

Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model

Iris K. Minichmayr^{1,2}, Jason A. Roberts^{3,4}, Otto R. Frey⁵, Anka C. Roehr⁵, Charlotte Kloft^{1*†} and Alexander Brinkmann^{5†}

¹Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Kelchstr. 31, 12169 Berlin, Germany; ²Graduate Research Training program PharMetX, Freie Universitaet Berlin, Berlin, Germany, and Universitaet Potsdam, Potsdam, Germany; ³University of Queensland Centre for Clinical Research, Faculty of Medicine, and Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, Australia; ⁴Departments of Intensive Care Medicine and Pharmacy, Royal Brisbane and Women's Hospital, Brisbane, Australia; ⁵Department of Pharmacy and Department of Anaesthesia and Intensive Care Medicine, General Hospital of Heidenheim, Heidenheim, Germany

*Corresponding author. Tel: +49-30-838-50676; Fax: +49-30-838-450656; E-mail: charlotte.kloft@fu-berlin.de

†Shared senior authorship.

Received 19 June 2017; returned 26 September 2017; revised 25 November 2017; accepted 18 December 2017

Background: Optimal antibiotic exposure is a vital but challenging prerequisite for achieving clinical success in ICU patients.

Objectives: To develop and externally validate a population pharmacokinetic model for continuous-infusion meropenem in critically ill patients and to establish a nomogram based on a routinely available marker of renal function.

Methods: A population pharmacokinetic model was developed in NONMEM[®] 7.3 based on steady-state meropenem concentrations (C_{ss}) collected during therapeutic drug monitoring. Different serum creatinine-based markers of renal function were compared for their influence on meropenem clearance (the Cockcroft–Gault creatinine clearance CL_{CRCG} , the CL_{CR} bedside estimate according to Jelliffe, the Chronic Kidney Disease Epidemiology Collaboration equation and the four-variable Modification of Diet in Renal Disease equation). After validation of the pharmacokinetic model with independent data, a dosing nomogram was developed, relating renal function to the daily doses required to achieve selected target concentrations (4/8/16 mg/L) in 90% of the patients. Probability of target attainment was determined for efficacy ($C_{ss} \geq 8$ mg/L) and potentially increased likelihood of adverse drug reactions ($C_{ss} > 32$ mg/L).

Results: In total, 433 plasma concentrations (3.20–48.0 mg/L) from 195 patients (median/ $P_{0.05}$ – $P_{0.95}$ at baseline: weight 77.0/55.0–114 kg, CL_{CRCG} 63.0/19.6–168 mL/min) were used for model building. We found that CL_{CRCG} best described meropenem clearance ($CL = 7.71$ L/h, $CL_{CRCG} = 80$ mL/min). The developed model was successfully validated with external data ($n = 171$, 73 patients). According to the nomogram, daily doses of 910/1480/2050/2800/3940 mg were required to reach a target $C_{ss} = 8$ mg/L in 90% of patients with $CL_{CRCG} = 20/50/80/120/180$ mL/min, respectively. A low probability of adverse drug reactions (<0.5%) was associated with these doses.

Conclusions: A dosing nomogram was developed for continuous-infusion meropenem based on renal function in a critically ill population.

Introduction

Appropriate dosing of antibiotic therapy is considered pivotal to decrease morbidity and improve outcome in critically ill patients with bacterial infections.^{1–3} However, unpredictable physiological changes that cause altered and highly variable pharmacokinetics

pose a significant challenge to effective antibiotic dosing in this population.⁴ To further complicate issues, ICUs often harbour bacterial strains with reduced antibiotic susceptibility, increasing the risk of treatment failure due to subtherapeutic concentrations.^{5–7}

Recent data have shown that licensed doses of different classes of antibiotics frequently do not achieve pharmacokinetic/

pharmacodynamic (PK/PD) targets in critically ill patients.^{8–10} Data from a large prospective multicentre study suggested that empirical dosing of β -lactam antibiotics would result in unsatisfactory exposure in a large portion of ICU patients (19%/41% for $fT_{>MIC} < 50\%/100\%$) infected with less susceptible pathogens, particularly if presenting high renal function and receiving intermittent instead of prolonged or continuous infusion.¹⁰

