ORIGINAL CLINICAL REPORT

OPEN

Impact of Various Estimated Glomerular Filtration Rate Equations on the Pharmacokinetics of Meropenem in Critically Ill Adults

Erin F. Barreto, PharmD, MSc[1]
Jack Chang, PharmD, MSc[2,3]
Andrew D. Rule, MD[4,5]
Kristin C. Mara, MSc[6]
Laurie A. Meade, RN[7]
Johar Paul, RRT[7]
Paul J. Jannetto, PhD[8]
Arjun P. Athreya, PhD[9]
Marc H. Scheetz, PharmD, MSc[2,3]
For the BLOOM Study Group
.

IMPORTANCE: Meropenem dosing is typically guided by creatinine-based estimated glomerular filtration rate (eGFR), but creatinine is a suboptimal GFR marker in the critically ill.

OBJECTIVES: This study aimed to develop and qualify a population pharmacokinetic model for meropenem in critically ill adults and to determine which eGFR equation based on creatinine, cystatin C, or both biomarkers best improves model performance.

DESIGN, SETTING, AND PARTICIPANTS: This single-center study evaluated adults hospitalized in an ICU who received IV meropenem from 2018 to 2022. Patients were excluded if they had acute kidney injury, were on kidney replacement therapy, or were treated with extracorporeal membrane oxygenation. Two cohorts were used for population pharmacokinetic modeling: a richly sampled development cohort ($n = 19$) and an opportunistically sampled qualification cohort ($n = 32$).

MAIN OUTCOMES AND MEASURES: A nonlinear mixed-effects model was developed using parametric methods to estimate meropenem serum concentrations.

RESULTS: The best-fit structural model in the richly sampled development cohort was a two-compartment model with first-order elimination. The final model included time-dependent weight normalized to a 70-kg adult as a covariate for volume of distribution (Vd) and time-dependent eGFR for clearance. Among the eGFR equations evaluated, eGFR based on creatinine and cystatin C expressed in mL/min best-predicted meropenem clearance. The mean (SE) Vd in the final model was 18.2 (3.5) liters and clearance was 11.5 (1.3) L/hr. Using the development cohort as the Bayesian prior, the opportunistically sampled cohort demonstrated good accuracy and low bias.

CONCLUSIONS AND RELEVANCE: Contemporary eGFR equations that use both creatinine and cystatin C improved meropenem population pharmacokinetic model performance compared with creatinine-only or cystatin C-only eGFR equations in adult critically ill patients.

KEYWORDS: beta-lactams; critical illness; cystatin C; extended-spectrum beta-lactamase; multidrug resistance; pharmacokinetics; sepsis

Carbapenems are one of the primary classes of antibiotics used to treat critically ill patients with multidrug-resistant infections. Structural modifications distinguish carbapenems from other beta-lactams and confer potency, stability, and resistance to beta-lactamases (1). For this reason, carbapenems exhibit broad antimicrobial spectrums of activity and are recommended as a first-line therapy for patients with infections from extended spectrum β-lactamase producing enterobacterales (ESBL-E) (2, 3).

Meropenem pharmacokinetics are highly variable in adult critically ill patients (4) with 15-45% variability in Vd and clearance observed within and

DOI: 10.1097/CCE.0000000000001011

KEY POINTS

Question: In critically ill adults treated with meropenem, a hydrophilic renally eliminated carbapenem, which estimated glomerular filtration rate (eGFR) equation best predicts drug clearance?

Findings: In this prospective study we developed and qualified a population pharmacokinetic model for meropenem suitable for critically ill adults. Among the creatinine- and cystatin C-based eGFR equations evaluated, the $eGFR_{cr\text{-}cysC}$ expressed in mL/min best-predicted meropenem clearance.

Meaning: Integration of cystatin C into pharmacokinetic models of meropenem reduces variability to a greater extent than when eGFR is modeled only with creatinine. Dosing algorithms which include creatinine and cystatin C are likely to aid in precision meropenem therapy for critically ill adults.

between patients at routinely used doses (5). As a time-dependent antibiotic, meropenem trough concentrations below the minimum inhibitory concentration of the organism increase the risk for clinical and microbiologic failure, and development of antimicrobial resistance (6–8). Excessively high meropenem concentrations have resulted in toxicity (9, 10), albeit rarely.

Across population pharmacokinetic (PK) models for meropenem in critically ill patients, the primary covariate of drug clearance is estimated glomerular filtration rate (eGFR) (11). Approximately 70% of the administered meropenem dose is excreted unchanged by the kidney within 12 hours (12). The majority of meropenem PK studies have used a creatinine-based calculation of GFR as a covariate for drug clearance (11). As the terminal byproduct of skeletal muscle catabolism, numerous nonrenal factors influence the serum creatinine concentration in critically ill patients. Cachexia, deconditioning, and malnutrition, for example, lead to decreased creatinine production and overestimation of GFR (13). Serum cystatin C is an endogenous protease inhibitor that is eliminated via glomerular filtration and can be used to estimate GFR. Cystatin C is less affected by some of the nonrenal factors that influence creatinine and may be less biased and more precise than creatinine-based estimates in the critically ill patient population (14, 15). Rarely cystatin C has been incorporated into meropenem pharmacokinetic models, but the data appear promising (16, 17). Therefore, the objectives of this study were to develop and validate a population PK model for meropenem in critically ill adults and evaluate contemporary eGFR equations based on serum creatinine and/or cystatin C as covariates for meropenem clearance.

MATERIALS AND METHODS

Setting

This prospective population pharmacokinetic study was conducted in critically ill patients treated at a single academic medical center, Mayo Clinic (Rochester, MN). In 2022, there were approximately 160 adult ICU beds and 15,000 total ICU admissions at Mayo Clinic in Rochester, MN. Critically ill individuals 18 years old or older treated with meropenem between 2018 and 2022 were evaluated for eligibility. Meropenem selection, dosing, escalation, or de-escalation throughout therapy were at the discretion of the care team and unaffected by study procedures. Meropenem levels were not available clinically during the study timeframe. Doses were determined by an interdisciplinary critical care team inclusive of a critical care pharmacist (available 7 d/wk) and aided by a standardized antimicrobial guide (18). The guide provides meropenem dose recommendations based on categorical thresholds of the Cockcroft-Gault estimated creatinine clearance as shown in **Table S1** (http://links.lww.com/CCX/B279). The typical meropenem dose for critically ill patients with a creatinine clearance greater than 80 mL/min at the study center was 500 mg every 6 hours delivered as a 30-minute infusion. No patients in the present study were treated with extended infusion meropenem. The study was approved by the Mayo Clinic Institutional Review Board (18-004992, 21-003184), performed in accordance with the Helsinki Declaration, and reported in accordance with the ClinPK statement (19).

