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PHARMACOLOGY

Population Pharmacokinetics/Pharmacodynamics and Clinical Outcomes of Meropenem in Critically Ill Patients

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ABSTRACT Several pathophysiological changes can alter meropenem pharmacokinetics in critically ill patients, thereby increasing the risk of subtherapeutic concentrations and affecting therapeutic outcomes. This study aimed to characterize the population pharmacokinetic (PPK) parameters of meropenem, evaluate the relationship between the pharmacokinetic/pharmacodynamic index of meropenem and treatment outcomes, and evaluate the different dosage regimens that can achieve 40%, 75%, and 100% of the dosing interval for which the free plasma concentrations remain above the MIC of the pathogens ($fT_{>MIC}$) targets. Critically ill adult patients treated with meropenem were recruited for this study. Five blood samples were collected from each patient. PPK models were developed using a nonlinear mixed-effects modeling approach, and the final model was subsequently used for Monte Carlo simulations to determine the optimal dosage regimens. A total of 247 concentrations from 52 patients were available for analysis. The two-compartment model with linear elimination adequately described the data. The mean PPK parameters were clearance (CL) of 4.8 L/h, central volume of distribution (V_C) of 11.4 L, peripheral volume of distribution (V_P) of 14.6 L, and intercompartment clearance of 10.5 L/h. Creatinine clearance was a significant covariate affecting CL, while serum albumin level and shock status were factors influencing V_C and V_P, respectively. Although 75% of the drug-resistant infection patients had $fT_{>MIC}$ values of >40%, approximately 83% of them did not survive the infection. Therefore, 40% $fT_{>MIC}$ might not be sufficient for critically ill patients, and a higher target, such as 75 to 100% $fT_{>MIC}$, should be considered for optimizing therapy. A 75% $fT_{>MIC}$ could be reached using approved doses administered via a 3-h infusion.

KEYWORDS critically ill, population pharmacokinetic, meropenem, time above MIC, clinical cure

Severe sepsis and septic shock are common conditions and prominent causes of morbidity, mortality, and economic burden to patients in intensive care units (ICUs) (1, 2). Early initiation of appropriate antimicrobial therapy has been demonstrated to be the most effective intervention for reducing mortality in these patients (3, 4).

Meropenem is a broad-spectrum carbapenem antibiotic with potent activity against Gram-negative bacilli, Gram-positive cocci, and anaerobic bacteria. It is a small hydrophilic molecule with a low level of protein binding (<2%) and is excreted mainly through the kidney with a short half-life (approximately 1 h) (5). This antibiotic agent is frequently used for the empirical treatment of sepsis and other severe nosocomial infections in ICUs. The antibacterial activity of meropenem depends on the percentage of the dosing interval for which the free plasma concentrations remain above the MIC of the pathogens ($fT_{>MIC}$) (6, 7). Generally, a $fT_{>MIC}$ of at least 40 to 50% of the dosing

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interval is considered sufficient for carbapenems. However, a higher $fT_{>MIC}$ target may be required in critically ill patients (8, 9). Optimizing the meropenem dosage regimen to achieve this target is a significant challenge for physicians attending to patients in ICUs. This is due to sepsis-related pathophysiological changes that may alter meropenem pharmacokinetics, including volume of distribution and total drug clearance, resulting in a highly variable plasma concentration.

Although the pharmacokinetic parameters of meropenem in critically ill patients have been widely studied, most studies have been conducted on small patient populations (10–15). The small cohort size may impact accuracy and is unlikely to capture all the variability of pharmacokinetic parameters in critically ill patients. Moreover, clinical data on the relationship between meropenem exposure and treatment outcomes is limited. Therefore, the objectives of this study were to characterize the population pharmacokinetic parameters of meropenem in critically ill patients, evaluate the relationship between meropenem exposure and clinical outcomes, and evaluate the different dosage regimens that can achieve 40%, 75%, and 100% $fT_{>MIC}$ targets.

RESULTS

Patient characteristics. Fifty-two critically ill patients were included in this study, 48 of whom were in the medical ICU, and the remaining four patients were in the surgical ICU. The median (range) age, weight, and creatinine clearance estimated by the Cockcroft-Gault equation ($CL_{CR\text{-}CG}$) were 63 years (29 to 91 years), 61.5 kg (27.8 to 86 kg), and 44.6 mL/min (6.2 to 161.1 mL/min), respectively. The majority of the patients had pneumonia (63%) and received meropenem doses ranging from 1 to 6 g/day. The patient characteristics are shown in Table 1.

Population pharmacokinetic (PK) modeling. In total, 256 unbound meropenem concentrations were obtained from the 52 patients. Of these, 7 (3%) and 9 (3%) concentrations were below the lower limit of quantitation (LLOQ) and lower limit of detection (LOD), respectively. All detectable concentrations, including points below the LLOQ, were included as continuous data, while concentrations below the LOD were discarded. As a result, the remaining 247 concentrations ranging from 0.12 to 127.7 mg/L were analyzed.

A two-compartment model with first-order elimination best described the meropenem concentration-time profiles. The proportional error model adequately described the residual variability, whereas the combined proportional and additive error model did not perform significantly better. Interindividual variability (IIV) was implemented for all PK parameters. However, the IIV for intercompartmental clearance was small and was therefore fixed at zero. Regarding covariate analysis, implementing $CL_{CR\text{-}CG}$ calculated using ideal body weight (IBW) on meropenem clearance (CL) provided the largest reduction in objective function value (OFV) compared to other renal function markers. Therefore, it was included in the final model. Serum albumin (ALB) and shock state significantly affected the volume of distribution in the central (V_C) and peripheral (V_P) compartments, respectively. The addition of ALB to V_C resulted in a decrease in the IIV of V_C to near zero; therefore, it was fixed to zero in the final model. When the effects of these covariates were combined, no other covariates showed significance. The backward deletion process did not remove the covariates. Therefore, these covariates were retained in the model. The population pharmacokinetic (PPK) parameters of the base and final models are summarized in Table 2. In the final model, the individual PK parameters were best described using the following equations:

$$\mathrm{CL\,(L/h)} = 5.16 \times (1 + 0.016 \times [\mathrm{CL_{CR\text{-}CG}} - 50])$$

$$\mathrm{V_C(L)} = 11.1 \times (1 - 0.255 \times [\mathrm{ALB} - 2.5])$$

$$\mathrm{V_P(L)} = 10.3 + 11.3\,(\text{if shock})$$

Goodness-of-fit plots (Fig. 1) indicated that the fit of the final model was reasonably good, with no obvious biases. The prediction-corrected visual predictive check (pcVPC)