Continuous infusion has been demonstrated to improve PK/PD target attainment in various further studies of time-dependent antibiotics, both for plasma and, importantly, peripheral target sites of infection.^{9,11,12} Apart from improved drug exposure, previous studies have associated continuous infusion also with higher clinical cure rates in patients with severe sepsis^{13,14} and ventilator-associated pneumonia¹⁵ or better 30 day survival in patients with respiratory infections.¹⁶ Furthermore, a recent meta-analysis suggested decreased hospital mortality in patients treated with continuous infusion of β -lactams, including meropenem.¹⁷

Meropenem is an intravenous broad-spectrum carbapenem antibiotic frequently employed for the empirical treatment of severe nosocomial infections and is an appealing candidate for continuous infusion owing to its time-dependent antibacterial activity, short PK half-life and sufficient stability in infusion solutions at room temperature.^{18–21} Meropenem elimination is a major source of PK variability and predominantly occurs via renal excretion.^{18,22,23} As measurements of creatinine clearance (CL_{CR}) are not routinely performed, surrogates of kidney function, e.g. based on serum creatinine (SCr), are frequently employed to guide dosing of renally cleared drugs such as meropenem.²⁴ However, there have been discussions of their accuracy in critically ill patients and evidence is lacking regarding which marker of renal function should be used to inform dose adjustments for meropenem.²⁵

Therefore, the present work aimed to develop and externally validate a population PK model for continuous-infusion meropenem considering routinely available markers of renal function in a large cohort of critically ill patients. We then sought to develop a nomogram translating renal function into daily doses of meropenem required to achieve specific target concentrations.

Patients and methods

Patients and ethics

We retrospectively analysed meropenem plasma concentrations collected during routine therapeutic drug monitoring (TDM) at the medical centre of Heidenheim, Germany (Kliniken Landkreis Heidenheim gGmbH) between 2009 and 2011. Adult critically ill patients, who received continuous infusion of meropenem and did not undergo renal replacement therapy, were analysed. The research was approved by the responsible institutional ethics committee (reference number 351/14; 12/2014).

Calculation of renal function

Renal function was estimated using the following SCr-based equations: Cockcroft–Gault creatinine clearance (CL_{CRG} ;²⁶ standard Cockcroft–Gault formula based on total body weight: CL_{CRG_WT}), the ‘bedside estimate’ of CL_{CR} suggested by Jelliffe (CL_{CRJEL} ²⁷), the four-variable Modification of Diet in Renal Disease (MDRD²⁸) formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI²⁹) equation. Furthermore, variants of CL_{CRG} using different weight measures [Supplementary information: total, ideal, lean and adjusted body weight (WT, IBW, LBW and ABW, respectively); see Supplementary data available at JAC Online] or modified SCr

values (CL_{CRG_mod} : if SCr < 1 mg/dL, SCr set to 1 mg/dL) were determined. To facilitate the comparison between the formulas, each was investigated as both normalized to a standard body surface area (BSA) of 1.73 m² (adjusted ‘adj’, e.g. $CL_{CRG_WT_adj}$) as well as in their unadjusted form.

Drug administration

An initial loading dose of 500 mg, or in exceptional cases 1000 mg (as a 30 min intravenous infusion) was administered at the start of meropenem therapy (Meropenem[®], AstraZeneca GmbH, Wedel, Germany). Subsequently, the maintenance dose was delivered as a continuous infusion (0.5–2 g reconstituted in 50 mL of 0.9% sodium chloride) via a syringe pump. Daily doses of meropenem were left to the discretion of the attending physician and were guided by the local dosing protocol based on CL_{CRG} , susceptibility of presumed/known causative pathogens and site of infection. In cases of severe infection with susceptible pathogens, steady-state concentrations (C_{ss}) of 8–16 mg/L were targeted (8 mg/L represents 4 \times the non-species-related PK/PD breakpoint for susceptibility $S \leq 2$ mg/L according to EUCAST as well as the susceptibility breakpoint for common pathogens such as Enterobacteriaceae or *Pseudomonas aeruginosa*). Over the course of therapy, doses were adjusted according to measured meropenem concentrations, identified pathogens and treatment response. Infusion syringes were changed every 6–24 h to comply with internally performed stability tests, revealing meropenem stability ($\geq 90\%$ of initial amount, no turbidity) at 23°C over 8/18/24 h for 50/20/10 mg/mL solutions (0.9% sodium chloride; see Supplementary information and Figure S1 for further details as well as previous evidence on the stability of meropenem).

