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# Population Pharmacokinetics and Pharmacodynamics of Meropenem in Critically Ill Patients: How to Achieve Best Dosage Regimen According to the Clinical Situation

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## Abstract

**Background and Objectives** Meropenem is frequently used for the treatment of severe bacterial infections in critically ill patients. Because critically ill patients are more prone to pharmacokinetic variability than other patients, ensuring an effective blood concentration can be complex. Therefore, describing this variability to ensure a proper use of this antibiotic drug limits the rise and dissemination of antimicrobial resistance, and helps preserve the current antibiotic arsenal. The aims of this study were to describe the pharmacokinetics of meropenem in critically ill patients, to identify and quantify the patients' characteristics responsible for the observed pharmacokinetic variability, and to perform different dosing simulations in order to determine optimal individually adapted dosing regimens.

**Methods** A total of 58 patients hospitalized in the medical intensive care unit and receiving meropenem were enrolled, including 26 patients with renal replacement therapy. A population pharmacokinetic model was developed (using NONMEM software) and Monte Carlo simulations were performed with different dosing scenarios (bolus-like, extended, and continuous infusion) exploring the impact of clinical categories of residual diuresis (anuria, oliguria, and preserved diuresis) on the probability of target attainment (MIC: 1–45 mg/L).

**Results** The population pharmacokinetic model included five covariates with a significant impact on clearance: glomerular filtration rate, dialysis (continuous and semi-continuous), renal function status, and volume of residual diuresis. The clearance for a typical patient in our population is 4.20 L/h and volume of distribution approximately 44 L. Performed dosing regimen simulations suggested that, for equivalent doses, the continuous infusion mode (with loading dose) allowed the obtaining of the pharmacokinetic/pharmacodynamic target for a larger number of patients (100% for MIC  $\leq$  20 mg/L). Nevertheless, for the treatment of susceptible bacteria (MIC  $\leq$  2 mg/L), differences in the probability of target attainment between bolus-like, extended, and continuous infusions were negligible.

**Conclusions** Identified covariates in the model are easily accessible information in patient health records. The model highlighted the importance of considering the patient's overall condition (renal function and dialysis) and the pathogen's characteristics (MIC target) during the establishment of a patient's dosing regimen.

## 1 Introduction

Bacterial infections in critically ill patients are still a major issue in modern medicine, due to their high prevalence (approximately 50% [1]) and important mortality rate (up to 60% in special situations like septic shock or sepsis [1–4]). Two main issues arise when critically ill patients have to be treated with an antibiotic therapy. First, the available therapeutic arsenal of anti-infection medicines is limited.

Bacterial pathogens responsible for infections in the intensive care unit (ICU) are generally less sensitive than pathogens found in other care units [5, 6], and multidrug-resistant bacteria (MDRB) are on the rise [7, 8].

Second, dosing regimens are rarely adapted to the patients' needs. Most dosing guidelines are currently built on pharmacokinetics studies but without ICU patients, and as a result exclude all the pharmacokinetic variability observed in critically ill patients. Due to their critical condition and related pathophysiological changes, ICU patients are more prone to pharmacokinetic variability than other patients [9–13]. To predict the impact of critically ill patients' pharmacokinetic variability on drug exposure is complex,

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## Key Points

Meropenem is a broad-spectrum antibiotic used in critically ill or ICU patients.

Sources of pharmacokinetic variability in ICU patients are large and ensuring an efficient dose is complex.

Information on pharmacokinetics and pharmacodynamics of meropenem helps to obtain a better antibiotic treatment outcome in patients.

suggesting that empirical dosing strategies are not the best way to achieve effective exposures [14, 15].

Therefore, it is crucial to study and describe this pharmacokinetic variability to ensure a proper use of antibiotic drugs, i.e., select the dose that will generate the optimal drug exposure [16, 17], thus limiting the rise and dissemination of antimicrobial resistance, and preserving the current therapeutic arsenal [18].

Meropenem is a broad-spectrum antibiotic drug prescribed for MDRB infections or empirical treatment of serious infections, commonly administered in critically ill patients. Meropenem is a hydrophilic small molecule with a low-level of protein binding ( $f < 2\%$ ) and a large tissue distribution. The drug is mainly eliminated by the kidneys (~ 70% of the dose excreted in the urine after 12 h) and partially eliminated as an inactive metabolite (~ 28%). Meropenem is a dialyzable drug with a linear pharmacokinetics between 500 mg and 2 g. Like all carbapenems, Meropenem has a time-dependent antibacterial efficiency: to obtain an optimal bactericidal activity, the blood concentration must be maintained above the minimum inhibitory concentration (MIC) during at least 40 % of the dosing interval ( $40\% T > \text{MIC}$ ) [19].

The aims of this study are to describe the pharmacokinetics of meropenem in critically ill patients, to identify and quantify the patients' characteristics responsible for the observed pharmacokinetic variability, and to perform different dosing simulations in order to determine optimal individually adapted dosing regimens.

## 2 Methods

This non-interventional study protocol was approved by the Ethics Committee (study ID: CIMER, 2019\_IRB-MTP\_03-01). Blood concentrations of meropenem were collected retrospectively from November 2017 to February

2019 in patients of the ICU of the university hospital of Montpellier (France).

### 2.1 Patients

Inclusion criteria were known or suspected infection of a critically ill patient in the medical ICU and treated with meropenem. Exclusion criterion was age ( $< 18$  years old). Main causes of admission in the ICU were severe organ failure (heart, kidney, liver, respiratory, or hematologic), immunodeficiency, hematologic malignancies, severe metabolic complications, vital distress situations, and cardiac arrest victims (acute or prolonged phase).