Model Building Populations

Two unique cohorts with similar eligibility criteria were used for model development and qualification. Model development was performed in a richly sampled cohort of 19 patients collected from 2021 to 2022. Model qualification occurred in a separate opportunistically

sampled cohort of 32 patients collected from 2018 to 2021. Eligible adults (≥ 18 yr) were hospitalized in an ICU and treated with meropenem for at least 24 hours at a consistent dose and interval (e.g., 500 mg every 6 hr). Dose 1 of meropenem was defined as the beginning of the study antibiotic course. Individuals were excluded if they received any meropenem in the 4 days before the study antibiotic course or if more than one dose of meropenem for the study antibiotic course was administered before ICU admission. Individuals were also excluded if they demonstrated stage II or higher acute kidney injury (AKI; ≥ two-fold increase in serum creatinine from baseline or urine output < 0.5 mL/kg/hr for at least 12 hr [20]) or recovering stage II or higher AKI (21) at meropenem initiation. Critically ill patients treated with kidney replacement therapy or extracorporeal membrane oxygenation (ECMO) at meropenem initiation were excluded.

Richly Sampled Cohort (Development Cohort) (IRB Number 21-003184). Individuals who met the above criteria and had an indwelling IV catheter suitable for blood sampling were eligible for participation. Candidates or their legally authorized representative(s) provided written informed consent. A study nurse performed standardized blood collections from the IV catheter surrounding the earliest meropenem dose after enrollment. Up to five blood samples were collected per patient immediately before a dose (–0.5 hr), at 0.5, 1, and 3 hours after the start of the infusion, and 1 hour before the next scheduled dose (**Fig. S1**, http://links.lww.com/CCX/B279). Meropenem concentrations were assayed at each time point. If the IV access became unavailable or meropenem was discontinued no further study samples were obtained. Collected blood samples were centrifuged and aliquoted by the Clinical Trials Research Unit. Serum samples for meropenem concentrations were frozen at –80°C before analysis in batches monthly by the Mayo Clinic Clinical Mass Spectrometry Laboratory (22). Meropenem concentrations were not reported in the electronic health record. Serum creatinine and cystatin C concentrations were assayed from the –0.5-hour sample timepoint. Aliquots for serum creatinine and cystatin C concentrations were analyzed by clinical laboratories in real time and reported in the electronic health record.

Opportunistically Sampled Cohort (Qualification Cohort) (IRB Number 18-004992). In a separate cohort of 32 similar adult patients treated with meropenem in the ICU, opportunistic and sparse biospecimen sampling (23) was used to obtain serum meropenem, creatinine, and cystatin C concentrations. Clinical residual specimen availability was reviewed for patients treated with meropenem in the ICU who met eligibility criteria. Blood is collected at least twice daily for ICU patients as part of routine clinical care. Any remaining sample is stored at 4°C for "add-on" laboratory tests which may be clinically indicated. Up to three unused clinical blood samples were obtained for the research study (Fig. S1, http://links.lww.com/CCX/B279). No samples were obtained during drug infusion. As has been previously described by our group (24), residual blood samples for this study were stored at 4°C for no more than 4 days before being pulled and frozen at –80°C for this study. Samples were thawed in batches approximately monthly, aliquoted, and serum was processed for meropenem, creatinine, and cystatin C concentrations. Meropenem concentrations were assayed from all serum samples. Creatinine and cystatin C concentrations were assayed from the first available sample per patient. Meropenem, creatinine, and cystatin C concentrations were not reported in the electronic health record.

Assays

The standardized—isotope dilution mass spectrometry (IDMS) traceable—Roche enzymatic creatinine assay (Roche, Basel, Switzerland) was used to determine creatinine concentrations. In patients receiving IV catecholamines, known to interfere with enzymatic assays, an IDMS-traceable Roche Jaffe creatinine assay was used instead (Roche Cobas Integra 400 Plus chemistry analyzer). A particle-enhanced turbidimetric assay measured cystatin C concentrations (before May 2021: Gentian AS, Moss, Norway; After May 2021: Roche, Basel, Switzerland). The assay was traceable to the internationally certified cystatin C reference material (ERM-DA471/International Federation of Clinical Chemistry and Laboratory Medicine) used to develop the cystatin C-based Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equations. Total meropenem concentrations were determined using our previously validated liquid chromatography-tandem mass spectrometry assay (22). The lower limit of meropenem quantification was 0.5 mg/L.

Electronic Health Record Data Collection

Information about patient demographics (e.g., age, sex, self-reported race/ethnicity), body habitus (e.g.,

weight, body mass index [BMI]), comorbid conditions (e.g., chronic conditions including CKD, history of immunosuppressive conditions including transplant and cancer, acute conditions including sepsis), laboratory findings (e.g., C-reactive protein), severity of illness (e.g., Acute Physiology and Chronic Health Evaluation score [APACHE] and Sequential Organ Failure Assessment [SOFA]), and exact meropenem doses and administration times were obtained electronically from the Mayo Clinic Unified Data Platform and the Mayo Clinic METRIC Data Mart (25). Manual verification of at least 10% of the data was performed by study team members (E.F.B. and L.A.M.).

Population Pharmacokinetic Modeling

A nonlinear mixed-effects population pharmacokinetic model was developed in Monolix (Lixoft SAS, 2021, Version 2021R1; Antony, France) using the meropenem concentration–time data.