Blood sampling and analytical assays

Blood samples were drawn in the clinical routine setting at steady-state, at the earliest 6–24 h after the start of treatment. Meropenem concentrations were directly analysed following sampling. Total concentrations were measured using a validated HPLC method with UV detection based on a previously published assay.³⁰ For the analysis, 250 μ L of patient sample was added to 50 μ L of internal standard (0.2 mg/mL ertapenem) and 500 μ L acetonitrile:methanol (LiChrosolv[®]), 1:1 v/v. Following centrifugation (5–10 min, 1800 g, 4°C), 200 μ L of supernatant was mixed with 600 μ L of water for injection and 50 μ L of the solution was analysed by HPLC (Shimadzu Germany GmbH, Duisburg; the system comprised two LC-10AD vp pumps, an SIL-10AF vp autoinjector, an SCL-10A vp system controller and an SPD-M10A vp diode array detector, wavelength 300 nm). Chromatographic separation was achieved using an RP-C18 column protected by a precolumn and gradient elution with a mobile phase composed of two buffers (A: water containing 0.5% formic acid; B: acetonitrile containing 0.25% formic acid and 4.75% water) at a flow rate of 1 mL/min over 15 min (retention time of meropenem and ertapenem: 8.5 and 10 min, respectively). The linear calibration range of meropenem was 1.00–50.0 mg/L. The relative standard deviation of interday and intraday precision was very low, 2.05%–2.76% and 0.30%–0.80%, respectively, and the relative error ($\leq \pm 1.5\%$) indicated high accuracy. SCr concentrations were determined by a modified Jaffe method using an Architect c8000 system (Abbott, Abbott Park, IL, USA).

Population PK modelling

Population PK modelling was performed using NONMEM[®] 7.3 (Icon Development Solutions, Ellicott City, MD, USA), PsN 3.7.6 (Uppsala University, Uppsala, Sweden), the first-order conditional estimation with interaction method and the \$PRED subroutine. Descriptive statistics and graphical analyses were conducted using R 3.2.2 (CRAN.R-project.org). Total meropenem clearance (L/h) was estimated from administered daily doses and corresponding C_{ss} (mg/L) [$CL = \text{daily dose (mg)}/(24 \text{ h} \cdot C_{ss})$].

Renal function markers were implemented as covariates on clearance using linear and power functions (see [Supplementary information](#) for further details on the development of the PK model).

Following covariate analysis, further subgroup analyses were conducted. To assess the impact of multiple measurements per individual, model parameters were also estimated for a subset comprising only the first observation of each patient. A potential impact of unstable renal function on the parameter estimates was investigated by exclusion of all affected individuals and re-estimation of the model parameters. Unstable SCr was defined as >50% change from one measurement to the next, and from the first to the last measurement of individual observation periods.

Model adequacy was judged by statistical significance, i.e. decrease in the objective function value ($\Delta\text{OFV} \geq 3.84$, $\alpha = 0.05$, $\text{df} = 1$ for nested models; see [Supplementary information](#) for further explanation), precision and plausibility of parameter estimates, standard goodness-of-fit plots (e.g. observed versus population and versus individual predicted concentrations, conditional weighted residuals versus predicted concentrations) and percentage of explanation of between-subject variability (BSV) associated with CL. A non-parametric bootstrap ($n = 1000$ replicate datasets) and prediction-corrected visual predictive checks (VPCs) were used to evaluate the precision of estimates and the predictive performance of the model.

External validation of the model

To check external validity, the model was applied to data independently gathered in 2014 in the same clinical setting, i.e. in the same ICUs, but in a different sample of adult critically ill patients, who required intensive care, received continuous infusion of meropenem and did not undergo renal replacement therapy. Measured meropenem concentrations of the external dataset were compared with those predicted by the developed model by means of goodness-of-fit plots, VPCs and calculation of normalized prediction distribution errors.

