropenem plasma and filtrate–dialysate fluid samplings were included in the analysis ($n = 101$). An independent dataset from 43 individuals undergoing meropenem TDM between April and September 2013 was used for external model validation.

Clinical and laboratory data included age, gender, body weight, serum creatinine, SAPS II and APACHE II scores,[25,26] hospital and ICU length of stay, and overall survival. Data on clinical and microbiological documentation of infection as well as severity at presentation were collected. Pharmacological data included meropenem dosing schedule, timing, infusion time, use of CRRT, i.e. haemofiltration or haemodiafiltration, with predilution, post-dilution and effluent flow rates. CL_{CR} was calculated with the Cockcroft–Gault equation.[27] ARC was defined as CL_{CR} between 130 and 160 mL/min. CRRT was performed using 1.2 m^2 filters (Aquarius system with Aquamax Hemofilter; Baxter, USA). Filter flow rate was calculated as the sum of pre-dilution, post-dilution and effluent flow rates.

Infectious episodes were categorized according to the modified definitions from the International Immunocompromised Host Society: microbiologically documented infection with or without bacteraemia, clinically documented infection, or fever of unknown origin.[28] The sites of infection were characterized based on the clinical and microbiological documentation. The severity of infection was classified according to international definitions.[29]

Microbiological data for pathogens documented in cultures included species identification and MIC of meropenem. EUCAST epidemiological MIC cut-off values were used for analysis in the absence of a quantified MIC. MIC_{50} and MIC_{90} of the isolated microorganisms were calculated. Two mg/L is the clinical MIC breakpoint for meropenem susceptibility in the majority of bacteria according to EUCAST.[30]

Sample collection and analysis

For patients participating in the prospective study or from the TDM programme, 3 mL venous blood samples were collected at steady-state, i.e. after a minimum of three identical doses, usually 2–4 days after initiating meropenem therapy and after a change in meropenem dosage. The 30 patients included in the prospective study had samples drawn at peak (1 h) and trough (8–12 h) hours after drug administration, depending on the meropenem regimen used. The patients from the TDM programme had samples drawn at trough. The blood collection procedure at serial timepoints during the dosing interval in 15 patients from the Robatel *et al.*[14] study is described in that publication. Data on plasma and filtrate–dialysate meropenem concentrations in 15 patients from Robatel *et al.*[14,31] were extracted from the study database.

Blood samples were collected in citrated tubes and immediately stored at 4°C in the hospitalization unit. The samples were centrifuged within 1 hour and frozen at −80°C. Meropenem plasma concentrations were quantified by UPLC-MS for the prospective study and the TDM programme or by HPLC-UV for the Robatel *et al.*[14] study. Both methods were validated according to international analytical standards (±15% inaccuracy and precision) as recommended by the FDA and the Conference Report of the Washington Conference on 'Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies' and the Arlington Workshop.[32–36] An internal cross-validation showed a concordance of meropenem concentrations (accuracy ±95%) measured with the two analytical methods.

PK analysis

Data analysis was performed using the non-linear mixed effect modelling program NONMEM® ver. 7.2[37] with the PSN-toolkit v. 3.5.3 and Xpose4.[38–41] A stepwise procedure was undertaken to determine the model that best

Table 1. Recommended meropenem dosing regimens according to creatinine clearance

	Creatinine clearance (mL/min)				
	>90	60 to <90	30 to <60	15 to <30	CRRT[14]
Standard dosing[a]	1000 mg q8h	1000 mg q8h	1000 mg q12h	500 mg q8h	1000 mg q12h
Dosing in severe infections	2000 mg q8h	2000 mg q8h	2000 mg q12h	1500 mg q12h	1500 mg q12h

[a]Manufacturer's recommendations.[12]

fitted the data. Graphical exploration, figures generation and statistical analyses were performed using the R package v. 2.15.1 (http://www.r-project.org/) and STATA® v.13 (StataCorp LP).

Base model

Model development was first conducted on the rich plasma and filtrate–dialysate data collected in 15 patients of the Robatel *et al.*[14] study. Multicompartment models with linear elimination were compared to describe plasma concentration–time profiles. Distinct meropenem clearance was assumed for patients undergoing CRRT versus those with spontaneous renal clearance (CL_{CRRT} or $CL_{no\text{-}CRRT}$). Meropenem extracorporeal clearance due to CVVHDF was directly integrated in the model using the relationship $CL_{CRRT} = S_c \cdot Q_{FD}$, where S_c is the sieving coefficient, defined as the ratio between plasma and filtrate–dialysate concentrations, and Q_{FD} the filtrate–dialysate flow. A residual CL (CL_{res}) was estimated to account for the non-renal elimination of meropenem. Total meropenem clearance in patients undergoing CRRT was assumed to be the sum of $CL_{CRRT} + CL_{res}$. Estimated parameters were drug clearances ($CL_{no\text{-}CRRT}$, CL_{res}), volumes of distribution as well as S_c. Between-subject variability was described by exponential errors following a log-normal distribution. Proportional, additive and mixed proportional-additive error models were compared to describe residual variability in plasma and filtrate–dialysate fluid.