TABLE 1 Demographics and clinical characteristics of the study population

Characteristic[a]	Patients (n = 52)[b]
Male	31 (59.6)
Age (yrs)	63 (48.0 to 74.0)
Body wt (kg)	61.5 (53.4 to 69.8)
Body mass index (kg/m^2)	22.9 (20.6 to 25.4)
APACHE II score	20 (14 to 23)
SOFA score	8 (6 to 11)
Inotropic or vasopressor used	20 (38.5)
Mechanical ventilator	46 (88.5)
Sepsis[c]	51 (98.1)
Septic shock[c]	18 (34.6)
$CL_{CR\text{-}CG}$ (mL/min)	44.6 (24.2 to 80.7)
Serum lactate (mmol/L)	3.4 (1.7 to 5.7)
Serum albumin (g/dL)	2.4 (2.0 to 2.9)
Hypoalbuminemia[d]	28 (53.8)
Cumulative fluid balance (L)[e]	3.6 (1.7 to 5.9)
Primary infection site	
Respiratory	33 (63.5)
Intraabdominal	8 (15.4)
Genitourinary	6 (11.5)
Others	5 (9.6)
Meropenem dosage regimens	
LD 2 g, 1 g q8 h	24 (46.2)
LD 2 g, 1 g q12 h	10 (19.2)
LD 2 g, 0.5 g q12 h	6 (11.5)
Others	12 (23.1)

[a]$CL_{CR\text{-}CG}$, creatinine clearance estimated using Cockcroft-Gault formula based on ideal body weight; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score; LD, loading dose; q, every.
[b]Data are expressed as n (%) or median (interquartile range).
[c]Patient diagnosed according to sepsis-3 criteria.
[d]Hypoalbuminemia was defined as a serum albumin level less than 2.5 g/dL.
[e]The sum of daily fluid balance from the first day of intensive care admission until plasma meropenem was measured.

plot (Fig. 2) also confirmed the adequate predictive performance of the model, as the 5th, 50th, and 95th percentiles of the observed data laid within the 95% confidence interval of the corresponding percentiles of the model prediction.

Microbiological finding. Of the 52 patients, a pathogen was identified in 31 patients (60%). The most commonly isolated microorganisms were *Klebsiella pneumoniae* (33%), *Escherichia coli* (21%), *Pseudomonas aeruginosa* (15%), and *Acinetobacter baumannii* (9%) (Table 3). The median MIC values of meropenem for *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* were 0.023, 0.125, and 32 mg/L, respectively.

PK/pharmacodynamic (PD) analysis and treatment outcomes. Although 31 patients had documented bacterial infections, only 20 were included in the clinical outcome assessment. Patients whose specific MIC data of causative pathogens were unavailable (n = 7) and those with infections caused by intrinsically meropenem-resistant pathogens (n = 4) were excluded from the analysis. The baseline clinical characteristics are shown in Table 4.

Overall, 90% (18/20) of patients achieved a PK/PD target of 40% $fT_{>MIC}$. For higher thresholds of 75% and 100% $fT_{>MIC}$ target, only 70% (14/20) and 55% (11/20) of the patients achieved these targets. The average $fT_{>MIC}$ and the proportion of patients reaching the $fT_{>MIC}$ targets were higher in the clinical success group than in the failure group. Similar findings were observed in the survivor group. The results of the clinical outcome analyses are presented in Table 5.

Dosing optimization. The simulation results indicated that all current standard dosage regimens provided a higher probability of achieving traditional 40% $fT_{>MIC}$ target than 90% against pathogens, with MIC values ranging from 0.0625 to 2 mg/L. When considering the more aggressive target of 75% $fT_{>MIC}$, the standard doses could

TABLE 2 Population pharmacokinetic parameters of meropenem from the base and final model

Parameter[a]	Base model (OFV = 1,382.7) Estimate (% RSE[a])	Final model[b] (OFV = 1,334.9) Estimate (% RSE[a])	% Shr[a]	Median (95% CI[a]) of bootstrap estimate
Fixed-effect parameters				
CL (L/h)	4.8 (11.9)	5.16 (9.8)		5.19 (4.22 to 6.21)
θ_1		0.016 (8.9)		0.016 (0.012 to 0.018)
V_C (L)	11.4 (11.5)	11.1 (10.8)		11.1 (7.89 to 12.79)
θ_2		−0.255 (30.5)		−0.258 (−0.418 to −0.103)
V_P (L)	14.6 (12.0)	10.3 (31.7)		10.49 (7.35 to 14.72)
θ_3		11.3 (43.1)		11.42 (3.54 to 22.57)
Q (L/h)	10.5 (30.4)	9.37 (38.4)		9.40 (6.06 to 22.57)
Interindividual variability (IIV, % CV[a])				
IIV on CL	86.1 (9.5)	60.5 (11.4)	1.0	59.4 (45.7 to 72.8)
IIV on V_C	30.0 (38.9)	Fixed to 0		
IIV on V_P	63.7 (18.8)	47.7 (22.1)	36.3	45.7 (23.7 to 66.5)
IIV on Q	Fixed to 0			
Residual variability (%)				
Proportional	24.1 (11.0)	26.0 (8.3)	13	25.6 (21.1 to 29.7)

[a]% RSE, percentage of relative standard error; % Shr, percentage of shrinkage; % CV, percentage of coefficient of variation; OFV, minimum objective function value; CI, confidence interval; CL, total clearance; V_C, central volume of distribution; V_P, the peripheral volume of distribution; Q, intercompartment clearance; $CL_{CR\text{-}CG}$, creatinine clearance estimated by Cockcroft-Gault equation; ALB, serum albumin (g/dL); Shock, a clinical state requiring vasopressors or inotropes to maintain a mean arterial pressure greater than 65 mm Hg.

[b]The final PK model parameters:

$$CL\,(L/h) = 5.16 \times \left(1+\theta_1 \times [CL_{CR\text{-}CG} - 50]\right)$$

$$V_C(L) = 11.1 \times (1+\theta_2 \times [ALB - 2.5])$$

$$V_P(L) = 10.3 + \theta_3 \times SHOCK$$

be achieved at an optimal probability of target attainment (PTA) for isolates with MIC values of ≤2 mg/L in patients with $CL_{CR\text{-}CG}$ values of >25 mL/min when administered by extended infusion over 3 h (Fig. 3). For 100% $fT_{>MIC}$ target, a larger dose is required to reach an optimal PTA. The meropenem regimens needed to achieve optimal PTA for 40% $fT_{>MIC}$, 75% $fT_{>MIC}$, and 100% $fT_{>MIC}$ targets are reported in Table 6.