The pharmacokinetic model was developed from the richly sampled cohort (development cohort) in a stepwise fashion. One- and two-compartment structural models were first evaluated. All parameters were assumed to be log-normally distributed. Next, candidate covariates with biologic plausibility and/or previously described relationships to meropenem pharmacokinetics were then evaluated in a stepwise fashion. Candidate covariates considered included age, sex, race, ethnicity, presence of liver disease, presence of sepsis, APACHE III and SOFA scores, albumin concentration, C-reactive protein concentration, height, body surface area (BSA), and BMI (11). Weight and eGFR were modeled as time-dependent covariates. In the case of eGFR, creatinine, and cystatin C were only assayed once for research purposes. The remaining values used for modeling time-dependent change were taken from clinically available data. Continuous covariates were log-transformed for analysis whereas weight and BSA were standardized to a 70-kg adult with a 1.73-m^2 BSA. eGFR was standardized to normal adult kidney function at 120 mL/min. Estimation of GFR was based on the Cockcroft-Gault estimated creatinine clearance and the 2012 and 2021 CKD-EPI eGFR equations with creatinine, cystatin C, or both (expressed in mL/min/1.73 m^2 or mL/min) (**Table S2**, http://links.lww.com/CCX/B279). Progression of covariate-based models was guided by the rule of parsimony, minimization of the –2 log likelihood (–2LL), and the corrected Bayesian Information Criterion (BICc) (**Table 1**) (26, 27). Residual error models were evaluated (i.e., constant, proportional, and combined error models) with observed versus individual concentration prediction plots and the residual error parameters. Final model selection was based on the –2LL, BICc, goodness-of-fit plots, and visual predictive checks. The coefficient of determination (R^2) for observed versus predicted concentrations was calculated for all models.

The best-fit final model was assessed for qualification in the opportunistically sampled cohort. Mean population parameter estimates from the best-fit final model in the richly sampled cohort were used as a prior for fitting the observed concentrations in the opportunistically sampled cohort. The meropenem PK model was considered qualified if 90% of the individual predictions fell within the prediction interval of the model in the opportunistically sampled cohort. Mean absolute error (MAE) was calculated to describe model accuracy (Table 1). Bias was reported with the mean prediction error (MPE).

RESULTS

Demographic and Patient Characteristics

Fifty-one critically ill adults treated with meropenem were included in the richly sampled (n = 19), and opportunistically sampled (n = 32) cohorts. The cohorts were statistically similar for most factors, with the exception of a higher Charlson Comorbidity Index, a lower percentage of patients with sepsis, and a higher APACHE III score in the richly sampled cohort (**Table 2**). The overall mean eGFR was 60–97 mL/min (depending on the equation). One patient (2%) had a Cockcroft-Gault estimated creatinine clearance of less than 30 mL/min and 11 patients (22%) were greater than or equal to 130 mL/min. During therapy, eGFR changed by a median (interquartile range [IQR]) 0.2 (–4, 5) mL/min. Three patients (6%) had an eGFR change greater than or equal to 30 mL/min during the study. Median (IQR) time to first sample from meropenem initiation was 24 hours (13, 41) among the meropenem concentrations collected during therapy (excluding concentrations collected before meropenem administration in the opportunistically sampled cohort) (**Fig. S2**, http://links.lww.com/CCX/B279).

TABLE 1.
Terms and Descriptions

Term	Description
Nonlinear mixed-effects population pharmacokinetic modeling	A statistical model which incorporates both fixed and random effects to describe the pharmacokinetic and pharmacodynamic parameters of a population. A nonlinear function is used to relate drug concentration to model parameters and independent variables. Mixed effects describe "fixed effects" which do not vary across the population, and "random effects" which describe variance associated with individual samples from a population (27)
−2 Log likelihood (−2LL)	A statistical calculation used to compare two or more nested models (e.g., pharmacokinetic model ± kidney function estimate included). Broadly, the −2LL quantifies how well a model fits the observed data, whereas a better-fit model is indicated by a lower −2LL. Traditional inferential statistics can be applied, generating p values and allowing standard biomedical interpretations (e.g., $p < 0.05$). In brief, critical value differences greater than 3.84 for a single degree of freedom change (i.e., changing the kidney function estimate included) are associated with $p < 0.05$ using a chi-square distribution
Corrected Bayesian Information Criterion (BICc)	A statistical calculation that is an extension of −2LL which allows comparisons of models. Importantly, as opposed to −2LL, BICc allows non-nested models with different numbers of parameters to be compared (e.g., pharmacokinetic one-compartment vs. two-compartment models). A decrease in the BICc indicates improvement in the model fit. The BICc also includes a penalty for each additional parameter so as to penalize models for "over-fitting." General rules of thumb have been proposed to describe the degree of difference between models, but are nonetheless arbitrary. ΔBICc of greater than 10 is very strong evidence in favor of the model with the lower BICc ΔBICc of 6–10 is strong evidence ΔBICc of 2–6 is positive evidence ΔBICc of 0–2 is considered weak evidence As with all model evaluation strategies, biologic plausibility and purpose for model creation are important driving factors (26, 27)
Mean absolute error	Describes accuracy and indicates the degree to which model predictions deviate from the observed data on average. Value closer to 0 indicates greater accuracy. $\frac{1}{n}\sum_{i=1}^{n}\lvert\text{predicted concentration} - \text{observed concentration}\rvert$
Mean prediction error (MPE)	Describes bias. MPE may be positive or negative and values closer to 0 suggest less bias. $\frac{1}{n}\sum_{i=1}^{n}(\text{predicted concentration} - \text{observed concentration})$

Development of the Pharmacokinetic Model in the Richly Sampled Cohort

The PK model was developed using 72 meropenem concentrations in the 19 patients from the richly sampled cohort. Total meropenem concentrations ranged from undetectable (< 0.5 mg/L) to 47.2 mg/L.