### 2.2 Drug Administration

All patients received meropenem (Meropenem<sup>®</sup> IV, intravenous, AstraZeneca, or its generic products) via infusion or IV bolus. Drug administration information (dose, type, time, etc.) was collected in the hospital electronic medical record system. Meropenem dosing regimen was left up to the clinician decision (1 or 2 g Q6H, Q8H, or Q12H  $\pm$  loading dose). Pharmacokinetic/pharmacodynamic objective was to maintain serum concentration:  $C_{\text{meropenem}} = 5 \times \text{MIC}$  during 100% of time.

### 2.3 Demographic and Clinical Data

The patients' demographic, clinical, and biological data were recorded. Age, height, weight, sex, volume of residual diuresis, settings of renal replacement therapy (RRT, type of RRT—continuous or semi continuous—and session timetables), co-medications, shock-state associated information, standard blood test results, isolated micro-organisms, and meropenem corresponding MICs and number of days of antibiotic therapy were collected. Creatinine clearance values were derived from biological test results (blood and urine), using Cockcroft–Gault, modification of diet in renal disease (MDRD), chronic kidney disease-epidemiology collaboration (CKD-EPI) formulas or urine/plasma creatinine ratio. Patient data were included in the pharmacokinetic analysis if they contained informed dosing history and at least one adequately documented and quantifiable meropenem concentration per patient.

### 2.4 Sample Analysis

Actual times for data sampling were left at the discretion of the treating physician, depending on clinical observations. Meropenem concentrations were determined with pharmacokinetic samples (5 mL of venous blood in a serum clot activator tube) collected during routine therapeutic drug monitoring (TDM). For stability purposes, samples were

stored at  $-80^{\circ}\text{C}$  until assay. After adaptation, the bioanalytical method [20] was validated according to the requirements of the NF EN ISO 15189 standard (accreditation of medical biology laboratories) and the recommendations of the European Medicines Agency for TDM context [21]. Total serum concentrations of meropenem were measured using ultra-high-precision liquid chromatography (UHPLC) with a diode array ultraviolet detection (UHPLC UltimateTM 3000 System; ThermoFisher Scientific). The analytical column used was a HPLC Hypersil™ Gold pentafluorophenyl 100 mm, 2.1 mm diameter, 1.9  $\mu\text{m}$  grain size (ThermoFisher Scientific). Two mobile phases were used for the sample analysis: mobile phase A was composed of milli-Q water with a 10-mM concentration of phosphoric acid, while mobile phase B was pure acetonitrile. Analysis data acquisition and control were possible with Chromeleon™ software. Limit of quantification for meropenem was 3 ng/mL.

## 2.5 PopPK Analysis

Pharmacokinetic data from the study were analyzed by a non-linear mixed-effects modeling approach using NONMEM (v7.4.1) and its first-order conditional estimation method with the INTERACTION option. The development of the model followed a three-stage strategy: (1) selection of a structural model, (2) covariate screening and selection, and (3) evaluation of the final model. Outliers were defined as data points in the dataset that appear to be outside the norm for that particular dataset (e.g., data with conditional weighted residuals  $> 5$ ) based on inspection of the results from a preliminary PopPK run. A maximum 5% omission of these outliers was possible upon report and justification.

After visual inspection of the data and a literature review [22–35], different structural models have been explored to describe the pharmacokinetic data (one- and two-compartment(s) models with a first-order elimination rate). Additive, exponential, proportional, and combined error models were tested for residual variability. Both additive and log-normal models were evaluated for between-subject variability (BSV). Selection criteria decreased in both objective function value (OFV) and Akaike's information criterion (AIC); acceptance criteria included precision of parameters estimation and goodness-of-fit plots. The model with the lowest values of OFV and AIC was selected if data description and parameter estimation precision were adequate (i.e., relative standard errors for fixed and random effects  $< 30\%$  and  $< 50\%$ , respectively).

In a second stage, collected demographic, biologic, and clinical variables that were considered credible for affecting the pharmacokinetic of meropenem were tested for inclusion as covariates in the structural model, following the step-wise covariate modeling (SCM) method [36]. The impact

of continuous covariates and categorical covariates was, respectively, considered with six and three different functions (Supplementary Material) during the forward selection step ( $\Delta\text{OFV} = 3.84$ ,  $p < 0.05$ ). A covariate was kept in the model if there was a significant improvement in the fit over the previous model step (i.e., decrease in BSV of the parameter and decrease in OFV/AIC). The relevance for each included covariate was evaluated during the backward deletion step ( $\Delta\text{OFV} = 10.8$ ,  $p < 0.001$ ). Criteria for the final SCM model were: a “minimization successful” result, a decrease in the between-subject variability of the parameter on which the covariate was retained, an accurately estimated covariance matrix, a result of three significant digits for each fixed parameter, and reaching acceptance criteria.

In a last stage, the final model was evaluated using graphical and statistical internal validation methods. Prediction-corrected visual predictive checks were performed, the bootstrap resampling technique was used to build the PopPK parameters confidence intervals (CI), and normalized prediction distribution errors (NPDE) were computed to assess prediction discrepancies. In addition, to evaluate the predictive quality of the final model, different scores were computed: root-mean-squared error (RMSE) and mean prediction error (MPE) to evaluate the precision and bias, respectively [37].

## 2.6 Pharmacokinetic/Pharmacodynamic Simulations

The pharmacokinetic/pharmacodynamic target was the probability of target attainment (PTA) and defined by the number of simulated patients who achieved  $100\% T > \text{MIC}$ . To perform the simulations, the population median value of glomerular filtration rate (GFR) was used while exploring the impact of the three categories of residual diuresis (50 mL, 250 mL, and 750 mL), corresponding, respectively, to anuria state ( $< 100 \text{ mL}/24 \text{ h}$ ), oliguria state ( $100\text{--}500 \text{ mL}/24 \text{ h}$ ), and preserved diuresis ( $> 500 \text{ mL}/24 \text{ h}$ ). Each simulation generated meropenem concentration-time profiles for 1000 subjects per dosing regimen using the parameters from the PopPK final model. Monte Carlo dosing regimen simulations were performed with bolus-like administration (infusion over 30 min), extended infusion (infusion over 5 h), and continuous infusion. Different dosing scenarios for both bolus and extended infusion were generated: 1 g Q6H or Q8H and 2 g Q6H or Q8H. Dosing scenarios for continuous infusion were generated with 1 g loading dose (unique 30-min infusion) followed by continuous IV infusion Q4H or Q6H. Choice of exploring these particular dosing regimens falls on Montpellier's medical ICU clinical habits in treating patients with meropenem.