DISCUSSION

The current study characterized PK properties and provided the dosage regimens of meropenem needed to achieve 40%, 75%, and 100% $fT_{>MIC}$ targets in a critically ill population. A two-compartment model with first-order elimination adequately described the PK profiles of meropenem. The ICU patient population in this study was remarkably diverse in terms of clinical and biological characteristics, which contributed to the high IIV of the PK parameters in the model. The population mean CL in the current analysis was approximately 4.75 L/h, similar to that obtained in previous PK studies in which the PK of meropenem was quantified in patients with moderate to severe renal impairment (2.1 to 7.7 L/h) (12, 15–18). Consistent with the expectation that a large proportion of meropenem would be renally excreted, renal function was the main factor influencing meropenem CL. $CL_{CR\text{-}CG}$ showed a better ability to predict meropenem CL than creatinine clearance estimated by the Jelliffe equation ($CL_{CR\text{-}JEL}$) or estimated glomerular filtration rate (GFR) using the four- and six-variable modification of diet in renal disease study equation (GFR_{MDRD}) or the chronic kidney disease epidemiology collaboration equation (GFR_{EPI}). The superiority of $CL_{CR\text{-}CG}$ has been described in previous studies (16, 19). The average volume of distribution at steady state ($V_{SS} = V_C + V_P$) in the current study was 22.4 L, within the range of that previously reported in critically ill patients (range, 20.7 to 37.9 L). Hypotension had a significant effect on the V_P of meropenem. In patients with hypotension, the V_P of meropenem

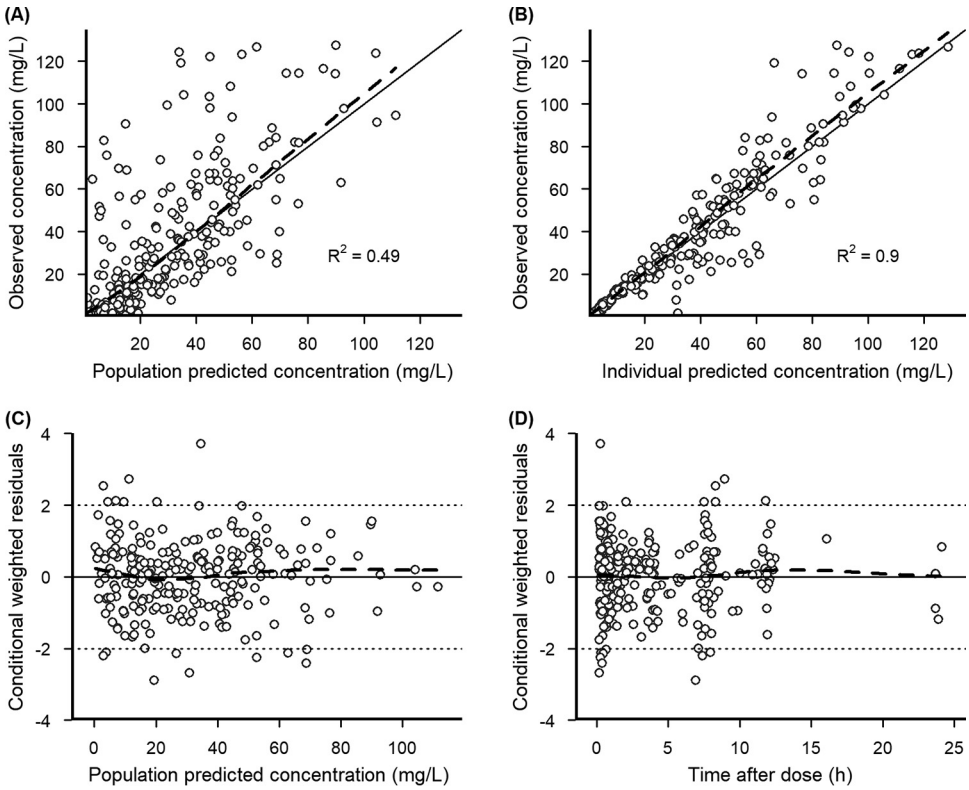

FIG 1 Goodness-of-fit plots of the final pharmacokinetic model. Observed meropenem concentration versus population-predicted (A) and individual-predicted (B) concentration. Conditional weighted residuals versus population predicted (C) and time after dose (D). Solid lines represent the line of identity, and the dashed line is the locally weighted smoothing (LOESS) line to indicate trends.

was increased by approximately 50%. In response to hypotension, a large volume of fluid resuscitation and inotropic agents are frequently prescribed to restore the mean arterial pressure. Intravenous fluid administration led to a significant increase in total body water, which substantially increased the volume of distribution (V_D). Low serum albumin levels

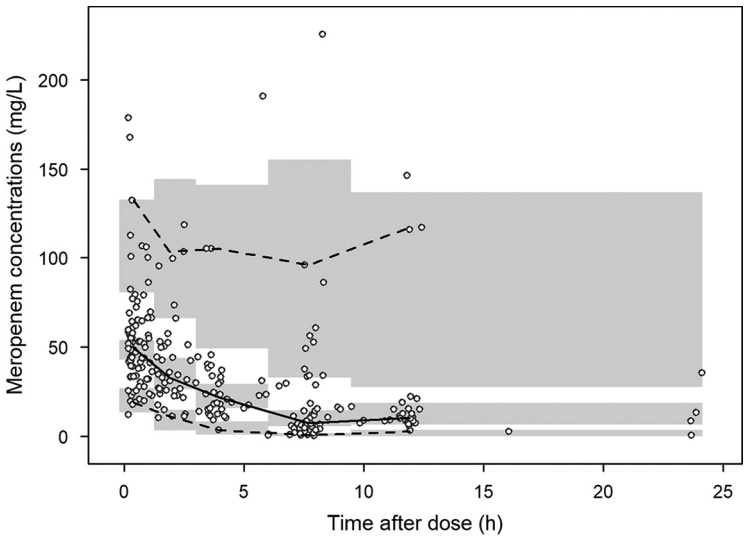

FIG 2 Prediction-corrected visual predictive check (pcVPC) of the final model. Open circles are observed concentrations. The solid line represents the 50th percentiles of the observation, and dashed lines represent the 2.5th and 97.5th percentiles of the observations. The shaded areas are the 95% confidence intervals around the 2.5th, 50th, and 97.5th of the simulated data.

TABLE 3 Microbiologic characteristics (86 isolates from 31 patients) and meropenem susceptibility

Pathogen[a]	No. of isolates	Meropenem MIC range (mg/L)[a]
Klebsiella pneumoniae	12	0.023
Klebsiella pneumoniae (ESBL)	14	0.032 to 0.5
Klebsiella pneumoniae (CRE)	2	≥32
Klebsiella pneumoniae (CRE)	1	12
Escherichia coli	15	0.01 to 0.023
Escherichia coli (ESBL)	3	0.023
Pseudomonas aeruginosa	10	0.064 to 1.0
Pseudomonas aeruginosa (CR-GNB)	3	≥32
Acinetobacter baumannii	2	0.38
Acinetobacter baumannii (CR-GNB)	6	≥32
Burkholderia pseudomallei	3	0.75
Enterococcus faecium	6	≥32
Enterobacter cloacae	1	0.032
Enterobacter aerogenes	1	0.047
Providencia stuartii	3	0.023
Stenotrophomonas maltophilia	2	ND
Moraxella catarrhalis	1	ND
Bacillus spp.	1	ND

[a]ESBL, extended-spectrum β-lactamases; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRE, carbapenem-resistant *Enterobacteriaceae*; ND, not determined.

were also found to increase the V_C significantly. When serum albumin levels decreased from 3.5 to 2.5 and 1.5 g/dL, the V_C of meropenem increased by 34% and 68%, respectively. An increase in V_D caused by hypoalbuminemia has been documented in several studies, particularly in highly protein-bound antibiotics (18, 20–23). Meropenem is a low protein binding antibiotic; therefore, it is unlikely that hypoalbuminemia would have a significant influence on meropenem V_D due to a change in drug binding. One possible explanation for this association is that it might be the pathophysiological consequence of hypoalbuminemia. By reducing intravascular oncotic pressure, hypoalbuminemia promotes fluid extravasation and tissue edema formation. Moreover, the loss of intravascular volume owing to hypoalbuminemia necessitates a large volume of fluid therapy to maintain tissue perfusion. Edema formation and aggressive fluid therapy contribute to an increase in the V_D of antibiotics. The hydrophilic nature of meropenem renders it sensitive to this phenomenon.