One- and two-compartment models were assessed. The two-compartment model fit the data well and was parameterized as population clearance (CL, expressed in L/hr), Vd in the central compartment (V1, expressed in L), Vd in the peripheral compartment (V2, expressed in L), and intercompartmental clearance (Q, expressed in L/hr). The population mean parameter estimate (SE) in the final model for CL was 11.5 (1.3) L/hr, V1 was 18.2 (3.5) liters, V2 was fixed at 137.4 liters, and Q was 4.2 (1.4) L/hr. Inclusion of weight (decrease in BICc from base model by 7) and eGFR (decrease in BICc from base model by greater than or equal to 44 depending on equation) as time-dependent covariates improved the model fit. No other covariates significantly improved model performance. In an analysis designed to identify the best-performing eGFR equation for meropenem clearance, the 2021 CKD-EPI $eGFR_{cr\text{-}cysC}$ expressed in mL/min was most closely associated with meropenem clearance (**Table 3**). All equations with cystatin C predicted meropenem pharmacokinetics better than creatinine-only equations. Among the creatinine-only eGFR equations, the 2021 CKD-EPI $eGFR_{cr}$ (mL/min) was most closely

TABLE 2.
Baseline Patient Characteristics and Demographics

Characteristic	Richly Sampled Cohort ($n = 19$)[a]	Opportunistically Sampled Cohort ($n = 32$)[a]	p
Age (yr)	68 (49, 78)	65 (55, 69)	0.44
Male (n; %)	11 (58)	23 (72)	0.31
Non-Hispanic White (n; %)	18 (95)	28 (88)	0.53
Weight			
Hospital admission (kg)	71 (63, 90)	76 (65, 94)	0.76
ICU admission (kg)	73 (60, 90)	75 (65, 90)	0.68
Meropenem initiation (kg)	76 (62, 93)	78 (65, 91)	0.60
Body mass index (kg/m^2)	25 (23, 32)	27 (23, 31)	0.84
≥ 30 kg/m^2	6 (32)	10 (31)	0.98
Body surface area (m^2)	1.9 (1.7, 2.1)	1.9 (1.7, 2.1)	0.84
Charlson comorbidity index (n; %)[b]	5 (3, 9)	2 (1, 6)	0.038
Operative reason for admission (n; %)	6 (32)	7 (22)	0.66
Select concurrent exposures/conditions at meropenem initiation (n; % unless otherwise specified)			
Diabetes mellitus	2 (11)	10 (31)	0.092
Liver disease	1 (5)	6 (19)	0.18
Chronic kidney disease	5 (26)	7 (22)	0.72
Metastatic cancer	0 (0)	3 (9)	0.28
Transplant history[c]	1 (5)	8 (25)	0.074
Corticosteroid exposure	7 (37)	16 (50)	0.36
C-reactive protein[b,d]	59 (51, 170)	315 (–, –)	0.19
Sepsis	13 (68)	30 (94)	0.016
Invasive mechanical ventilation	7 (37)	8 (25)	0.37
Vasopressor use	13 (68)	22 (69)	0.98
Acute Physiology and Chronic Health Evaluation III score	97 (88, 142)	79 (69, 104)	0.018
Sequential Organ Failure Assessment score	10 (4, 12)	7 (4, 10)	0.32
Kidney parameters at meropenem initiation			
Serum creatinine (mg/dL)	1.1 (0.6, 1.3)	0.9 (0.6, 1.2)	0.77
Cystatin C (mg/L)	1.6 (0.9, 2.1)	1.3 (1.0, 2.0)	0.55
Meropenem parameters			
Time to drug initiation from ICU admission (hr)	31 (4, 91)	34 (4, 186)	0.68
Dose (g)			0.50
0.5 g	16 (84)	30 (94)	
1 g	2 (11)	1 (3)	
2 g	1 (5)	1 (3)	
Interval (n; %)			0.04
6 hr	11 (58%)	27 (84%)	
8 hr	8 (42%)	5 (16%)	

[a]Values expressed as means ± SDs or counts with percentages unless noted.
[b]Median with interquartile range due to data distribution.
[c]Includes five individuals with a stem cell transplant, four with a solid organ transplant.
[d]Available in seven patients (six development, one qualification).

TABLE 3.

Comparison of Estimated Glomerular Filtration Rate Equations as a Covariate for Meropenem Clearance in the Richly Sampled (Development) Cohort (*n* = 19)

	eGFR[a] (Mean ± SD)	Corrected Bayesian Information Criterion[b]	−2LL[b]
Base model (two-compartment, first order)		507	477
Cockcroft-Gault estimated creatinine clearance (mL/min)	92 ± 52	463	433
2012 CKD-EPI $eGFR_{Cr}$ (mL/min/1.73 m^2)	76 ± 33	459	429
2021 CKD-EPI $eGFR_{Cr}$ (mL/min/1.73 m^2)	78 ± 32	459	428
2012 CKD-EPI $eGFR_{CysC}$ (mL/min/1.73 m^2)	52 ± 30	457	427
2012 CKD-EPI $eGFR_{Cr\text{-}CysC}$ (mL/min/1.73 m^2)	62 ± 30	457	426
2021 CKD-EPI $eGFR_{Cr\text{-}CysC}$ (mL/min/1.73 m^2)	63 ± 31	456	426
2012 CKD-EPI $eGFR_{Cr}$ (mL/min)	80 ± 32	454	424
2021 CKD-EPI $eGFR_{Cr}$ (mL/min)	82 ± 31	454	423
2012 CKD-EPI $eGFR_{CysC}$ (mL/min)	55 ± 30	452	422
2012 CKD-EPI $eGFR_{Cr\text{-}CysC}$ (mL/min)	65 ± 28	452	421
2021 CKD-EPI $eGFR_{Cr\text{-}CysC}$ (mL/min)	67 ± 29	446	421

−2LL = −2 Log likelihood, BICc = corrected Bayesian Information Criterion, CKD-EPI = chronic kidney disease epidemiology collaborative, Cr = creatinine, cysC = cystatin C, eGFR = estimated glomerular filtration rate.

[a]eGFR was modeled as a time-dependent covariate in pharmacokinetic models, allowing variation with each new creatinine or cystatin C assessment. Only eight patients (five in the richly sampled, three in the opportunistically sampled) had greater than 1 value for cystatin C used in time-dependent eGFR modeling. The mean eGFR represented in this column reflects the first value for the patient.