## 3 Results

### 3.1 Demographic Characteristics

A total of 58 patients were enrolled in the study. From the 133 serum concentrations collected, 13 were below the limit of quantification and 5 were considered outliers during a preliminary PopPK run. As a consequence, 115 serum concentrations were reported in the total dataset, with an average of 2 samples per patient. Table 1 summarizes the patients' demographic and biological characteristics. Of the total patients, 26 were prescribed RRT, of whom 6 received continuous RRT, 10 received semi-continuous RRT (either sustained low-efficiency dialysis or intermittent hemodialysis), and 10 were given a combination of previously cited RRT techniques and plasmapheresis was used. Residual diuresis is routinely monitored in the medical ICU, hence more than 2000 values of residual diuresis volume were collected for our study population. Some patients have experienced the states of anuria, oliguria, and/or preserved diuresis in the same hospital stay.

### 3.2 PopPK Model

Pharmacokinetic observations were better described by a one-compartment model with a linear clearance, using a log-normal inter-individual variability on both parameters (clearance and volume of distribution). No omega block structure was retained between the two BSVs. Residual

variability was best described by a proportional error model. Significant covariates were GFR (using the MDRD formula), presence of a dialysis session (continuous: DIA\_C, or semi-continuous: DIA\_SC), renal function status (RFS) and volume of residual diuresis (RD), all influencing meropenem clearance (Table 2).

The volume of residual diuresis was found to be associated with clearance except during a semi-continuous dialysis session.  $GFR_{MDRD}$  greatly improved the goodness-of-fit and the OFV in patients with an impaired renal function, but had no impact when patients were under dialysis. All covariate relationships are described in Fig. 1. A comparison between PopPK parameters of both the structural model and the final model is displayed in Table 3. The clearance for a typical patient in our population is 4.20 L/h and the volume of distribution is approximately of 44 L.

### 3.3 Model Evaluation

Goodness-of-fit plots for the final model were evaluated and showed no apparent visual bias for the predictions, as shown in Fig. 2. Plots of observations versus individual/population predictions (IPRED/PRED) showed a good impression of data fitting along the identity line. Plots of conditional weighted residuals (CWRES) versus time after dose also displayed a uniformity of distribution along the  $y = 0$  line and contained values between  $-3$  and  $3$ . A prediction-corrected VPC confirmed the predictive performance of the model, as shown in Fig. 3. CWRES versus PRED, IWRES versus IPRED, IWRES versus time after dose, quantile-quantile

**Table 1** Demographics and biological characteristics of patients included in the study

Variable	<i>n</i> (%)	Mean (SD)	Median	Range	Reference values
Female	17 (29)				
Male	41 (71)				
Age (year)		62 (14.7)	64	18–85	
Weight (kg)		72 (17.2)	68	39.5–124	
BMI (kg/m <sup>2</sup> )		25 (6.1)	24	15–42	18.5–24.9
Albumin (g/L)		26 (4.3)	26	15–40	36–45
Lactates (mM)		2 (1.9)	1.4	0.5–22.7	5–22
Serum creatinine (μM)		154 (109)	131	15–737	50–130
Urine creatinine (mM)		3.9 (2.9)	3.2	0.1–17.2	8–18
Serum urea (mM)		13 (9.4)	10	0.5–46	2.5–7.1
Residual diuresis (mL/24 h)		1316 (1422)	845	0–7300	> 500
CRCL <sub>CG</sub> (mL/min)		72 (60)	52	10–376	F: 95 ± 20 M: 110 ± 20
$GFR_{MDRD}$ (mL/min/1.73 m <sup>2</sup> )		78 (84)	49	7–567	120
RFS = 1 (i.e., GFR > 120 mL/min/1.73 m <sup>2</sup> )	7 (12)				

*BMI* body mass index, *CRCL<sub>CG</sub>* creatinine clearance using Cockcroft–Gault formula, *GFR<sub>MDRD</sub>* glomerular filtration rate using 4-variable MDRD formula ( $MDRD = 186.3 \times (\text{creatinine} \times 0.0113)^{-1.154} \times \text{age}^{-0.203} \times A \times B$  with creatinine = μmol/L,  $A = 0.742$  if female,  $B = 1.21$  if African), *RFS* renal function status

**Table 2** Covariates/clearance relationship

Covariate name	Relationship	$\Delta OFV$	
$GFR_{MDRD}$	$CL1 = \theta_{CL} + \theta_{MDRD} \times GFR_{MDRD}$	- 58.8	Step 1
Continuous dialysis	$CL2 = CL1 \times (1 - DIA_C) + \theta_{DIA_C} \times DIA_C$	- 9.4	Step 2
Renal function status	$CL3 = CL2 \times (1 - RFS) + \theta_{RFS} \times RFS$	- 12.6	Step 3
Residual diuresis	$CL4 = CL3 + \theta_{RD} \times ((RD/845) - 1)$	- 9.6	Step 4
Semi-continuous dialysis	$CL5 = CL4 \times (1 - DIA_{SC}) + \theta_{DIA_{SC}} \times DIA_{SC}$	- 12.9	Step 5
	$CL_{final} = CL5 \times \exp(\omega^{CL})$		