Carbapenems exhibit time-dependent antibacterial activity; that is, their antibacterial activity is best correlated with $fT_{>MIC}$. Generally, it has been suggested that the $fT_{>MIC}$ of carbapenems should be at least 40 to 50% for an optimal antibactericidal effect (7). In this study, all patients with drug-susceptible infections had $fT_{>MIC}$ values greater than 40%, and clinical response was observed in all patients. Seventy-five percent of the patients with resistant organisms also achieved this conservative target; however, approximately 83% did not survive the infection. This suggests that a target of 40% $fT_{>MIC}$ might not be sufficient for critically ill patients. When $fT_{>MIC}$ reached 75% and 100%, the clinical success rates increased to 71% and 91%, respectively. The proportion of patients who achieved 75% $fT_{>MIC}$ or 100% $fT_{>MIC}$ was higher in the clinical success group than in the failure group. There were seven patients with no specific MIC values for causative pathogens. When using the Clinical and Laboratory Standards Institute breakpoint (24) to calculate $fT_{>MIC}$ for these patients, the finding was consistent with our primary approach; the percentage of patients achieving 75% $fT_{>MIC}$ and 100% $fT_{>MIC}$ remained higher in the clinical success group than in the failure group (82.4% versus 40 to 70%). However, these observations might have been biased by the unbalanced MIC distribution between the groups. In our study, patients in the treatment failure group were infected by pathogens with higher MIC values than those in the success group (12 to 32 mg/L versus 0.023 to 32 mg/L). Therefore, the treatment failure and mortality rates were expected to be higher in patients infected with

TABLE 4 Comparison of baseline characteristics between clinical success and failure groups

Characteristic[a]	Clinical outcome[b]		Survival during ICU admission[b]	
	Success (n = 13)	Failure (n = 7)	Alive (n = 14)	Dead (n = 6)
Male	7 (53.8)	3 (42.9)	7 (50)	3 (50)
Age (yrs)	63.3 (55.2 to 76.5)	65.1 (63 to 71.6)	61.8 (46.4 to 75.7)	67.3 (64.0 to 72.8)
Body wt (kg)	62 (51 to 68)	60 (59 to 67.2)	59.5 (50.8 to 67.6)	62.5 (60 to 68.2)
APACHE II[c]	20 (19 to 22)	28 (16.5 to 29.5)	20 (17.5 to 21.8)	28 (20.5 to 30.3)
SOFA[c]	9 (6 to 11)	10 (8 to 12)	8 (6.0 to 10.8)	10 (8.5 to 13.0)
Inotropic or vasopressor used	10 (76.9)	7 (100)	11 (78.6)	6 (100)
Mechanical ventilator	11 (84.6)	7 (100)	12 (85.7)	6 (100)
Sepsis[d]	13 (100)	7 (100)	14 (100)	6 (100)
Septic shock[d]	6 (46.2)	4 (57.1)	6 (42.9)	4 (66.7)
$CL_{CR\text{-}CG}$ (mL/min)	45.5 (38.6 to 84.5)	69.2 (30.5 to 82.1)	46.7 (39 to 84.3)	52.9 (27.4 to 77.6)
Serum lactate (mmol/L)	2.3 (1.6 to 6.1)	4 (1.8 to 7.1)	2.3 (1.3 to 5.6)	4.1 (2.5 to 8.5)
Hypoalbuminemia	9 (69.2)	6 (85.7)	10 (71.4)	5 (83.3)
Primary infection site				
Respiratory	6 (46.1)	7 (100)	8 (57.1)	5 (83.3)
Genitourinary	3 (23.1)	0	3 (21.4)	0
Intraabdominal	2 (15.4)	0	1 (7.1)	1 (16.7)
Others	2 (15.4)	0	2 (14.3)	0
MIC (mg/L)	0.032 (0.023 to 32)[e]	32 (12 to 32)[e]	0.07 (0.023 to 32)[e]	32 (12 to 32)[e]
Meropenem monotherapy	12 (92.3)	2 (28.6)	13 (92.9)	1 (16.7)
Concomitant antimicrobials				
Colistin	1 (7.7)	3 (42.8)	1 (7.1)	4 (66.7)
Vancomycin	0	1 (14.3)	0	1 (16.7)
Other	0	1 (14.3)	0	0

[a]The information was from the first day of infection.
[b]Data are expressed as n (%) or median (interquartile range), unless otherwise stated.
[c]Evaluation on the first day of ICU admission.
[d]Patient diagnosed according to sepsis-3 criteria.
[e]Median (minimum-maximum).

resistant organisms, regardless of PK/PD achievement. Notably, one patient in the clinical success group was infected with multidrug-resistant *Pseudomonas aeruginosa* (MIC of 32 mg/L). The successful treatment of this patient was achieved by using a combination therapy of colistin and the highest licensed dose of meropenem, which was able to provide an individual $fT_{>MIC}$ above the 40% target. This indicates that MIC value is not the only factor determining prognosis. Other factors, such as disease severity, other combination antibiotics, and PK/PD achievement, might also affect treatment outcome. Unfortunately, we did not have enough data to control for other important variables and were limited by the study design. Nevertheless, considering the high mortality rate even when 40% $fT_{>MIC}$ was achieved and the fact that higher exposure was associated with improved outcomes (8, 25), maintaining a higher threshold of 75 to 100% $fT_{>MIC}$ should be considered for optimizing therapy in critically ill patients.

The simulation results demonstrated that the prolonged infusion time of meropenem to 3 h and shortened dosing interval provided a greater likelihood of achieving

TABLE 5 Pharmacokinetic/pharmacodynamic indices and clinical outcomes of 20 critically ill patients

Parameter	Overall (n = 20)[a]	Clinical outcome			Survival during ICU admission		
		Success (n = 13)[a]	Failure (n = 7)[a]	P value	Alive (n = 14)[a]	Dead (n = 6)[a]	P value
MIC (mg/L)	0.023 to 32	0.032 (0.023 to 32)	32 (12 to 32)	0.001	0.07 (0.023 to 32)	32 (12 to 32)	0.003
No. resistant pathogen (%)	8 (40)	1 (7.7)	7 (100)	0.001	2 (14.3)	6 (100)	0.001
$\%fT_{>MIC}$	100 (6.3 to 100)	100 (50 to 100)	81.3 (6.3 to 100)	0.017	100 (6.3 to 100)	85.6 (8.8 to 100)	0.279
$fT_{>MIC} \geq 40\%$	18 (90)	13 (100)	5 (71.4)	0.111	13 (92.9)	5 (83.3)	0.521
$fT_{>MIC} \geq 75\%$	14 (70)	10 (76.9)	4 (57.1)	0.613	10 (71.4)	4 (66.7)	1.000
$fT_{>MIC} = 100\%$	11 (55)	10 (76.9)	1 (14.3)	0.017	10 (71.4)	1 (16.7)	0.05

[a]Data are presented as median (minimum-maximum) or n (%).