[b]BICc and −2LL are tools to use to compare models where lower values indicate improved model fit. As shown in Table 1, a difference in BICc of greater than 10 is very strong evidence in favor of the model with the lower BIC; a difference of 6–10 is strong evidence; a difference between two and six is positive evidence; and a difference of 0–2 is considered weak evidence (39, 40). The 2021 CKD-EPI $eGFR_{Cr\text{-}CysC}$ (mL/min) had the lowest BICc and −2LL and thus was selected as the eGFR equation for use in the final model.

associated with meropenem clearance. Evaluation of individual fit plots (**Fig. S3**, http://links.lww.com/CCX/B279) and visual predictive checks showed good fit of the final model (**Table 4**) to the data (Fig. S1, http://links.lww.com/CCX/B279). Between-subject variability (ω) (SE) was ωCL: 0.43 (0.088), ωV1: 0.61 (0.15), and ωQ: 0.71 (0.52).

In the final two-compartment model, the observed concentration versus population-predicted meropenem concentrations resulted in an R^2 of 0.71, MAE of 4.2 mg/L, and MPE of -0.03 mg/L. The observed concentration versus individual-predicted concentrations resulted in an R^2 of 0.9, MAE of 1.6 mg/L, and MPE of −0.39 mg/L (**Fig. 1**).

Qualification of the Pharmacokinetic Model in the Opportunistically Sampled Cohort

To qualify the PK model, the mean (SE) population parameter estimates from the final model (CL 11.5 [1.3] L/hr and V1 18.2 [3.5] L) were used as a Bayesian prior for fitting the 86 observed concentrations from the 32 patients in the opportunistically sampled cohort. Resulting individual fits in the opportunistically sampled cohort were similar to those identified in the richly sampled cohort (Fig. S3, http://links.lww.com/CCX/B279). The mean (SE) population parameter estimate from the opportunistically sampled cohort for CL was 11.5 (2.0) L/hr and for V1 was 33.1 (7.3) liters. There was a low proportion of outliers (3.5%) outside the 90% prediction interval on the observed versus individual concentration prediction plot. The observed concentration versus population-predicted meropenem concentrations resulted in an R^2 of 0.71, MAE of 2.7 mg/L, and MPE of 0.38 mg/L. The observed concentration versus individual-predicted concentrations resulted in an R^2 of 0.89, MAE of 1.4 mg/L, and MPE of −0.30 mg/L (**Fig. S4**, http://links.lww.com/CCX/B279). Between-subject variability (SE) was low for both CL (ωCL: 0.34 [0.096]) and V1 (ωV1: 0.49 [0.25]).

TABLE 4.
Final Meropenem Population Pharmacokinetic Model Parameters in the Richly Sampled (Development) Cohort

	Value	SE	Relative SE %
Fixed effects			
CL	11.5	1.31	11.4
V1	18.2	3.48	19.2
Q	4.2	1.35	32.4
V2[a]	137.4	–	–
SD of the random effects			
ωCL	0.43	0.09	20.3
ωV1	0.61	0.15	23.9
ωQ	0.71	0.52	73.0
Error model parameters			
b	0.25	0.033	12.8

CL = population clearance, Q = intercompartmental clearance, V1 = population volume of distribution in the central compartment, V2 = population volume of distribution in the peripheral compartment, ωCL = between-subject variability in clearance, ωQ = between-subject variability in intercompartmental clearance, ωV1 = between-subject variability in volume of distribution in the central compartment.
[a]Fixed value based on population estimate.

DISCUSSION

In this prospective single-center study of critically ill adults treated with meropenem, we developed a population pharmacokinetic model using parametric methods. A two-compartment model with first-order elimination best fit the data. Significant covariates in the model included normalized weight for Vd and normalized eGFR for clearance. Several eGFR equations were analyzed as covariates for meropenem clearance. The 2021 CKD-EPI $eGFR_{cr\text{-}cysC}$ equation expressed in mL/min best-reduced model variability among those analyzed. The model was qualified in an independent cohort of critically ill adults with high accuracy and low bias.

Carbapenems, such as meropenem, are often selected as a last resort for critically ill patients with drug-resistant gram-negative organisms (2) due to their consistent effectiveness and limited adverse effects. Nevertheless, estimates indicate that 18% of all *Pseudomonas aeruginosa* isolates exhibit intermediate susceptibility or resistance to meropenem (28). Optimized meropenem dosing facilitates clinical and microbiologic cure and limits the development of drug resistance (8). Meropenem concentrations are frequently insufficient in critically ill patients. Estimates indicate that between 30% and 79% of critically ill patients fail to achieve the minimum meropenem concentration necessary to successfully treat an infection (7, 29, 30). Insufficient carbapenem concentrations are associated with a need for additional antibiotics, prolonged durations of therapy, longer lengths of stay, and increased mortality (7, 29, 31).

Kidney function has consistently been a factor in meropenem target attainment in studies of the critically ill given that 70% of the drug is excreted unchanged in the urine (12). In one study of 147 patients treated with beta-lactams, 32 patients of whom received meropenem, the odds of target achievement were 0.14 (95% CI, 0.03–0.49) among adults with an eGFR greater than or equal to 90 mL/min/1.73 m^2 (29). In a separate evaluation of 47 critically ill adults treated with meropenem, a u-shaped curve existed where the poorest target attainment was observed in either patients with augmented renal clearance (i.e., estimated creatinine clearance $[eCrCl]_{Cockcroft\text{-}Gault} \geq$ 130 mL/min) or in patients with severe renal insufficiency (i.e., $eCrCl_{Cockcroft\text{-}Gault}$ 15–29 mL/min) (30). Other studies have suggested that lower eGFRs were associated with improved target attainment (32, 33). In the present study of 51 critically ill patients, we reinforce the clear importance of GFR in the clearance