The obtained base model was extended and refined on the complete model-building dataset, distinguishing patients undergoing CRRT. Distinct intra-individual variabilities were associated with rich, TDM study and routine TDM data. We assumed a similar S_c for CVVH and CVVHDF as a negligible difference of meropenem extraction has been found between the two methods.[42]

Covariate analysis

Visual inspection of the relationships between individual Bayesian parameter estimates and the covariates was carried out first. Sequential forward insertion followed by backward deletion was then conducted for covariate testing using linear or non-linear functions (continuous covariates centred on the population median; dichotomous variables coded as 0/1). Missing values were imputed to the median population value for continuous covariates. Baseline characteristics evaluated for their impact on meropenem PK were gender, age, body weight and CL_{CR}.

Parameter estimation and model selection

The data were fitted using the first-order conditional estimation method with interaction. Difference in NONMEM® objective function value (ΔOFV), along with diagnostic goodness-of-fit plots, were employed to discriminate between hierarchical models (as ΔOFV for nested models approximates a χ^2 distribution). A 3.8 ($P = 0.05$) and 6.6 ($P = 0.01$) point change for one additional parameter for forward insertion and backward deletion procedures, respectively, was considered statistically significant.

Model validation

The final model stability was assessed by the bootstrap method, computing 2000 replicates of the original dataset.[38,39] The derived median parameter values with their CIs (95% CI) were compared with original estimates. Prediction-corrected visual predictive checks (pcVPC) were performed by simulations based on the final PK model with variability using 1000 individuals to calculate median and 90% prediction intervals with their 95% CI.[38–41] Finally, population and individual *post hoc* concentrations derived from applying the final PK model on the external model validation dataset were analysed to assess model accuracy by mean prediction error.[43,44]

Dosing regimen simulations

Monte Carlo simulations based on the final model with variability were undertaken to assess the adequacy of different meropenem dosing regimens. One thousand 70 kg individuals were simulated for each regimen assuming uniformly distributed Q_{FD} or CL_{CR} over the range of interest (i.e. Q_{FD}: 1000 to <2000 mL/h or 2000 to <3000 mL/h; CL_{CR}: 15 to <30, 30 to <60, 60 to <90, 90 to <130 or 130–160 mL/min) for patients with and without CRRT, respectively. Analysed meropenem dosing regimens included 0.5, 1 and 2 g q12h and q8h as well as 1.5 g q12h with 30 min infusion for subjects undergoing CRRT or with impaired renal function (CL_{CR} <60 mL/min). These meropenem dosing regimens were based on manufacturer and hospital recommendations (Table 1). Meropenem infusions >30 and 120 min for six dosing regimens (0.75/1.5 g q6h, 0.5/1 g q4h and 1/2 g q8h) were simulated for normal clearance (60 mL/min<CL_{CR}<130 mL/min) and ARC. Finally, the performance of continuous meropenem infusions using the same total daily dose as in the above regimens was simulated for comparison. The PTA was calculated over a range of doubling MICs from 0.125 to 64 mg/L with a target of 100% $fT_{>MIC}$. Regimens with PTAs >90% were considered appropriate.

Results

Model development was performed on 380 meropenem plasma concentrations in 101 ICU patients (median per patient 2, range 1–20), in addition to 129 filtrate–dialysate samples (9, 7–10). Eighty plasma concentrations from 43 patients (1, 1–8) were analysed for model validation. Patient characteristics in model building and external validation datasets are shown in Table 2. Forty-nine percent of patients underwent CRRT, 32% of the remaining cases had a CL_{CR} >60 mL/min.

One hundred and twenty-seven meropenem-susceptible pathogens were documented with an MIC_{50} of 0.125 mg/L (IQR 0.125–0.5 mg/L) and an MIC_{90} of 2 mg/L (Table 3). *P. aeruginosa* was isolated in 20 (15.7%) microbiologically documented infections.