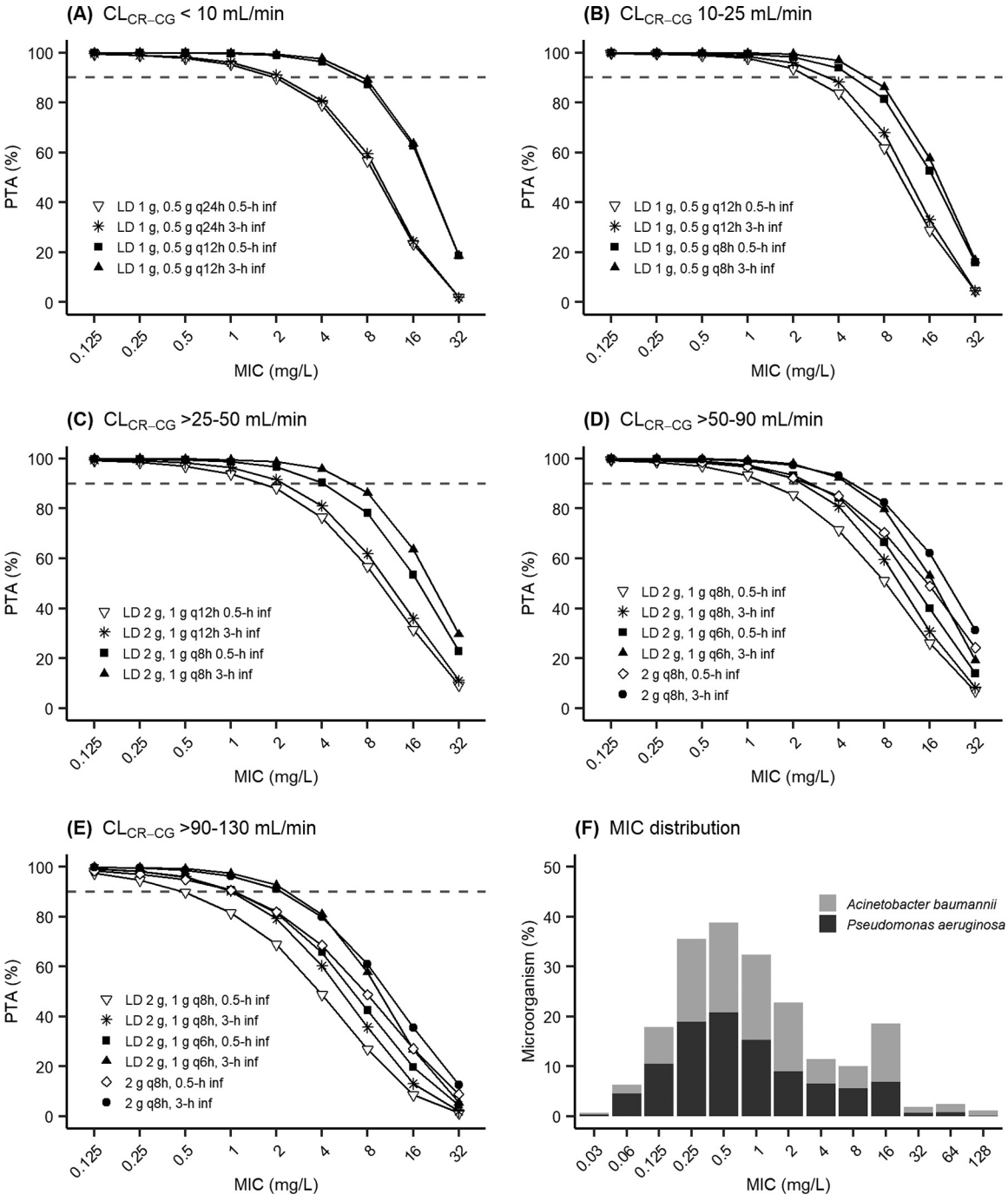

FIG 3 Probability of target attainment (PTA) for meropenem regimens achieving 75% $fT_{>MIC}$ target during 24 to 48 h after administration. Five groups were categorized according to creatinine clearance calculated by the Cockcroft and Gault equation (CL_{CR-CG}) as <10 mL/min (A), 10 to 25 mL/min (B), >25 to 50 mL/min (C), >50 to 90 mL/min (D), and >90 to 130 mL/min (E). (F) A histogram showing international MIC distribution of meropenem for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from the EUCAST database (October 2021) is shown. The horizontal dashed line denotes the PTA of 90%; LD, loading dose.

PK/PD targets than the 30-min intermittent infusion. The advantage of the extended infusion strategy has already been documented in other studies (10, 12, 26). However, the extended administration strategy did not significantly improve PTA in patients with severe renal impairment in the current analysis, particularly when CL_{CR-CG} was less than 10 mL/min. A similar trend was observed in previous studies (27, 28). The elimination of meropenem is a first-order process, and it is renally excreted. In our population

TABLE 6 Meropenem dosing recommendation against pathogens with MIC values of ≤2 mg/L

	$fT_{>MIC}$ target[a]		
CL_{CR-CG} (mL/min)[a]	40% $fT_{>MIC}$	75% $fT_{>MIC}$	100% $fT_{>MIC}$
90.1 to 130	LD 2 g, 1 g q8h (II)[b]	LD 2 g, 1 g q6h (EI)	LD 2 g, 2 g q6h (EI)
50.1 to 90	LD 2 g, 1 g q8h (II)[b]	LD 2 g, 1 g q8h (EI)	LD 2 g, 2 g q6h (EI)
25.1 to 50	LD 2 g, 1 g q12h (II)[b]	LD 2 g, 1 g q12h (EI)	LD 2 g, 1 g q6h (EI)
10 to 25	LD 1 g, 0.5 g q12h (II)[b]	LD 1 g, 0.5 g q12h (II)[b]	LD 1g, 0.5 g q6h (II)
<10	LD 1 g, 0.5 g q24h (II)[b]	LD 1 g, 0.5 g q24h (II)[b]	LD 1 g, 0.5 g q8h (II)

[a]%$fT_{>MIC}$, percentage of dosing interval where unbound meropenem concentration is above the MIC; CL_{CR-CG}, creatinine clearance estimated using standard Cockcroft-Gault formula based on ideal body weight; LD, loading dose; II, intermittent infusion (0.5 h); EI, extended infusion (3 h).
[b]Current standard regimen according to drug label information.

with reserved renal function, the elimination half-life ($t_{1/2,\ \beta}$) was approximately 1 h. Therefore, a short regular dosing interval and prolonged infusion duration were observed to be the best strategies for maximizing $fT>$MIC. When CL_{CR-CG} declined to less than 10 mL/min, the $t_{1/2,\ \beta}$ of meropenem was prolonged to 4.3 to 7.4 h. Extending the infusion time to 3 h, which is less than the $t_{1/2,\ \beta}$, generated an only 20 to 25% higher trough concentration and resulted in a slightly higher PK/PD target achievement rate (86.9% versus 88.6%). However, when the infusion duration was increased to 24 h (continuous infusion) in the corresponding dose, the PTA increased from 88.6% to 99.4%. Therefore, we inferred that the infusion duration should be longer than the $t_{1/2,\ \beta}$ of meropenem to maximize the advantage of an extended infusion strategy.