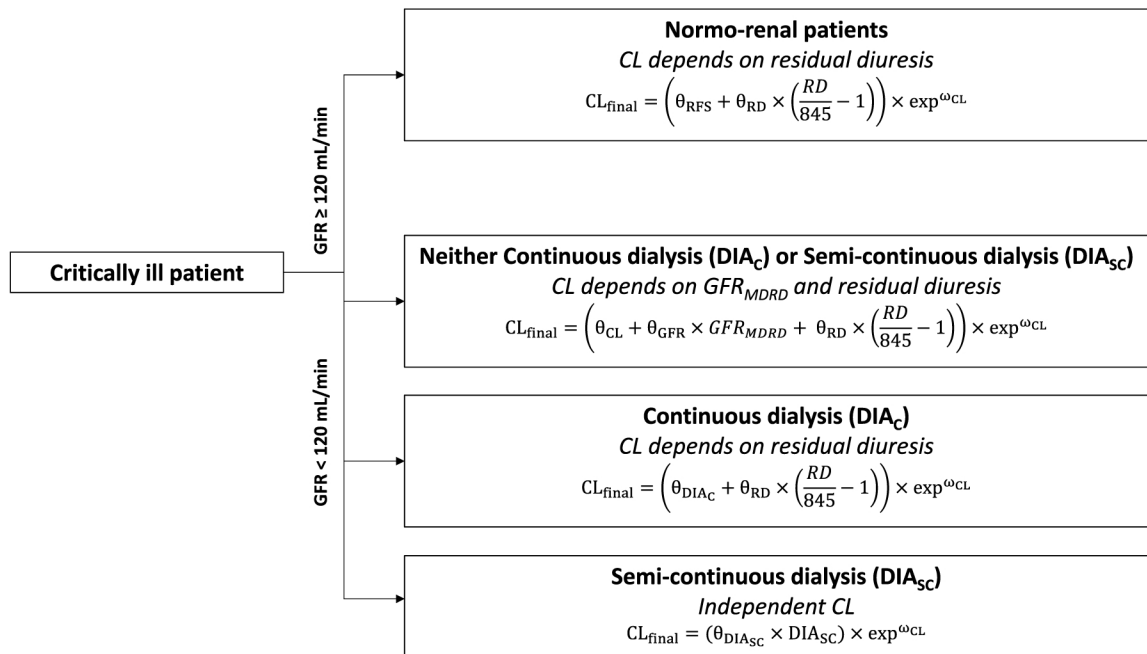
$\Delta OFV$  difference of objective function value,  $GFR_{MDRD}$  glomerular filtration rate using MDRD formula, (Semi-) continuous dialysis  $DIA_C$  and  $DIA_{SC} = 1$  if continuous or semi-continuous dialysis is “on” and = 0 if dialysis is “off”,  $RFS$  renal function status = 1 if  $GFR \geq 120\text{mL}/\text{min}$ , else = 0

plots for CWRES and NPDE are presented in Supplementary material. Statistical distribution (median value and 95% CI) for the final PopPK parameters obtained from the bootstrap analysis are shown in Table 4. Convergence rate for the bootstrap analysis was of 93.8% (of 1000 runs), suggesting good stability of the PopPK model. The 95% CI were reasonably narrow and median bootstrap values for parameters were in good agreement with the final PopPK parameters, indicating the robustness of the final model. The final model’s mean bias (MPE) and precision (RMSE) for IPRED were - 7.03% and 29.4%, respectively, better than those computed for PRED, which were - 8.24% and 53.6%, respectively. The tendency to underpredict meropenem concentration was noticed in both the structural model and the final model for individual and population predictions. Figure 4 presents

final individual clearance values of patients depending on different categories of  $GFR_{MDRD}$ , and stratified by the type of dialysis technique used. Final individual clearance values depending on different states of diuresis and stratified by type of dialysis technique are shown in Fig. 5.

### 3.4 Pharmacokinetic/Pharmacodynamic Achievement

PTA computed from the results of the simulations performed to evaluate different dosing regimens (bolus-like, extended, and continuous infusion) in different states of residual diuresis (without dialysis) are shown in Figs. 6, 7, and 8. A PTA of > 90% was considered acceptable for a pharmacodynamic target of 100%  $T > MIC$  for meropenem.



**Fig. 1** Summary of covariate relationships for the computation of clearance for each type of patient.  $CL$  clearance,  $RFS$  renal function status,  $RD$  residual diuresis,  $GFR$  glomerular filtration rate,  $\theta$  PopPK parameters

**Table 3** PopPK parameters comparison between structural model and final model

Population parameters	Structural model		Final model	
	Estimate	RSE (%)	Estimate	RSE (%)
CL (L/h)	5.48	10.2	4.20 <sup>a</sup>	NA
V (L)	60.3	22.6	43.9	17.0
BSV_CL (% CV)	77.4	24.4	30.8	37.0
BSV_V (% CV)	80.5	55.3	87.6	31.2
Prop_Res_Err (% CV)	38.8	27.3	32.1	19.0