Table 2. Patient demographics and clinical characteristics

Characteristics	Model building ($n = 101$)	External validation ($n = 43$)
Age, years	63 (49–70)	62 (50–69)
Male, *n* (%)	57 (56)	30 (70)
Body weight, kg	72 (58–85)	74 (64–87)
APACHE score,[a] points	22 (17–25)	22 (18–26)
SAPS II score,[a] points	38 (27–48)	38 (26–48)
Calculated CL_{CR},[b,c] *n* (%)		
>130 mL/min (ARC)	11 (11)	9 (21)
90–129 mL/min	7 (7)	10 (23)
60 to <90 mL/min	14 (14)	6 (14)
30 to <60 mL/min	17 (17)	5 (12)
15 to <30 mL/min	7 (7)	3 (7)
<15 mL/min	1 (1)	1 (2)
CRRT,[c,d] *n* (%)	49 (49)	12 (28)
ICU LOS,[a] days	22 (10–34)	17 (9–29)
Hospital LOS,[a] days	44 (28–78)	38 (25–77)
Duration of antibiotic therapy,[a,e] days	9 (6–14)	8 (5–14)
Classification of infection,[a,e] *n* (%)		
MDI-B	33 (33.7)	16 (32.0)
MDI-NB	34 (34.7)	22 (44.0)
CDI	9 (9.2)	10 (20.0)
FUO	22 (22.5)	2 (4.0)
Severity of infection,[a,e] *n* (%)		
sepsis	48 (49.0)	26 (52.0)
septic shock	31 (31.6)	16 (32.0)
multi-organ failure	7 (7.1)	1 (2.0)
Site of infection,[a,e] *n* (%)		
pneumonia	40 (40.8)	27 (54)
vascular catheter-related bacteraemia	12 (12.2)	5 (10)
cellulitis	12 (12.2)	2 (4)
peritonitis	9 (9.1)	5 (10)
other	3 (3.1)	9 (18)
unknown origin	22 (22.5)	2 (4)
Deaths, *n* (%)	39 (39)	17 (40)

Data are presented as median (IQR) or number (%).
APACHE, Acute Physiology and Chronic Health Evaluation; SAPS II, Simplified Acute Physiology Score II; LOS, length of stay; MDI, microbiologically documented infection with (-B) or without (-NB) bacteraemia; CDI, clinically documented infection; FUO, fever of unknown origin.
[a]No data available for patients from the study by Robatel *et al.*[14]
[b]Median CL_{CR} for each patient not receiving CRRT was retrieved for assigning the patient to the appropriate CL_{CR} subgroup.
[c]Seven patients in the model-building dataset and three in the external validation dataset received CRRT for a limited period of time during their ICU stay. They were assigned to the CRRT group and one of the calculated CL_{CR} subgroups.
[d]CRRT includes haemofiltration and haemodiafiltration.
[e]Eight patients presented multiple infectious episodes.

Base model

A two-compartment model including CL_{CRRT} with interpatient variability assigned to CL_{res}, S_c and central volume of distribution (V_c) best described the rich meropenem dataset collected in the Robatel *et al.*[14] study ($\Delta OFV = -218$, $P < 0.001$ compared with a one-compartment model). No-fit improvement was observed by assigning an interpatient variability to the intercompartmental clearance (Q) or to the peripheral volume of distribution (V_p) or by using three compartments ($\Delta OFV > -2.5$, $P = 0.11$). Residual variability for plasma and filtrate–dialysate concentrations was described by a mixed error model. The PK model applied to the entire model-building dataset with the additional estimation of $CL_{no\text{-}CRRT}$ provided an adequate characterization of the data. Equal interpatient variability was associated with both clearances. The final population base parameters with interpatient variability (CV%) were: $CL_{no\text{-}CRRT}$ 8.0 L/h (57%), CL_{res} 3.5 L/h (57%), S_c 0.75 (27%), V_c 17 L (60%), Q 13 L/h and V_p 16 L. The calculated mean total clearance was 4.8 L/h (IQR 3.5–6.3 L/h) in patients undergoing CRRT.

Covariate analysis

Univariate analyses showed a significant 62% lower meropenem $CL_{no\text{-}CRRT}$ in patients with impaired (CL_{CR} 30 mL/min) versus normal (CL_{CR} 100 mL/min) renal function ($\Delta OFV = -66$, $P < 0.001$). Furthermore, a 100% decrease in $CL_{no\text{-}CRRT}$ was observed by doubling the age compared with the median population value ($\Delta OFV = -15$, $P = 0.0001$). No associations were identified between age and CL_{CRRT} ($\Delta OFV = -2.9$, $P = 0.09$) or between gender or body weight and $CL_{CRRT}/CL_{no\text{-}CRRT}$ ($\Delta OFV > -1.2$, $P = 0.27$). Body weight on V_c using an allometric function resulted in a marked improvement of fit ($\Delta OFV = -20$, $P < 0.001$), but without further improvement by introducing a gender effect ($\Delta OFV = 0$, $P = 1$). Multivariate analyses and backward deletion allowed discarding the effect of age on $CL_{no\text{-}CRRT}$ while maintaining the effect of CL_{CR} in addition to body weight on V_c. The final model parameter values with bootstrap estimations are presented in Table 4.