Based on the PTA results for achieving the 75% $fT_{>MIC}$ target, the current standard intermittent infusion of meropenem dosages are only sufficient to be used empirically for covering susceptible pathogens (MIC $\leq$ 2 mg/L) in patients with severe renal impairment (CL_{CR-CG} < 25 mL/min). For mild-to-moderate renal function, an extended infusion strategy of the standard dosage regimen is required to achieve optimal PTA. When targeting 100% $fT_{>MIC}$, a daily dose up to 2- to 3-fold the current standard dose is required for covering susceptible pathogens. The drug concentration at the site of infection is also a crucial determinant for obtaining a good clinical outcome. For pneumonia, which was the common infection in our study, epithelial lining fluid penetration (ELF) was the most clinically relevant compartment to estimate intrapulmonary drug concentrations. Studies performed in critically ill patients reported that the meropenem concentration in ELF was much lower than that in the plasma, and the ELF penetration ratio ranged from 0.2 to 0.3 (29–31). The standard intermittent infusion of meropenem doses (1 to 2 g every 8 h) failed to achieve 40 to 50% $fT_{>MIC}$ in ELF against pathogens with MIC values ≤2 mg/L (30, 32). The use of extended infusion has been shown to increase the penetration ratio of meropenem. However, even an extended infusion of the highest licensed meropenem dose fails to achieve 40% $fT_{>MIC}$ in ELF (30). Although continuous infusion appeared to increase meropenem exposure in ELF compared with extended infusion, it might not be sufficient to cover all intermediate organisms causing nosocomial pneumonia in critically ill patients (29). Considering our simulation results and this ELF penetration issue, meropenem should be administered by extended infusion in all ICU patients to achieve a 75% $fT_{>MIC}$ target in the plasma and increase meropenem exposure in ELF.

The strength of the current study is that both the drug exposure and meropenem MIC were determined; therefore, relationships between pharmacodynamic parameters and clinical outcomes could be evaluated. Although the present study has some strengths, it also has several limitations. First, because most of the plasma concentrations were measured at a steady state and there was limited blood sampling during the distribution phase, the incorporation of IIV into V_C and V_P resulted in a moderate level of ETA shrinkage. Second, this study was not designed to assess the PK/PD index and clinical outcomes as

the primary objectives. Only 20 patients were available for pharmacodynamic analysis, and only 8 patients were infected by resistant pathogens. The small sample size and imbalance in the clinical demographics of the groups did not allow us to draw a definite conclusion about the optimal cutoff PK/PD index of meropenem in critically ill patients. Future controlled studies with larger population sizes are required to elucidate the appropriate pharmacodynamic cutoffs for meropenem in critically ill patients.

Conclusions. The PPK model presented in this study contributes to a better understanding of the pharmacokinetics of meropenem in critically ill patients. Renal function was significantly associated with meropenem CL, while hypotension and low serum albumin levels increased the V_D of meropenem. Achieving 40% $fT_{>MIC}$ might not be sufficient for critically ill patients, and a higher target, such as 75 to 100% $fT_{>MIC}$, should be considered for optimizing therapy. A 75% $fT_{>MIC}$ could be reached using approved doses administered by 3-h infusion; however, twice the licensed dose was necessary to reach the 100% $fT_{>MIC}$ target.

MATERIALS AND METHODS

Study population and design. This was a prospective, single-center, observational pharmacokinetic study conducted at Songklanagarind Hospital, an academic hospital and the largest tertiary care center in southern Thailand. The inclusion criteria were (i) age of ≥18 years, (ii) confirmed or suspected bacterial infection, (iii) intravenous meropenem therapy, and (iv) hospitalization in a medical or surgical ICU. The exclusion criteria were (i) requirement of renal replacement therapy, (ii) pregnancy or breastfeeding, and (iii) a history of meropenem hypersensitivity.

The study protocol was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 61-061-14-1). Written informed consent was obtained from the patients or their legally authorized representatives before enrollment.

Meropenem administration and blood sampling. Meropenem doses prescribed according to the attending physician's decision were administered intravenously over 30 min using a venous catheter. After 24 h of therapy, 3 mL of blood was obtained via an indwelling arterial catheter from the arm that was not used for the intravenous infusion. A total of 5 blood samples per patient were randomly collected at the following sampling windows: shortly before meropenem administration and 0 to 0.5, 0.6 to 2.5, 2.6 to 4.0, and 4.1 to 12 h after meropenem administration. All blood samples were collected in heparinized tubes, immediately placed in an ice bath, and rapidly separated by centrifugation (2,000 × *g* at 4°C for 10 min) within 15 min of collection. Plasma supernatants were then preserved at −80°C until they were assayed in 4 weeks.

Unbound plasma meropenem assay. Unbound plasma meropenem concentrations were measured using reverse-phase high-performance liquid chromatography (HPLC) based on a validated assay reported by Ozkan et al. (33). The unbound fraction of meropenem was extracted by transferring 500 μL of the sample to an ultrafiltration device (Nanosep 10K device, Pall Corp., Northborough, MA) and centrifuged at 13,000 rpm at 4°C for 30 min. Fifty microliters of the filtrates was injected into the HPLC system for analysis and chromatographically separated with a reversed-phase column (μBondapak C_{18} column, 3.9 × 300 mm; Waters Associates). The mobile phase consisted of 15 mM KH_2PO_4, acetonitrile, and methanol (94:4:2 [vol/vol/vol], adjusted to a pH of 4.6), which flowed through the column at a rate of 1 mL/min. Transitional masses were monitored using a photodiode array detector (Waters, 2996; Waters Associates, Milford, MA) at a wavelength of 296 nm. The chromatograms were evaluated and integrated using a Waters 746 data module (Waters Associates). The LOD and LLOQ were 0.15 and 0.5 μg/mL, respectively. The intra- and interassay coefficients of variation were consistently less than 5%. The accuracy values ranged from 102.91% to 108.08%, and the recovery values ranged from 103.37% to 117.85%. Three meropenem concentrations (2, 32, and 128 μg/mL) with five replicates were used for this validation.

Microbiology. All antimicrobial susceptibility tests were conducted at the Microbiology Laboratory at Songklanagarind Hospital, Hat Yai, Thailand. MIC values for meropenem were evaluated using the Epsilometer test methodology (Liofilchem MIC test strips, Envimed, Thailand) for each patient in whom the microorganism was identified.

Outcome assessment. The primary treatment outcome was the clinical response, which was classified as either success or failure. Clinical success was defined as the resolution or improvement of infection-related clinical signs and symptoms at the end of meropenem therapy with no need to add or change the antibacterial therapy. Clinical failure was defined as the persistence or worsening of any clinical signs or symptoms of infection, the emergence of any new clinical signs or symptoms of infection, or the need for additional systemic antibacterial medication at the end of meropenem therapy. Subsequent deescalation to other narrow-spectrum antibiotics, according to microbiological results, was considered a standard of care and did not imply treatment failure. The secondary treatment outcome was ICU mortality.