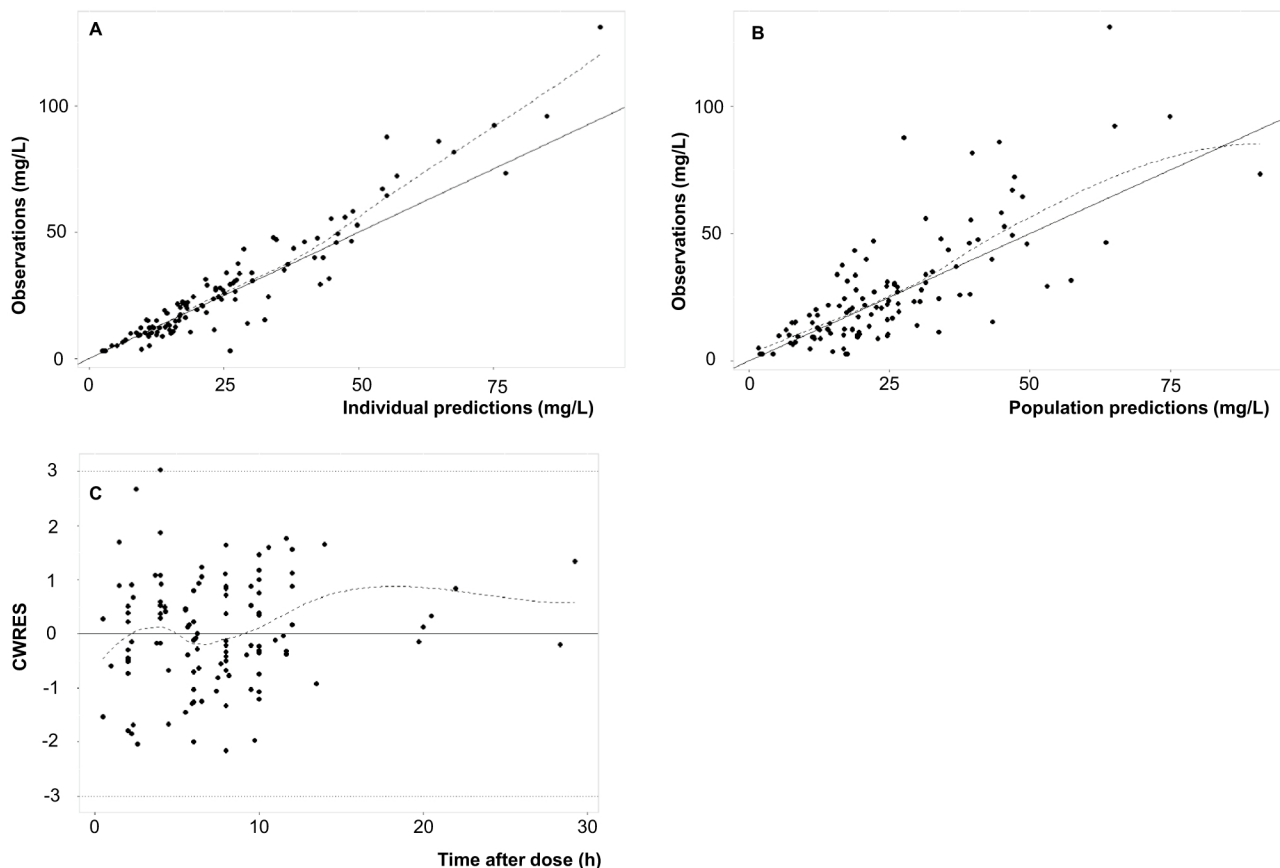
RSE relative standard error,  $RSE(\%) = \frac{SE}{Estimation} \times 100$ , CL total body clearance, V apparent volume of distribution, BSV\_CL between-subject variability associated with CL, BSV\_V between-subject variability associated with V, Prop\_Res\_Err proportional residual error, CV coefficient of variation,  $CV(\%) = \sqrt{e^{\sigma^2} - 1} \times 100$

<sup>a</sup>The value presented here reflects the clearance for a typical patient in our population:  $CL_{\text{typical patient}} = \theta_{CL} + \theta_{GFR} \times GFR_{\text{median}} + \theta_{RD} \times \left(\frac{RD_{\text{median}}}{845} - 1\right)$

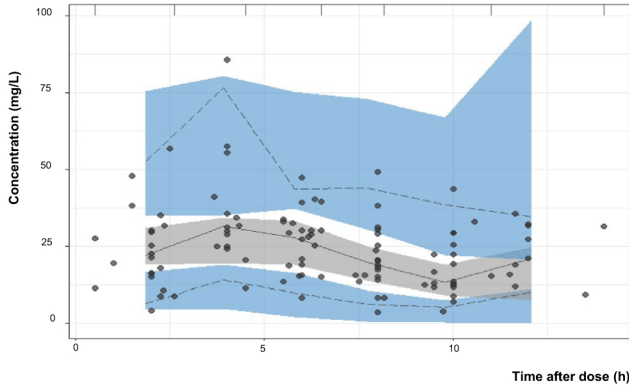
## 4 Discussion

Our study and specifically its dataset have been used as part of a complementary work [38], where the predictive ability

of both the literature and the tweaked models on TDM concentrations of meropenem in critically ill patients was compared. This approach required the subsetting of our data and led to insufficient overall results, even when applying the Bayesian approach with prior information [39], which comforted us in our strategy of building a new PopPK model from an unsplit dataset. Our main finding is the identification and quantification of an important pharmacokinetic variability, partly due to a high heterogeneity among the critically ill patients included in this study, and related to the ICU patient status. The BSV has been explained, to a relatively large extent, by five covariates, all included in the relationship with CL. The inclusion of a renal function marker on meropenem's clearance was expected, and was already identified in the scientific literature. Unexpectedly, the renal function marker to have the most mathematical significant impact on CL was  $GFR_{MDRD}$ , rather than the GFR estimated by the CKD-EPI formula or another marker. The 4-variable MDRD formula has been controversial because of a less optimal performance in estimating the actual GFR of patients in critical care settings [40]. Nevertheless,  $GFR_{MDRD}$  appeared as a clinically impactful covariate. A significant relationship



**Fig. 2** Goodness-of-fit plots for the final model. **A** Observations versus individual predictions (IPRED), **B** observations versus population predictions (PRED), **C** conditional weighted residuals (CWRES) versus time after dose