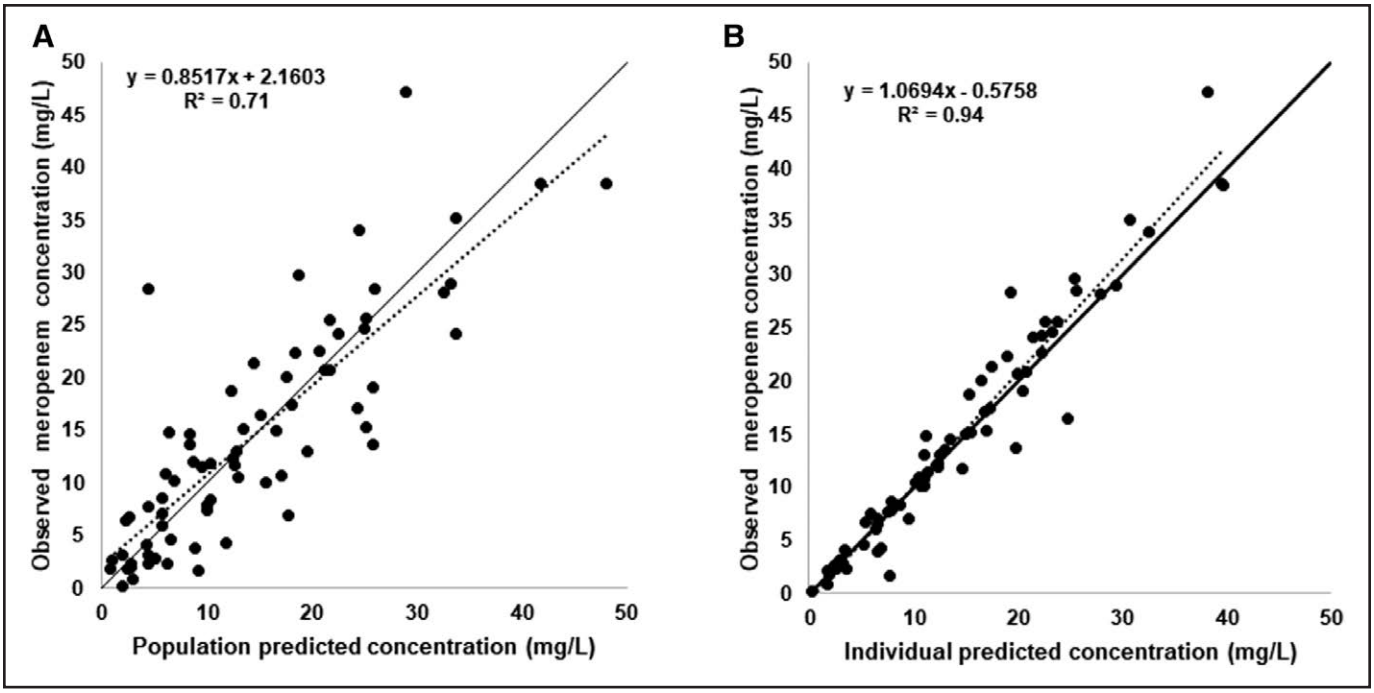

Figure 1. Goodness-of-fit plots during model development using data from the richly sampled cohort ($n = 19$). **A**, The observed concentrations (measured values for the study; *y*-axis) versus population-predicted concentrations (*x*-axis). In this plot, the model parameters (e.g., Vd) are fixed at the mean (population) values for all patients. The *solid black line* is the line of identity ($x = y$) and the *dashed black line* reflects the line of best fit. Mean absolute error (MAE) was 4.2 mg/L and mean prediction error (MPE) was −0.03 mg/L. **B**, The observed concentrations (measured values for the study; *y*-axis) versus individual predicted concentrations (*x*-axis). In this plot, the model parameters (e.g., Vd) are unique to each patient. The graphs demonstrate the expected improvement in model performance when individual values are used as compared with the mean (population) values (i.e., R^2 is improved in the **A**). For the individual predictions, few outliers (4.2%) were outside the 90% prediction interval on the observed versus individual concentration prediction plot. MAE was 1.6 mg/L and MPE was −0.39 mg/L.

of meropenem. Across the development and qualification cohorts, the mean eGFR of patients in this study ranged from 60 to 97 depending on the equation. Less than one-fourth of patients were at extremes of kidney function thus limiting the ability to draw conclusions specifically about these subgroups.

Across population PK studies of meropenem in the critically ill, eGFR was most commonly calculated with the Cockcroft-Gault estimated creatinine clearance (11). We are aware of two studies that incorporated cystatin C into meropenem PK evaluations (16, 17). Cystatin C is a low molecular weight protein, freely filtered at the glomerulus and reabsorbed and catabolized by proximal tubular cells (13). It has been suggested as a viable adjunct or alternative to creatinine at the bedside to improve the accuracy and precision of drug dosing (34–36). In a population PK evaluation in 32 surgical ICU patients, 1/cystatin C concentration and the $eGFR_{CysC}$ better predicted meropenem clearance during continuous infusion therapy than the $eCrCl_{Cockcroft\text{-}Gault}$ (16). In a separate study of 19 critically ill patients, the serum cystatin C concentration better predicted meropenem trough concentrations than the serum creatinine (cystatin C: $R^2 = 0.41$; creatinine: $R^2 = 0.11$). Although cystatin C was better than serum creatinine, measured creatinine clearance appeared to outperform $eGFR_{CysC}$ (measured creatinine clearance: $R^2 = 0.76$; $eGFR_{Cystatin\ C}$: $R^2 = 0.31$) (17). The current study builds upon these previous findings. We demonstrated that a combination eGFR equation with both creatinine and cystatin C best-reduced model variability. This is in alignment with outpatient studies which demonstrate that the $eGFR_{cr\text{-}cysC}$ predicts measured GFR (identified after administration of a freely filtered exogenous substrate) more accurately and precisely than $eGFR_{cr}$ or $eGFR_{cysC}$ (37, 38). We have also previously demonstrated preference for $eGFR_{cr\text{-}cysC}$ in PK and dosing studies for vancomycin (35, 36).

Development and qualification of this population pharmacokinetic model is the first step toward identifying a more accurate and precise meropenem dosing model for critically ill adults. We envision future

studies, likely using simulation methods, will compare the probability of target attainment with dosing guided by this model versus standard creatinine-only approaches to meropenem dosing and monitoring. The objective of these future studies will be to ask and answer whether this improved pharmacokinetic model makes a clinically significant difference in target attainment and dosing decisions made in practice. If promising, formal testing of a new dosing nomogram at the bedside, similar to the approach taken with vancomycin (36), is needed to establish the feasibility, acceptability, and effectiveness for meropenem target attainment.