Population pharmacokinetic analysis. The PPK model of meropenem was built using NONMEM software version 7.4.3 (Icon Development Solution, Ellicott City, MD, USA) along with Perl-Speaks-NONMEM version 5.2.6 (Uppsala University, Uppsala, Sweden) and Pirana software version 3.0.0 (Certara, NJ, USA). Graphical processing of the data and NONMEM output were performed in R version 3.6.0 and R Studio version 1.2.1335 (R Foundation for Statistical Computing, Vienna, Austria). First-order

conditional estimation with eta-epsilon interaction (FOCE-I) was used for parameter estimation throughout the analysis.

One-, two-, and three-compartment models with first-order elimination were evaluated to determine the optimal fit for the meropenem concentration-time data. The interindividual variability (IIV) of each parameter was modeled following an exponential error model, and the covariance terms were estimated for any interindividual error terms displaying significant correlations. The residual variability was modeled by considering additive, proportional, or combined additive and proportional error models.

After the appropriate structural model was established, several covariates of clinical interest were evaluated for their impact on PK parameters. These covariates were age, sex, actual body weight (BW), ideal body weight (IBW), adjusted body weight (ABW) (34), lean body weight (LBW) (35), body mass index, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, creatinine clearance estimated by the Cockcroft-Gault equation ($CL_{CR\text{-}CG}$) and by the Jelliffe equation ($CL_{CR\text{-}JEL}$) (36), estimated glomerular filtration rate (GFR) using the four- and six-variable modification of diet in renal disease study equation (GFR_{MDRD}) and the chronic kidney disease epidemiology collaboration equation (GFR_{EPI}), acute kidney injury, mechanical ventilation support, serum albumin, fluid balance, shock status (a clinical state requiring vasopressors or inotropes to maintain a mean arterial pressure greater than 65 mm Hg), and septic shock (based on the sepsis-3 criteria) (37). The $CL_{CR\text{-}CG}$ values were calculated using various weight measures (BW, IBW, ABW, and LBW) and compared for their predictive performance on PK parameters. The renal function markers normalized to a body surface area (BSA) of 1.73 m^2 (units in mL/min/1.73 m^2) and removal of BSA (units in mL/min) were also tested. Covariates were retained in the model if they led to significant improvement of model fit, as evaluated by a decrease in objective function value (OFV) of 3.84 ($P < 0.05$ for 1 degree of freedom [df]) for forward addition and an increase of OFV by 6.64 ($P < 0.01$ for 1 df) for a backward deletion step. Continuous covariates were scaled to the mean values.

OFV, Akaike's information criterion (AIC), parameter precision, and visual inspection of various goodness-of-fit plots were considered for model selection. A nonparametric bootstrap (n = 2,000) was performed to evaluate the robustness of the final model and obtain the confidence intervals of all parameter estimates. The predictive performance of the final model was examined using a pcVPC that compared the 5th, 50th, and 95th percentiles of the observed and simulated concentrations (n = 2,000).

Calculation of individual pharmacokinetic/pharmacodynamic (PK/PD) indices. The individual PK parameters from the final PPK model were used to calculate the PK/PD index. The percent $fT_{>MIC}$ of meropenem was determined for each patient whose MIC value was available. If patients were infected with more than one strain/pathogen, the pathogen with the highest MIC was chosen for the calculation of the percent $fT_{>MIC}$. Subsequently, the number of patients who achieved a $fT_{>MIC}$ above 40%, 75%, and 100% was counted and compared according to clinical outcomes.

The probability of target attainment (PTA). Monte Carlo simulations (n = 5,000) were performed using the NONMEM software version 7.4 to assess the PTA of various meropenem dosage regimens. The final PPK model and significant covariates were used to generate unbound concentration-time profiles over the first 24 to 48 h of the treatment course. The simulated scenarios were divided into five groups according to renal function ($CL_{CR\text{-}CG}$ < 10, 10 to 25, 25.1 to 50, 50.1 to 90, and 90.1 to 130 mL/min). $CL_{CR\text{-}CG}$ was considered to follow a uniform distribution in each range. Serum albumin level and shock status were also included in the model. Regarding the original data set, serum albumin and shock status were simulated using mean and standard deviations of 2.5 ± 0.65 g/dL and 35%, respectively. From the simulated concentration-time profiles, $fT_{>MIC}$ was determined for each virtual patient over a range of doubling MIC values, from 0.0156 to 128 mg/L. Then, the PTA was calculated as the percentage of patients who achieved 40% $fT_{>MIC}$, 75% $fT_{>MIC}$, and 100% $fT_{>MIC}$ targets. Regimens with PTAs of at least 90% were considered optimal.

Statistical analysis. All statistical analyses were performed using Stata software version 14.0 (StataCorp LP, College Station, TX, USA). Unless stated otherwise, continuous data are presented as median (interquartile ranges) and number (percentage) for categorical data. Continuous normally distributed data and nonnormally distributed data were analyzed by unpaired t test and Mann-Whitney U test, respectively. Categorical data were evaluated either by chi-square or Fisher's exact test, as appropriate. A two-sided P value of <0.05 was considered statistically significant in all analyses.

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REFERENCES

1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. 2017. Recognizing sepsis as a global health priority—a WHO resolution. N Engl J Med 377:414–417. https://doi.org/10.1056/NEJMp1707170.
2. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, Allegranzi B, Reinhart K. 2020. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med 46:1552–1562. https://doi.org/10.1007/s00134-020-06151-x.
3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. 2006.