**Fig. 3** Prediction-corrected visual predictive checks plot generated from 1000 simulations. Blue areas represent the 95% confidence intervals of the 97.5th percentile (up) and the 2.5th percentile (down) of the predictions, middle gray area represents the 95% confidence interval of the 50th percentile (median) of the predictions. Lines 97.5th percentile (up, dotted), 50th (middle solid line) and 2.5th percentile (down, dotted) of the observations. Black dots represent observed plasma concentrations

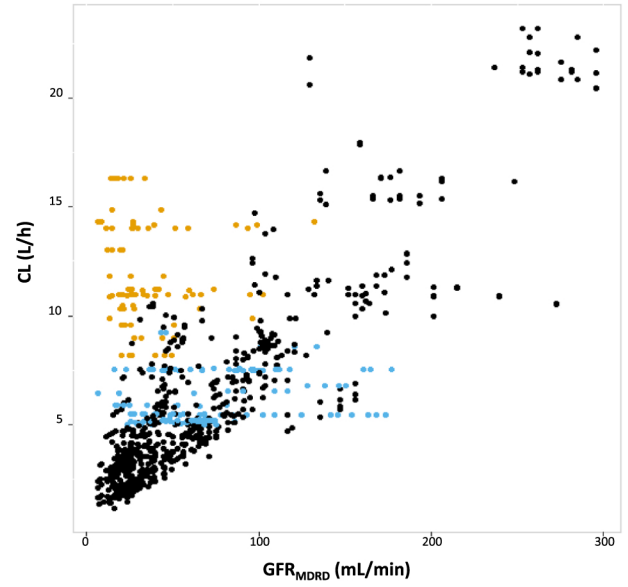
**Table 4** Population parameter estimates for the final model and bootstrap results

Population parameters	Estimate	RSE (%)	Bootstrap: median [95% CI]
<b>CL (L/h)</b>			
$\theta_{CL}$	1.36	23.9	1.35 [0.55–2.10]
$\theta_{GFR}$	0.058	17.8	0.056 [0.032–0.080]
$\theta_{DIA\_C}$	6.38	12.2	6.49 [5.19–7.83]
$\theta_{RFS}$	13.9	15.5	13.9 [7.92–21.5]
$\theta_{RD}$	0.60	31.7	0.64 [0.24–1.17]
$\theta_{DIA\_SC}$	11.0	20.6	10.9 [8.28–27.4]
<b>V (L)</b>			
$\theta_V$	43.9	17.0	44.7 [30.6–72.4]
$BSV\_CL$ (% CV)	30.8	37.0	26.7 [11.0–40.2]
$BSV\_V$ (% CV)	87.6	31.2	81.6 [16.5–146.9]
$Prop\_Res\_Err$ (% CV)	32.1	19.0	31.7 [23.5–43.0]

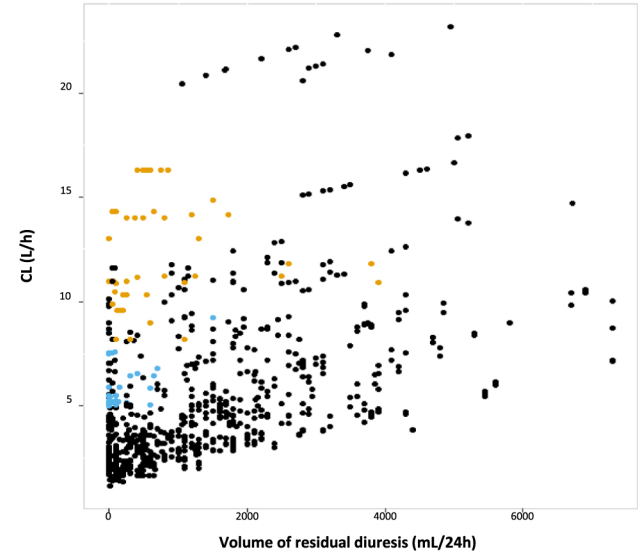
$RSE$  relative standard error  $RSE(\%) = \frac{SE}{Estimation} \times 100$ ,  $CI$  confidence interval,  $CL$  total body clearance,  $V$  apparent volume of distribution,  $\theta_{CL}$  typical value for CL in the population,  $\theta_{GFR}$  GFR covariate effect on clearance,  $\theta_{DIA\_C}$  and  $\theta_{DIA\_SC}$  continuous and semi-continuous dialysis covariates effect on CL,  $\theta_{RFS}$  renal function status covariate effect on CL,  $\theta_{RD}$  residual diuresis covariate effect on CL,  $\theta_V$  typical value for  $V$  in the population,  $BSV\_CL$  between subject variability associated with CL,  $BSV\_V$  between subject variability associated with  $V$ ,  $Prop\_Res\_Err$  proportional residual error,  $CV$  coefficient of variation  $CV(\%) = \sqrt{e^{\omega^2} - 1} \times 100$

was also observed between residual diuresis and meropenem clearance.

Our study is representative of the important population heterogeneity in ICU. However, normo-renal patients were



**Fig. 4** Individual clearance (CL) values according to their glomerular filtration rate ( $GFR_{MDRD}$ ) and stratified by renal replacement therapy techniques (RRT). Blue dots patients with continuous dialysis, yellow dots patients with semi-continuous dialysis, black dots patients without RRT



**Fig. 5** Individual clearance (CL) values according to their states of diuresis and stratified by renal replacement therapy techniques (RRT). Blue dots patients with continuous dialysis, yellow dots patients with semi-continuous dialysis, black dots patients without RRT

poorly represented in the study population (median value for GFR was 49 mL/min) explaining in part the slight discrepancies in CL that could be observed when varying the GFR value alone around the “RFS” threshold. As a result, our model is less satisfying in estimating high CL patients.