The study we report is not without limitations. Due to antimicrobial stewardship efforts to restrict meropenem utilization, a prolonged study period was needed for enrollment and the sample size was modest. Nevertheless, our sample size is on par with other population PK studies of meropenem use in critically ill adults (11) and similar if not slightly larger than other studies which have explored the relationship between cystatin C-based estimates of GFR and meropenem PK. The present study excluded patients with stage 2 or higher AKI. Although eGFR was modeled as a time-dependent covariate, exclusion of patients with moderate to severe AKI precluded a detailed assessment of meropenem pharmacokinetics in unstable kidney function. The eGFR equations studied were designed for use in stable kidney function. Future studies that include patients with AKI could probe kinetic $eGFR_{Cr}$ and kinetic $eGFR_{CysC}$ as covariates for meropenem clearance (39). We are aware of one study that suggested that the most recent kinetic $eGFR_{cr}$ equation (40) best-predicted vancomycin clearance in unstable kidney function (41). To the best of our knowledge, no such studies of kinetic $eGFR_{CysC}$ to predict medication elimination have been described. Patients treated with kidney replacement therapy were excluded, but meropenem pharmacokinetics during kidney replacement therapy have been explored in other studies (42–44). Although patients treated with ECMO were excluded from this cohort, it does not appear to significantly impact meropenem PK (30, 45). Patients in the richly sampled cohort were recruited during the COVID-19 pandemic which may have affected processes of care and rate of recruitment. The cystatin C assay at the study center was also updated in May 2021 which may have altered concentrations by up to 10% in patients with values less than 1.2 mg/L. Despite this, cystatin C consistently outperformed creatinine.

CONCLUSIONS

In this prospective population PK study of critically ill adults, we demonstrated that the 2021 $eGFR_{cr\text{-}cysC}$ equation best-predicted meropenem clearance. Cystatin C is an important adjunct or alternative to creatinine for estimating GFR in the critically ill. These data suggest that its application to meropenem dosing alongside creatinine has the potential to improve precision pharmacotherapy in the critically ill.

ACKNOWLEDGMENTS

The authors thank Kimberly Hamilton, Lindsay Fogelson, Brenda Anderson, and the rest of the Anesthesia Clinical Research Unit at Mayo Clinic for their assistance and contributions to study enrollment and data acquisition. Our appreciation is expressed to Dr. Ognjen Gajic, Kathryn Vollmer, and Mr. Matt Bjergum for their assistance with the study.

1 *Department of Pharmacy, Mayo Clinic, Rochester, MN.*

2 *Department of Pharmacy Practice, Chicago College of Pharmacy, Pharmacometrics Center of Excellence, Midwestern University, Downers Grove, IL.*

3 *Department of Pharmacy, Northwestern Medicine, Chicago, IL.*

4 *Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

5 *Division of Epidemiology, Mayo Clinic, Rochester, MN.*

6 *Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN.*

7 *Anesthesia Clinical Research Unit, Mayo Clinic, Rochester, MN.*

8 *Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.*

9 *Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

All authors had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the analysis. Drs. Barreto, Chang, Rule, Mara, Athreya, and Scheetz: designed the study, performed the statistical analysis, interpreted

the data, drafted, and critically revised the article. Dr. Jannetto was responsible for beta-lactam assay validation, sample measurement, and critical revision of the article. Drs. Meade and Paul were responsible for study enrollment, data collection and reporting, and critical revision of the article.

This project was supported, in part, by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) under award number K23AI143882 (principal investigator; Dr. Barreto). The funding source had no role in study design; data collection, analysis, or interpretation; writing the report; or the decision to submit the report for publication. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Dr. Scheetz declares a consultancy with DoseMe. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: Barreto.erin@mayo.edu

Mayo Clinic Institutional Review Board approved the study and waived the need for informed consent (18-004992, 21-003184).

An anonymized dataset may be made available upon reasonable request to the corresponding author.