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596. https://doi.org/10.1097/01.Ccm.0000217961.75225.E9.
4. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. 2014. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 42:1749–1755. https://doi.org/10.1097/CCM.0000000000000330.
5. Mouton JW, van den Anker JN. 1995. Meropenem clinical pharmacokinetics. Clin Pharmacokinet 28:275–286. https://doi.org/10.2165/00003088-199528040-00002.
6. Craig WA. 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10. https://doi.org/10.1086/516284.
7. Drusano GL. 2004. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2:289–300. https://doi.org/10.1038/nrmicro862.
8. Ariano RE, Nyhlén A, Donnelly JP, Sitar DS, Harding GK, Zelenitsky SA. 2005. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. Ann Pharmacother 39:32–38. https://doi.org/10.1345/aph.1E271.
9. McKinnon PS, Paladino JA, Schentag JJ. 2008. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (*T*>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31:345–351. https://doi.org/10.1016/j.ijantimicag.2007.12.009.
10. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. 2009. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 64:142–150. https://doi.org/10.1093/jac/dkp139.
11. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP. 2011. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 37:632–638. https://doi.org/10.1007/s00134-010-2105-0.
12. Jaruratanasirikul S, Thengyai S, Wongpoowarak W, Wattanavijitkul T, Tangkitwanitjaroen K, Sukarnjanaset W, Jullangkoon M, Samaeng M. 2015. Population pharmacokinetics and Monte Carlo dosing simulations of meropenem during the early phase of severe sepsis and septic shock in critically ill patients in intensive care units. Antimicrob Agents Chemother 59:2995–3001. https://doi.org/10.1128/AAC.04166-14.
13. Mathew SK, Mathew BS, Neely MN, Naik GS, Prabha R, Jacob GG, K S, Fleming DH. 2016. A nonparametric pharmacokinetic approach to determine the optimal dosing regimen for 30-minute and 3-hour meropenem infusions in critically ill patients. Ther Drug Monit 38:593–599. https://doi.org/10.1097/FTD.0000000000000323.
14. Mattioli F, Fucile C, Del Bono V, Marini V, Parisini A, Molin A, Zuccoli ML, Milano G, Danesi R, Marchese A, Polillo M, Viscoli C, Pelosi P, Martelli A, Di Paolo A. 2016. Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. Eur J Clin Pharmacol 72:839–848. https://doi.org/10.1007/s00228-016-2053-x.
15. Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, Wallis SC, Lipman J, Roberts JA. 2016. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. Int J Antimicrob Agents 48:542–546. https://doi.org/10.1016/j.ijantimicag.2016.08.015.
16. Minichmayr IK, Roberts JA, Frey OR, Roehr AC, Kloft C, Brinkmann A. 2018. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. J Antimicrob Chemother 73:1330–1339. https://doi.org/10.1093/jac/dkx526.
17. Lan J, Wu Z, Wang X, Wang Y, Yao F, Zhao B-X, Wang Y, Chen J, Chen C. 2022. Population pharmacokinetics analysis and dosing simulations of meropenem in critically ill patients with pulmonary infection. J Pharm Sci 111:1833–1842. https://doi.org/10.1016/j.xphs.2022.01.015.
18. Ehmann L, Zoller M, Minichmayr IK, Scharf C, Huisinga W, Zander J, Kloft C. 2019. Development of a dosing algorithm for meropenem in critically ill patients based on a population pharmacokinetic/pharmacodynamic analysis. Int J Antimicrob Agents 54:309–317. https://doi.org/10.1016/j.ijantimicag.2019.06.016.
19. Gijsen M, Elkayal O, Annaert P, Van Daele R, Meersseman P, Debaveye Y, Wauters J, Dreesen E, Spriet I. 2022. Meropenem target attainment and population pharmacokinetics in critically ill septic patients with preserved or increased renal function. Infect Drug Resist 15:53–62. https://doi.org/10.2147/IDR.S343264.
20. Onichimowski D, Będźkowska A, Ziółkowski H, Jaroszewski J, Borys M, Czuczwar M, Wiczling P. 2020. Population pharmacokinetics of standard-dose meropenem in critically ill patients on continuous renal replacement therapy: a prospective observational trial. Pharmacol Rep 72:719–729. https://doi.org/10.1007/s43440-020-00104-3.
21. Ramon-Lopez A, Allen JM, Thomson AH, Dheansa BS, James SE, Hanlon GW, Stewart B, Davies JG. 2015. Dosing regimen of meropenem for adults with severe burns: a population pharmacokinetic study with Monte Carlo simulations. J Antimicrob Chemother 70:882–890. https://doi.org/10.1093/jac/dku429.
22. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. 2011. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 50:99–110. https://doi.org/10.2165/11539220-000000000-00000.
23. Guilhaumou R, Benaboud S, Bennis Y, Dahyot-Fizelier C, Dailly E, Gandia P, Goutelle S, Lefeuvre S, Mongardon N, Roger C, Scala-Bertola J, Lemaitre F, Garnier M. 2019. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation-SFAR). Crit Care 23:104. https://doi.org/10.1186/s13054-019-2378-9.
24. Clinical and Laboratory Standard Institute (CLSI). 2022. Performance standard for antimicrobial susceptibility testing, CLSI supplement M100, 32nd ed. Clinical and Laboratory Standard Institute, Wayne, PA.
25. Zhou QT, He B, Zhang C, Zhai SD, Liu ZY, Zhang J. 2011. Pharmacokinetics and pharmacodynamics of meropenem in elderly Chinese with lower respiratory tract infections: population pharmacokinetics analysis using nonlinear mixed-effects modelling and clinical pharmacodynamics study. Drugs Aging 28:903–912. https://doi.org/10.2165/11595960-000000000-00000.
26. Jaruratanasirikul S, Sriwiriyajan S, Punyo J. 2005. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection. Antimicrob Agents Chemother 49:1337–1339. https://doi.org/10.1128/AAC.49.4.1337-1339.2005.
27. Alobaid AS, Wallis SC, Jarrett P, Starr T, Stuart J, Lassig-Smith M, Ordóñez Mejia JL, Roberts MS, Lipman J, Roberts JA. 2016. Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. Antimicrob Agents Chemother 60:4577–4584. https://doi.org/10.1128/AAC.00531-16.
28. Usman M, Frey OR, Hempel G. 2017. Population pharmacokinetics of meropenem in elderly patients: dosing simulations based on renal function. Eur J Clin Pharmacol 73:333–342. https://doi.org/10.1007/s00228-016-2172-4.
29. Benítez-Cano A, Luque S, Sorlí L, Carazo J, Ramos I, Campillo N, Curull V, Sánchez-Font A, Vilaplana C, Horcajada JP, Adalia R, Bermejo S, Samsó E, Hope W, Grau S. 2020. Intrapulmonary concentrations of meropenem administered by continuous infusion in critically ill patients with nosocomial pneumonia: a randomized pharmacokinetic trial. Crit Care 24:55. https://doi.org/10.1186/s13054-020-2763-4.
30. Frippiat F, Musuamba FT, Seidel L, Albert A, Denooz R, Charlier C, Van Bambeke F, Wallemacq P, Descy J, Lambermont B, Layios N, Damas P, Moutschen M. 2015. Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study. J Antimicrob Chemother 70:207–216. https://doi.org/10.1093/jac/dku354.
31. Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. 2011. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 55:1606–1610. https://doi.org/10.1128/AAC.01330-10.
32. Drusano GL, Lodise TP, Melnick D, Liu W, Oliver A, Mena A, VanScoy B, Louie A. 2011. Meropenem penetration into epithelial lining fluid in mice and humans and delineation of exposure targets. Antimicrob Agents Chemother 55:3406–3412. https://doi.org/10.1128/AAC.01559-10.
33. Ozkan Y, Kucukguzel I, Ozkan SA, Aboul-Enein HY. 2001. A rapid, sensitive high performance liquid chromatographic method for the determination of meropenem in pharmaceutical dosage form, human serum and urine. Biomed Chromatogr 15:263–266. https://doi.org/10.1002/bmc.68.
34. Erstad BL. 2004. Dosing of medications in morbidly obese patients in the intensive care unit setting. Intensive Care Med 30:18–32. https://doi.org/10.1007/s00134-003-2059-6.

35. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. 2005. Quantification of lean bodyweight. Clin Pharmacokinet 44:1051–1065. https://doi.org/10.2165/00003088-200544100-00004.
36. Jelliffe R. 2002. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am J Nephrol 22:320–324. https://doi.org/10.1159/000065221.
37. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J-L, Angus DC. 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315:801–810. https://doi.org/10.1001/jama.2016.0287.