**Fig. 6** Probability of target attainment (%) simulations of a bolus-like (30 min) of meropenem stratified by residual diuresis. Percentage of patients for whom the pharmacokinetic target is met ( $100\% T > MIC$ ): red < 50% of patients, orange 50–90% of patients, green > 90% of patients. *Anuric* patient residual diuresis of 50 mL/24 h, *oliguric* 250 mL/24 h, *preserved* 750 mL/24 h

Dose regimen	MIC (mg/L)									Residual diuresis
	≤1	2	4	8	10	16	20	32	45	
1g q8h	99.4%	99.1%	97.8%	94%	90.8%	77.8%	64.6%	26.2%	6.3%	Anuric
	99.3%	98.4%	96.7%	90.4%	86%	69.5%	57.4%	23.4%	5.5%	Oliguric
	99.1%	98.6%	96.4%	90%	85.1%	65.9%	48.9%	14.8%	2.9%	Preserved
1g q6h	99.9%	99.6%	99.1%	98.3%	97.6%	92.7%	87.3%	59.2%	28.6%	Anuric
	99.4%	99.4%	99.1%	96.9%	95.6%	90.5%	83.3%	51.8%	20.7%	Oliguric
	99.9%	99.8%	99%	96.1%	94.7%	85.2%	77%	41.7%	14.8%	Preserved
2g q8h	99.8%	99.4%	99.1%	97.8%	97%	94%	90.8%	77.8%	56.4%	Anuric
	99.7%	99.3%	98.4%	96.7%	95.6%	90.4%	86%	69.5%	49.6%	Oliguric
	99.7%	99.1%	98.6%	96.4%	94.8%	90%	85.1%	65.9%	40.8%	Preserved
2g q6h	100%	100%	99.9%	99.4%	99.2%	98.1%	97.5%	92.1%	82.1%	Anuric
	99.8%	99.8%	99.7%	99.1%	98.6%	97.2%	95.5%	87.8%	73.9%	Oliguric
	99.9%	99.9%	99.7%	98.9%	98.7%	97%	95.4%	87.1%	72.6%	Preserved

**Fig. 7** Probability of target attainment (%) simulations of an extended infusion (5 h) of meropenem stratified by residual diuresis. Percentage of patients for whom the pharmacokinetic target is met ( $100\% T > MIC$ ): red < 50% of patients, orange 50–90% of patients, green > 90% of patients. *Anuric* patient residual diuresis of 50 mL/24 h, *oliguric* 250 mL/24 h, *preserved* 750 mL/24 h

Dose regimen	MIC (mg/L)									Residual diuresis
	≤1	2	4	8	10	16	20	32	45	
1g q8h	100%	100%	99.9%	99%	98.1%	92.2%	83%	41.5%	11%	Anuric
	99.9%	99.8%	99.8%	98.2%	96.7%	86.5%	75.3%	34.6%	9.1%	Oliguric
	99.9%	99.9%	99.7%	98.5%	96.5%	85.1%	71.6%	26%	5.3%	Preserved
1g q6h	100%	100%	100%	100%	100%	100%	99.3%	82.7%	46%	Anuric
	100%	100%	100%	99.9%	99.9%	99.3%	97.1%	75.6%	39.2%	Oliguric
	100%	100%	100%	100%	100%	99.6%	96.9%	71%	28.9%	Preserved
2g q8h	100%	100%	100%	99.9%	99.6%	99%	98.1%	92.2%	75.5%	Anuric
	100%	99.9%	99.8%	99.8%	99.5%	98.2%	96.7%	86.5%	68.2%	Oliguric
	100%	99.9%	99.9%	99.7%	99.2%	98.5%	96.6%	85.1%	60.8%	Preserved
2g q6h	100%	100%	100%	100%	100%	100%	100%	100%	97.9%	Anuric
	100%	100%	100%	100%	100%	99.9%	99.9%	99.3%	94.3%	Oliguric
	100%	100%	100%	100%	100%	100%	100%	99.6%	94.2%	Preserved

Dose regimen	MIC (mg/L)									Residual diuresis
	≤1	2	4	8	10	16	20	32	45	
1g q6h	100%	100%	100%	100%	100%	100%	100%	89%	50.9%	Anuric
	100%	100%	100%	100%	100%	100%	99.6%	87.3%	48.8%	Oliguric
	100%	100%	100%	100%	100%	100%	99.7%	78.6%	35.6%	Preserved
1g q4h	100%	100%	100%	100%	100%	100%	100%	99.7%	92.3%	Anuric
	100%	100%	100%	100%	100%	100%	100%	99.1%	89.9%	Oliguric
	100%	100%	100%	100%	100%	100%	100%	98.4%	83.8%	Preserved

**Fig. 8** Probability of target attainment (%) simulations of a continuous infusion (with unique 1 g loading dose) of meropenem stratified by residual diuresis. Percentage of patients for whom the pharmaco-

kinetic target is met ( $100\% T > MIC$ ): red < 50% of patients, orange 50–90% of patients, green > 90% of patients. *Anuric* patient residual diuresis of 50 mL/24 h, *oliguric* 250 mL/24 h, *preserved* 750 mL/24 h

One could ponder the pertinence of keeping in the final model three covariates of similar information to the CL: GFR, RFS, and RD. We would argue that each covariate is bringing complementary additional information on the impact of the kidney function to the CL. Patient kidney function was an element particularly challenging to capture in our data. We favorably described it through the three parts of a greater whole: GFR, RFS, and RD.

In contrast to some published meropenem PopPK models developed in comparable populations, our final model did not find body size (weight, BMI, or BSA) to have a significant relationship with  $V$ . In the literature, the relationship

between diuresis and clearance was highlighted twice in critically ill patients [22, 26].