Model validation

The model was reliable: the obtained parameter estimates lied within the bootstrap 95% CI, differing by <6% from the bootstrap median values. The predictive model performance was corroborated by the pcVPC shown in Figure 1. Insignificant biases of 10% (95% CI −5% to 28%) and 20% (95% CI −7% to 55%) at individual and population prediction levels were calculated applying the final model with covariates to the external validation dataset.

Dosing simulations

PTA values for 100% $fT_{>MIC}$ obtained by Monte Carlo simulations of different recommended dosing regimens for patients with CRRT or CL_{CR} from 15 to >130 mL/min are shown in Tables 5 and 6, respectively, for intermittent administrations, and in Tables 7 and 8, respectively, for continuous infusions.

Using intermittent administration, recommended regimens of 1/1.5 g q12h over 30 min achieved 90% PTA for pathogens with MIC ≤2 mg/L in patients undergoing CRRT with a filtration rate of 1000 to <2000 mL/h; 1.5 g q12h or 1 g q8h schedules achieved adequate PTA in CRRT with a filtration rate of 2000 to <3000 mL/h.

Schedules of 0.5 g q8h and 1.5 g q12h over 30 min resulted in adequate PTA in subjects with CL_{CR} of 15 to <30 mL/min. For CL_{CR} of 30 to <60 mL/min, 1 and 2 g q12h regimens produced an

Table 3. MIC_{50} and MIC_{90} of documented meropenem-susceptible pathogens

Organisms	*N* (%)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Gram-negative			
P. aeruginosa	20 (15.7)	2	2
Enterobacter spp.	20 (15.7)	0.125	0.125
Escherichia coli	19 (15)	0.125	0.125
Klebsiella spp.	15 (11.8)	0.125	0.125
Klebsiella pneumoniae	7 (5.5)	0.125	0.125
Serratia marcescens	4 (3.1)	0.25	0.25
Others	18 (14.2)	0.25	2
Subtotal	96 (75.6)	0.125	2
Gram-positive			
Staphylococcus spp.	18 (14.2)	0.5	0.5
Staphylococcus aureus	4 (3.1)	0.5	0.5
Streptococcus spp.	10 (7.9)	0.125	2
Streptococcus pneumoniae	6 (4.7)	0.016	0.25
Others	3 (2.4)	2	2
Subtotal	31 (24.4)	0.5	2
Total	127 (100)	0.125	2

ECOFFs, EUCAST epidemiological cut-off values.
MIC_{50}, 50% of pathogens have an equal or lower MIC; MIC_{90}, 90% of pathogens have an equal or lower MIC. ECOFFs were used when measured MICs of the causative pathogens were not available.

expected PTA for MIC ≤1 mg/L, whereas only the second achieved 90% PTA for MIC ≤2 mg/L.

The recommended dosing 1 g q8h achieves an appropriate PTA for MIC ≤1 mg/L in patients with CL_{CR} <90 mL/min. A dose of 2 g q8h achieves 90% PTA for MIC ≤2 mg/L.

Neither 1 nor 2 g q8h schedules reached 90% PTA in subjects with CL_{CR} of 90 to <130 mL/min for MIC >0.5 mg/mL: regimens with four or six daily infusions over 120 min are required. The label doses of 1 and 2 g q8h barely reach 90% PTA for MIC ≤0.5 mg/L in patients with ARC, i.e. CL_{CR} of 130–160 mL/min. Only 1 g q4h infusions over 120 min reached 90% PTA for an MIC ≤2 mg/L in these patients.

When using the corresponding total daily dose administered in continuous infusion, 100% PTA for MIC of 2 mg/L was reached in all categories of renal function, including ARC.