REFERENCES

1. Papp-Wallace KM, Endimiani A, Taracila MA, et al: Carbapenems: Past, present, and future. *Antimicrob Agents Chemother* 2011; 55:4943–4960
2. Tamma PD, Aitken SL, Bonomo RA, et al: Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis* 2022; 75:187–212
3. Henderson A, Paterson DL, Chatfield MD, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN): Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. *Clin Infect Dis* 2021; 73:e3842–e3850
4. Gonçalves-Pereira J, Póvoa P: Antibiotics in critically ill patients: A systematic review of the pharmacokinetics of β-lactams. *Crit Care* 2011; 15:R206
5. Roberts JA, Kirkpatrick CMJ, Roberts MS, et al: 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* 2009; 64:142–150
6. Craig WA, Ebert SC: Killing and regrowth of bacteria in vitro: A review. *Scand J Infect Dis Suppl* 1990; 74:63–70
7. Roberts JA, Paul SK, Akova M, et al; DALI Study: DALI: Defining antibiotic levels in intensive care unit patients: Are current ß-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; 58:1072–1083
8. Tam VH, Schilling AN, Neshat S, et al: Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of Pseudomonas aeruginosa optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 2005; 49:4920–4927
9. Imani S, Buscher H, Marriott D, et al: Too much of a good thing: A retrospective study of β-lactam concentration–toxicity relationships. *J Antimicrob Chemother* 2017; 72:2891–2897
10. Abdul-Aziz MH, Alffenaar J-WC, Bassetti M, et al: Antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. *Intensive Care Med* 2020; 46:1127–1153
11. Li L, Sassen SDT, Ewoldt TMJ, et al: Meropenem model-informed precision dosing in the treatment of critically ill patients: Can we use it? *Antibiotics (Basel)* 2023; 12:383
12. B. Braun Medical Inc: Meropenem full prescribing information, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202106s007lbl.pdf. Accessed May 24, 2023
13. Teaford HR, Barreto JN, Vollmer KJ, et al: Cystatin C: A primer for pharmacists. *Pharmacy (Basel)* 2020; 8:35
14. Sangla F, Marti PE, Verissimo T, et al: Measured and estimated glomerular filtration rate in the ICU. *Crit Care Med* 2020; 48:e1232–e1241
15. Haines RW, Fowler AJ, Liang K, et al: Comparison of cystatin C and creatinine in the assessment of measured kidney function during critical illness. *Clin J Am Soc Nephrol* 2023; 18:997–1005
16. Kees MG, Minichmayr IK, Moritz S, et al: Population pharmacokinetics of meropenem during continuous infusion in surgical ICU patients. *J Clin Pharmacol* 2016; 56:307–315
17. Petersson J, Giske CG, Eliasson E: Standard dosing of piperacillin and meropenem fail to achieve adequate plasma concentrations in ICU patients. *Acta Anaesthesiol Scand* 2016; 60:1425–1436
18. Wilson JW, Estes LL: Mayo Clinic antimicrobial therapy: Quick guide. Oxford University Press, 2018. Available at: http://www.oxfordmedicine.com/view/10.1093/med/9780190696924.001.0001/med-9780190696924. Accessed November 20, 2023
19. Kanji S, Hayes M, Ling A, et al: Reporting guidelines for clinical pharmacokinetic studies: The ClinPK statement. *Clin Pharmacokinet* 2015; 54:783–795
20. Kellum J, Lameire N, Aspelin P, et al: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2:1–138
21. Chawla LS, Bellomo R, Bihorac A, et al; Acute Disease Quality Initiative Workgroup 16.: Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; 13:241–257
22. Bjergum MW, Barreto EF, Scheetz MH, et al: Stability and validation of a high-throughput LC-MS/MS method for the quantification of cefepime, meropenem, and piperacillin and tazobactam in serum. *J Appl Lab Med* 2021; 6:1202–1212
23. Tang Girdwood SC, Tang PH, Murphy ME, et al: Demonstrating feasibility of an opportunistic sampling approach for pharmacokinetic studies of β-lactam antibiotics in critically ill children. *J Clin Pharmacol* 2021; 61:565–573

24. Barreto EF, Chang J, Bjergum MW, et al: Adequacy of cefepime concentrations in the early phase of critical illness: A case for precision pharmacotherapy. *Pharmacotherapy* 2023;43:1112-1120
25. Herasevich V, Pickering BW, Dong Y, et al: Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. *Mayo Clin Proc* 2010; 85:247–254
26. Kass RE, Raftery AE: Bayes factors. *J Am Stat Assoc* 1995; 90:773–795
27. Mould DR, Upton RN: Basic concepts in population modeling, simulation, and model-based drug development—part 2: Introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol* 2013; 2:e38
28. Sader HS, Huband MD, Castanheira M, et al: Antimicrobial susceptibility of pseudomonas aeruginosa: Results from four years (2012-2015) of the international network for optimal resistance monitoring (INFORM) program in the United States. *Antimicrob Agents Chemother* 2017; 61:AAC.02252-16
29. Abdulla A, Dijkstra A, Hunfeld NGM, et al: Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: A two-center prospective study (EXPAT). *Crit Care* 2020; 24:1–12
30. Ehmann L, Zoller M, Minichmayr IK, et al: Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: A prospective observational study. *Crit Care* 2017; 21:1–14
31. Chua NG, Loo L, Hee DKH, et al: Therapeutic drug monitoring of meropenem and piperacillin-tazobactam in the Singapore critically ill population—a prospective, multi-center, observational study (BLAST 1). *J Crit Care* 2022; 68:107–113
32. Gan Y, Meng X, Lei N, et al: Meropenem pharmacokinetics and target attainment in critically ill patients. *Infect Drug Resist* 2023; 16:3989–3997
33. Tournayre S, Mathieu O, Villiet M, et al: Factors associated with meropenem pharmacokinetic/pharmacodynamic target attainment in septic critically ill patients treated with extended intermittent infusion or continuous infusion. *Int J Antimicrob Agents* 2023; 62:106868
34. Barreto EF, Rule AD, Murad MH, et al: Prediction of the renal elimination of drugs with cystatin C vs creatinine: A systematic review. *Mayo Clin Proc* 2019; 94:500–514
35. Frazee EN, Rule AD, Hermann SM, et al: Serum cystatin C predicts vancomycin trough levels better than serum creatinine in hospitalized patients: A cohort study. *Crit Care* 2014; 18:R110
36. Frazee E, Rule AD, Lieske JC, et al: Cystatin C-guided vancomycin dosing in critically ill patients: A quality improvement project. *Am J Kidney Dis* 2017; 69:658–666
37. Inker LA, Schmid CH, Tighiouart H, et al; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367:20–29
38. Inker LA, Eneanya ND, Coresh J, et al: New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021; 385:1737–1749
39. Behal ML, Flannery AH, Barreto EF: Medication management in the critically ill patient with acute kidney injury. *Clin J Am Soc Nephrol* 2023; 18:1080–1088
40. Chen S: Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol* 2013; 24:877–888
41. Pai MP, DeBacker KC: Modeling kinetic glomerular filtration rate in adults with stable and unstable kidney function: Vancomycin as the motivating example. *Pharmacotherapy* 2020; 40:872–879
42. Beumier M, Casu GS, Hites M, et al: β-lactam antibiotic concentrations during continuous renal replacement therapy. *Crit Care* 2014; 18:R105
43. Roberts JA, Joynt GM, Lee A, et al; SMARRT Study Collaborators and the ANZICS Clinical Trials Group: The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: Data from the multinational sampling antibiotics in renal replacement therapy study. *Clin Infect Dis* 2021; 72:1369–1378
44. Schatz LM, Brinkmann A, Röhr A, et al: Systematic evaluation of pharmacokinetic models for model-informed precision dosing of meropenem in critically ill patients undergoing continuous renal replacement therapy. *Antimicrob Agents Chemother* 2023; 67:e0010423
45. Donadello K, Antonucci E, Cristallini S, et al: β-lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: A case-control study. *Int J Antimicrob Agents* 2015; 45:278–282