In line with meropenem being a dialyzable drug, our analysis identified dialysis as a significant covariate for meropenem’s clearance. For median values of GFR and diuresis, without dialysis the typical value for clearance was 4.2 L/h, during a session of semi-continuous dialysis 11 L/h, and 6.4 L/h during a session of continuous dialysis. These clearance values are comparable with other clinical studies such as Braune et al. [22] (CL ~ 8 L/h using a semi-continuous dialysis) and Uildemolins et al. [26] (CL ~ 4.8 L/h using continuous dialysis in patients with preserved diuresis). Typical values of clearance in patients using semi-continuous

dialysis are higher than in patients using continuous dialysis, which is consistent with the technical characteristics of dialysis, the semi-continuous technique being considered to be more intensive, with a higher dialysate fluid flow.

In fact, without a dedicated pharmacokinetic study, evaluating and anticipating the impact of a dialysis session on a drug's concentration is a difficult task. The drug's extracorporeal excretion is the sum of the following clearances: dialysis, renal CL, and non-renal CL (hepatic and other ways). One of these clearances becomes clinically significant once its contribution to the total CL represents  $\geq 25\%$ . This means that, if dialysis corresponds to more than 25% of total CL, the dosing regimen needs to be adapted. Hence, one question arises: how to adapt the dosing of the drug? One frequently used possibility is to adapt the dose using creatinine total clearance, which is a surrogate for the sum of extracorporeal and renal (residual) clearances. Other more complex methods exist, using either the anuric dose or the anuric dosing interval [41]. Notwithstanding the method used, the pharmacokinetic impact of a RRT session on an antibacterial therapy should be adequately estimated to avoid under- or over-exposure, sources of treatment failure. The PopPK model presented here accounts for that impact and stresses to clinicians the different criteria they should consider when determining the optimal dosing regimen for a patient: (1) for patients without dialysis, we propose to consider  $GFR_{MDRD}$  and residual diuresis when adapting the dose, and (2) for patients using dialysis, the type of dialysis used will impact on the choice of a dosing regimen.

The high number of significant covariates retained in the final model strongly suggest a possible over-parameterization. It would be of much interest to evaluate the predictive performance of this PopPK model with new subjects. Clinicians considering using our PopPK model in Bayesian-feedback TDM settings should first go through this external validation process. To that effect, we are sharing the NONMEM control file of our final model (Supplementary Material). However, the important number of retained covariates in the model highlight the necessity to take into account the multiple clinical aspects of the critically ill patients, beside creatinine clearance, when administering meropenem. Above all, it again highlights the extensive pharmacokinetic variability that exists among patients treated in one mutual care unit. Because of the limited size population (notably for RRT patients), we did not collect technical aspects of RRT sessions (intensity, blood flow, type of membrane, etc.) in order to estimate the Sieving coefficient.

We performed simulations to evaluate the impact of residual diuresis on the type of administration of fixed doses of meropenem, aiming for a pharmacokinetic/pharmacodynamic target of  $100\% T > MIC$  more appropriate in ICU patients [42, 43]. To equivalent doses, the continuous infusion mode (with loading dose) allowed to attain the

pharmacokinetic/pharmacodynamic target for a larger number of patients. Nevertheless, for the treatment of susceptible bacteria ( $MIC \leq 2 \text{ mg/L}$ ), differences of PTA between bolus-like, extended, and continuous infusions are negligible. In such cases, the patient's need for liquid intake could overrule the mode of administration (bolus or infusion). The largest differences in PTA are found for the treatment of bacteria with a higher resistance breakpoint ( $MIC > 10 \text{ mg/L}$ ) in patients with preserved diuresis. For example, with a dosing regimen of  $1 \text{ g/6 h}$  and a  $MIC = 32 \text{ mg/L}$ , PTAs of bolus-like, extended, and continuous infusion were, respectively, 42%, 71%, and 79%, showing the capability of the extended and continuous infusions to reach for very high pharmacodynamic targets. As a whole, continuous infusion granted more PTA when treating high MIC bacteria. However, the use of the continuous infusion mode to attain high pharmacodynamic objectives should be considered with the utmost caution. For example, with a continuous infusion of  $1 \text{ g/4 h}$  in anuric patients, half of the simulated population had a meropenem concentration at steady-state maintained over  $67.4 \text{ mg/L}$ . These are very high concentrations and could lead to patients developing toxicity. Therefore, we strongly advocate the use of Bayesian-feedback TDM to avoid too low or too high exposures.

## 5 Conclusion

The introduction of effective antibacterial therapy in critical ill patients is complex. It must consider the patient's renal function and also the global clinical state of the patient, as the half-life time of meropenem in normo-renal ICU patients is twice longer than in healthy volunteers [19]. In patient monitoring, it is interesting for clinicians to dispose of clinical elements and landmarks for adjusting the dosing. These elements should be easily accessible in patient health records, which is the case for the covariates found in our model (GFR, residual diuresis, and dialysis information are routinely gathered data in the ICU). While slightly over-predicting meropenem concentrations, this model should be evaluated with a more sizable dataset. Nevertheless, it once again highlights the importance of considering the patient's overall condition (renal clearance, renal function, and dialysis) and the pathogen's characteristics (MIC target) during the establishment of a patient's dosing regimen (bolus, extended infusion, loading dose, dosing interval reduction).

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## Declarations

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**Conflict of interest** None to declare

**Ethical approval** The study protocol was approved by the Ethics Committee 2019\_IRB-MTP\_03-01.

**Consent to participate** Not applicable as this was a non-interventional retrospective study; patients were informed of their right of opposition to data collection.

**Consent for publication** Not applicable.

**Availability of data and material** On demand (email: sonia.khier@umontpellier.fr).

**Author contributions** AOJ collected majority of raw data, performed the literature review and analyses, and wrote the original manuscript, tables and figures. RL checked clinical raw data. CLS collected part of clinical raw data. ND challenged pharmacokinetic analyses and reviewed and revised the manuscript. SK supervised the work, designed and planned the work, reviewed the analyses, and wrote the manuscript, tables and figures.

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