Discussion

Meropenem blood concentration data in critically ill patients with susceptible life-threatening infections, including a subgroup undergoing CRRT, were analysed by a population PK approach aimed at evaluating the adequacy of recommended dosing regimens. Visual, internal and external model validations support the accuracy and stability of a two-compartment model with linear elimination.[44,45] Our estimates of PK parameters are consistent with previous reports. The high distribution volume in our dataset lies within the range of previously reported values.[13,14,44–60] Among tested covariates, body weight influenced the volume of distribution and CL_{CR} determined meropenem clearance in patients not undergoing CRRT.[45–47] In individuals undergoing

Table 4. Meropenem population PK parameter estimates with bootstrap evaluations

	Population model		Bootstrap evaluation	
Parameter	estimate	RSE[a] (%)	estimate	95% CI[b]
CL_{res} (L/h)	3.2	12	3.2	(2.5–4.0)
S_c	0.75	8	0.76	(0.65–0.88)
$TVCL_{no\text{-}CRRT}$ (L/h)	5.9	7	5.9	(5.2–6.8)
θ_{CLCR} (%)	0.71	21	0.69	(0.40–0.94)
TVV_c (L)	16	15	16	(11–21)
θ_{BW}	1.7	19	1.7	(1.0–2.4)
Q (L/h)	14	9	14	(12–18)
V_P (L)	15	4	15	(14–17)
BSV_{CL} (CV%)	40	12	40	(31–49)
BSV_{Sc} (CV%)	26	23	26	(14–37)
BSV_{Vc} (CV%)	51	15	48	(17–65)
$\sigma^c_{prop\ rich\ plasma}$ (CV%)	4.1	43	4.0	(1.0–7.9)
$\sigma^d_{add\ rich\ plasma}$ (mg/L)	2.7	16	2.6	(1.7–3.6)
$\sigma^c_{prop\ rich\ FD}$ (CV%)	11	28	11	(6–17)
$\sigma^d_{add\ rich\ FD}$ (mg/L)	2.5	13	2.5	(1.7–3.1)
$\sigma^c_{prop\ TDM\ routine}$ (CV%)	52	15	52	(36–67)
$\sigma^c_{prop\ ongoing\ trial}$ (CV%)	38	7	37	(31–43)

$CL_{CRRT} = CL_{res} + S_c * Q_{FD}$.
$CL_{no\text{-}CRRT} = TVCL_{no\text{-}CRRT} * \left(1 + \theta_{CLCR} \frac{CLCR - median\ CLCR}{median\ CLCR}\right)$.
$V_c = TVV_c * \left(\frac{BW}{medBW}\right)^{\theta_{BW}}$.

CL_{CRRT}, total meropenem clearance in patients undergoing CRRT; CL_{res}, meropenem residual clearance in CRRT patients; S_c, sieving coefficient; Q_{FD}, FD flow; FD, filtrate–dialysate; $TVCL_{no\text{-}CRRT}$, typical value of clearance for patients not receiving CRRT; θ_{CLCR}, increase in $CL_{no\text{-}CRRT}$ due to CL_{CR} variation with respect to its median value (median CL_{CR} = 44 mL/min); TVV_c, typical value of the V_c; θ_{BW}, allometric power describing the effect of BW normalized by its median value (median BW = 72 kg); BW, body weight; V_c, central volume of distribution; RSE, relative standard errors; BSV, between-subject variability.
[a]RSE are defined as the ratio between the standard error and the parameter estimate retrieved directly from NONMEM® output files.
[b]95% bootstrap CI.
[c]Proportional component of the residual variability.
[d]Additive component of the residual variability.

CRRT, residual clearance accounted for a large part of total renal clearance, with a CL_{res}/CL_{tot} ratio of 0.63. This finding, comparable with those in previous reports,[13,14,42,44,48–51,53,55,57,59,61] may be explained by a higher non-renal clearance, which was shown to increase from 20% in healthy patients to 50% in patients with severe renal impairment, particularly in those undergoing CRRT. An increased hepatic or spontaneous degradation of meropenem into inactivated metabolites is presumed in these patients.[62,63]

The large intra- and inter-individual variability characterizing meropenem PK confirms that individualized dosing is a key point in optimizing drug exposure and antimicrobial efficacy.[6,8] TDM is useful for identifying patients in whom meropenem blood concentrations lay outside the targeted therapeutic interval and who may benefit from individual dosing adjustment.[64–66] As TDM is not routinely available for real-time guidance for dose adjustments, optimizing dosing regimens according to CL_{CR} is an alternative

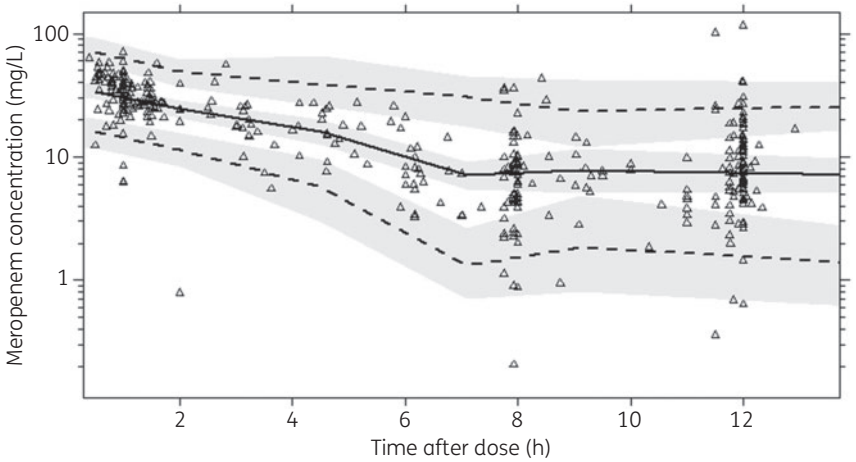

Figure 1. Prediction-corrected visual predictive check of the final PK model with observed meropenem concentrations (triangles), median simulated population prediction (solid line) with 90% prediction intervals (90% PI, dashed lines). Shaded areas represent the 95% CI of model-predicted percentiles.

Table 5. PTA for achieving 100% $fT_{>MIC}$ for different simulated meropenem dosing regimens in 70 kg patients undergoing CRRT as a function of CVVHDF filtration rate

	PTA (%) of 100% $fT_{>MIC}$ at the indicated MIC (mg/L)									
Filtration rate/dosing regimen	0.125	0.25	0.5	1	**2**	4	8	16	32	64
1000 to <2000 mL/min										
1 g q12h	100	100	99.4	96.9	**90.4**	75.6	47	14.8	1.6	0.1
1.5 g q12h	100	99.9	99.8	98.8	**95.7**	88.2	69.2	35.3	5.5	0.2
2000 to <3000 mL/min										
1 g q12h	99.5	98.8	97.7	94	**84.8**	64.7	32.7	7.1	0.3	0
1.5 g q12h	99.9	99.8	99.2	97.2	**90.8**	79.8	52.8	21.7	2.6	0
1 g q8h	*100*	*99.9*	*99.7*	*99.1*	***97.7***	*90.4*	*68.9*	*33.3*	*5.3*	*0.1*

Perfusion time was 30 min.
Results are shown in bold for an MIC of 2 mg/L, corresponding to the MIC_{90} of the isolated pathogens in the present study and to the clinical MIC breakpoint for meropenem susceptibility of the majority of bacteria according to EUCAST.
Alternative regimen showing a better PTA according to the renal function is shown in italics.

approach, particularly in critically ill populations with severe infections and altered renal elimination that may result in treatment failure.[7,19,21–23]

Considering a PK/PD target of 100% $fT_{>MIC}$, we observed that the risk of suboptimal drug exposure is low with recommended dosing regimens for an MIC_{50} of 0.125 mg/L. However, as species identification and antibacterial susceptibility of the causative pathogen are unknown when empirical meropenem is started, prompt coverage for the worst-case scenario needs to be achieved. In our study, the MIC_{90} was 2 mg/L, which corresponds to the clinical breakpoint for meropenem susceptibility of the majority of bacteria according to EUCAST.[30] A meropenem concentration of 2 mg/L is thus an appropriate MIC target for empirical antibacterial coverage in critically ill patients with severe infections. Our simulations emphasize the need for adjustment of recommended dosing regimens. While these schedules result in appropriate PTA in patients with impaired renal function, higher doses are needed when CL_{CR} is >60 mL/min. A combination of higher doses, shorter dosing intervals or longer infusion times represents an efficient strategy for optimizing PTA in intermittent administration, e.g. with 1.5 g q6h or 0.5 g q4h infused over 120 min. Identification of patients with ARC (CL_{CR} of 130–160 mL/min) is crucial, as standard meropenem regimens are insufficient in intermittent administration. Only a regimen of 1 g q4h infused over 120 min reaches an appropriate PTA for an MIC of 2 mg/L. Continuous infusion is also an option for optimally ensuring MIC coverage over the whole dosing interval in patients with ARC. These observations corroborate recent reports and highlight the importance for clinical ICU practice of meropenem regimen adjustment in patients with ARC.[7,19,21–23]

According to our data, the PK/PD target 100% $fT_{>4\times MIC}$ (i.e. 8 mg/L in the empirical setting) would not be achievable with intermittent meropenem infusions, at least not without a significant increase in the daily dosage. Whereas our simulations show that the recommended regimens fail to achieve this target at any level of renal function, a systematic use of continuous infusion would

Table 6. PTA for achieving 100% $fT_{>MIC}$ for different simulated meropenem dosing regimens in 70 kg patients as a function of renal creatinine clearance

	PTA (%) of 100% $fT_{>MIC}$ at the indicated MIC (mg/L)									
CL_{CR} (mL/min)/dosing regimen	0.125	0.25	0.5	1	**2**	4	8	16	32	64
15 to <30 mL/min										
0.5 g q8h	100	99.9	99.6	99.4	**98**	90.7	63.5	22.2	2.2	0
1.5 g q12h	100	100	100	99.6	**97.5**	92.5	79.4	48.3	14.7	1.1
30 to <60 mL/min										
1 g q12h	99.7	98.8	95.7	89.4	**76.3**	51.4	24.9	6.1	0.7	0
2 g q12h	99.9	99.4	98.7	96.6	**89.5**	75.4	49.8	24.1	6.1	0.7
60 to <90 mL/min										
1 g q8h	99.9	99.4	96.9	91.3	**79.4**	53.8	22.5	4.1	0.2	0
2 g q8h	100	100	99.8	97.8	**92.5**	79.4	52.8	20.6	4	0.1
90 to <130 mL/min										
1 g q8h	99.2/99.81[a]	96.2/98.1[a]	89.5/94.4[a]	75.5/83.1[a]	**53.1/60.8**[a]	27.3/34.1[a]	6.4/9[a]	0.8/1.2[a]	0/0[a]	0/0[a]
2 g q8h	99.4/100[a]	98.3/99.4[a]	95.8/97.7[a]	89.3/93.4[a]	**73.3/80.9**[a]	49/58.5[a]	26.7/34.4[a]	6.4/9.4[a]	0.8/1.1[a]	0/0[a]
1.5 g q6h	*100/100*[a]	*99.9/100*[a]	*99.5/99.9*[a]	*95.6/98.6*[a]	***85.3/92.3***[a]	*67.1/76.9*[a]	*37.5/48*[a]	*12.7/17*[a]	*1.8/2.9*[a]	*0/0*[a]
1 g q4h	*100/100*[a]	*100/100*[a]	*100/100*[a]	*99.5/100*[a]	***96/99.1***[a]	*83/91.6*[a]	*54.9/69.6*[a]	*22.2/31.5*[a]	*2.7 /4.1*[a]	*0.1/0.1*[a]
>130 mL/min										
1 g q8h	94.2/97[a]	86.5/92.2[a]	67.6/77.6[a]	47.5/57.4[a]	**26.7/32.9**[a]	10.5/14.5[a]	1.6/2.6[a]	0.1/0.1[a]	0/0[a]	0/0[a]
2 g q8h	98.2/99.1[a]	94.9/97.5[a]	85.5/92.1[a]	71.2/78.9[a]	**50.1/60.9**[a]	27.1/36[a]	8.1 /12.3[a]	1.1 /2.4[a]	0/0[a]	0/0[a]
1.5 g q6h	*99.5/100*[a]	*98.8 /99.3*[a]	*96.2 /98.1*[a]	*88 /93.3*[a]	***67.5/80.7***[a]	*40.6/53.2*[a]	*14.6/24.2*[a]	*2.1/4.1*[a]	*0/0.5*[a]	*0/0*[a]
1 g q4h	*100/100*[a]	*100/100*[a]	*99.4/100*[a]	*97.1/99.1*[a]	***87.3/95***[a]	*65/79.7*[a]	*33.2/47.7*[a]	*8.4/13.7*[a]	*0.4/0.7*[a]	*0/0*[a]

Perfusion time was 30 min unless indicated.
Results shown in bold are for an MIC of 2 mg/L, corresponding to the MIC_{90} of the isolated pathogens in the present study and to the clinical MIC breakpoint for meropenem susceptibility of the majority of bacteria according to EUCAST.
Alternative regimens showing a better PTA according to the renal function are shown in italics.
[a]Perfusion time was 120 min.

Table 7. PTA for achieving 100% $fT_{>MIC}$ using different simulated meropenem dosing regimens of continuous infusion in 70 kg patients undergoing CRRT as a function of CVVHDF filter rate

	PTA (%) of 100% $fT_{>MIC}$ at the indicated MIC									
Filtration rate/dosing regimen	0.125	0.25	0.5	1	**2**	4	8	16	32	64
1000 to <2000 mL/min										
2 g q24h	100	100	100	100	**100**	100	98.7	68.3	10.8	0.2
3 g q24h	100	100	100	100	**100**	100	99.9	92.3	39.5	2.9
2000 to <3000 mL/min										
1.5 g q24h	100	100	100	100	**100**	99.6	83.3	22.7	.8	0
2 g q24h	100	100	100	100	**100**	100	95.3	51.7	4.4	0.1

Results for an MIC of 2 mg/L are shown in bold, corresponding to the MIC_{90} of the isolated pathogens in the present study and to the clinical MIC breakpoint for meropenem susceptibility of the majority of bacteria according to EUCAST.

achieve target attainment. Indeed, continuous infusion shows adequate PTA for both targets (i.e. 100% $fT_{>MIC}$ and 100% $fT_{>4\times MIC}$), even with a standard dose of 3 g/day in patients with ARC. Waiting for clinical evidence on the benefit of this higher PK/PD target for patient outcomes, intermittent meropenem therapy is a suitable option for optimizing microbiological efficacy with a meropenem trough concentration >2 mg/L (MIC_{90} in our population and EUCAST susceptibility MIC breakpoint) as a conservative and recognized standard for PK/PD target.

The estimation of renal function based on CL_{CR} correlates poorly with the measured renal function in ICU patients, which represents a limitation in our study.[67,68] Although the adequacy of pooling patients investigated in different settings may be challenged, this heterogeneity has been accounted for by using distinct residual error models, which best preserved model robustness. EUCAST cut-off MICs were used when MICs of the causative pathogens were not available. Although this approach possibly overestimated the MIC_{90} in our ICU setting, a strategy for empirical meropenem

Table 8. PTA for achieving 100% $fT_{>MIC}$ using different simulated meropenem dosing regimens of continuous infusion in 70 kg patients as a function of renal creatinine clearance

	PTA (%) of 100% $fT_{>MIC}$ at the indicated MIC (mg/L)									
CL_{CR}/dosing regimen	0.125	0.25	0.5	1	**2**	4	8	16	32	64
15 to <30 mL/min										
1.5 g q24h	100	100	100	100	**100**	100	97.3	59.2	6.5	0.1
3 g q24h	100	100	100	100	**100**	100	100	96	57.1	6
30 to <60 mL/min										
2 g q24h	100	100	100	100	**100**	99.9	93	41.1	2.5	0
4 g q24h	100	100	100	100	**100**	100	100	92.7	40.8	1.6
60 to <90 mL/min										
3 g q24h	100	100	100	100	**100**	99.9	91.6	38.4	1.9	0
6 g q24h	100	100	100	100	**100**	100	99.9	92.8	40.2	2.2
90 to <130 mL/min										
3 g q24h	100	100	100	100	**100**	98.9	70.4	12.1	0.3	0
6 g q24h	100	100	100	100	**100**	100	99.6	73.6	12.8	0.6
>130 mL/min										
3 g q24h	100	100	100	100	**100**	96.8	50.7	5.2	0	0
6 g q24h	100	100	100	100	**100**	100	96.5	49.3	3.9	0.1

Results for an MIC of 2 mg/L are shown in bold, corresponding to the MIC_{90} of the isolated pathogens in the present study and to the clinical MIC breakpoint for meropenem susceptibility of the majority of bacteria according to EUCAST.

therapy in critically ill patients with severe infections that targets the coverage of an MIC of 2 mg/L, the clinical breakpoint for susceptibility in the majority of microorganisms, is suitable for optimizing clinical outcome. Finally, data regarding CRRT may vary according to haemofilter type and age, which might limit the application of our simulation in different CRRT settings.

In comparison with other studies, we present here a model based on a large sample size, which was externally validated with an independent dataset of critically ill patients with similar clinical characteristics. This methodological approach is often lacking in PK/PD studies and represents an advantage of the present study conferring robustness to our observations.[69] The adequacy of multiple meropenem dosing regimens over the whole range of renal function, from CRRT to ARC, was assessed with both short and prolonged intermittent infusions as well as with continuous infusions. PTA simulations over a large range of MIC values enable ICU physicians to optimize dosing strategies according to the PK/PD target (i.e. 100% $fT_{>MIC}$ or 100% $fT_{>4\times MIC}$) in the empirical setting (coverage of MIC_{90} or of the susceptibility MIC breakpoint) or according to the actually documented MIC in a given patient. Finally, insufficient antimicrobial coverage markedly characterizes patients with normal or augmented renal function. Efforts to optimize the use of meropenem should focus on this particular population. This is in agreement with recent reports highlighting the urgent need for sensitizing ICU physicians to the clinical efficiency of individualized meropenem dosing regimens in critically ill patients with ARC.[7,19,21–23]

Conclusions

The recommended meropenem dosing regimens in ICU patients with normal or augmented renal clearance do not ensure coverage of pathogens with MICs within the susceptible range. Strategies combining a higher dose, an increased number of daily administrations and prolonged infusion time, or continuous infusion, are required to optimize meropenem exposure and antimicrobial efficacy in susceptible life-threatening infections.

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Transparency declarations

None to declare.

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