Probability of target attainment analyses and development of a nomogram

Based on the structural and BSV parameter estimates of the model, Monte Carlo simulations ($n = 1000$) were performed to assess meropenem exposure for varying doses (1000–8000 mg/day) and renal function values reflective of the observed population. In addition to the probability of attaining a target concentration of 8 mg/L ($= 4 \times \text{EUCAST PK/PD susceptible/intermediate breakpoint for meropenem}^{31}$), the probability of target attainment (PTA) for a threshold of 32 mg/L ($= 4 \times \text{EUCAST PK/PD resistant breakpoint}^{31}$) was determined, which—if exceeded—would put patients unnecessarily at higher risk of adverse drug reactions without apparent additional therapeutic benefit.^{32,33}

For the nomogram, the 90th percentile of the BSV associated with CL and corresponding CL were calculated for varying renal function values and transformed into daily doses necessary to achieve target concentrations of 4, 8 and 16 mg/L.

Results

Patient characteristics

A total of 268 Caucasian critically ill patients who were admitted to an ICU were included in the analysis. Of these, 195 were considered for model development (433 of 604 meropenem concentrations); the most common indications for meropenem therapy (multiple options possible) were pneumonia (56.4%), sepsis (48.7%), peritonitis (23.6%), pancreatitis (4.10%), urinary tract infections (3.59%) and/or urosepsis (3.59%). Patients were mainly treated empirically, with a modal daily dose of 3000 mg/24 h

Table 1. Summary of patient characteristics at baseline (given as median and 5th–95th percentile)

Characteristic (unit)	Patients for model development (n = 195)	Patients for model validation (n = 73)
Sex (% male)	62.6	75.3
Age (years)	72.0 (45.7–84.0)	72.0 (42.2–87.4)
Body height (cm)	170 (155–180)	170 (158–185)
Total body weight (kg)	77.0 (55.0–114)	75.0 (53.2–108)
BMI (kg/m ²)	26.7 (20.3–39.8)	25.4 (19.5–36.2)
BSA (m ²)	1.87 (1.56–2.24)	1.88 (1.58–2.31)
IBW (kg)	65.6 (47.7–74.5)	65.7 (51.7–82.1)
LBW (kg)	54.5 (36.9–70.6)	55.9 (38.0–73.1)
ABW (kg)	71.0 (53.5–90.9)	74.7 (54.0–98.0)
SCr (mg/dL)	1.15 (0.51–3.16)	1.04 (0.55–3.86)
CL _{CRCG_WT} (mL/min)	63.0 (19.6–168)	66.4 (16.1–160)

BSA, body surface area; IBW, ideal body weight; LBW, lean body weight; ABW, adjusted body weight; SCr, serum creatinine; CL_{CRCG_WT}, standard Cockcroft–Gault creatinine clearance (see [Supplementary information](#) for the formulas underlying the body size descriptors).

(range 500–6000 mg/24 h), over a median duration of 6 days (range 1–33 days). Demographic and clinical data are described in Tables 1 and S1 (renal function markers).

Meropenem concentrations

A total of 433 meropenem concentrations (1–8/patient) were measured within up to 21 days during one course of therapy. Sixteen concentrations (3.70% of data) from six patients were determined during one ($n_{\text{patients}} = 5$) or two ($n_{\text{patients}} = 1$) further occasions, e.g. following separate hospital admissions, 18–104 days after the first treatment course. In >95% of all patients, the first sample was drawn after >12 h of therapy. The vast majority of individuals contributed to one or more further subsequent samples taken >24 h after the start of therapy.

Meropenem concentrations all exceeded the EUCAST clinical susceptibility breakpoint for Enterobacteriaceae of 2 mg/L³¹ (range 3.20–48.0 mg/L, median 14.0 mg/L). Thresholds of ≥ 4 , ≥ 8 and ≥ 16 mg/L were achieved for 99.8%, 90.3% and 40.9% of measurements, respectively. Most meropenem concentrations (61.9%) were assessed in the presence of renal impairment (CL_{CRCG} <50/50–<80 mL/min/1.73 m²: 38.6%/23.3%) and the fewest (15.0%) during augmented renal clearance (≥ 130 mL/min/1.73 m²).

Population pharmacokinetic modelling

All investigated markers of renal function significantly improved the model performance, most notably the standard Cockcroft–Gault formula (sorted by statistical significance, i.e. ΔOFV 283–200: CL_{CRCG_WT}–CL_{CRJEL}–CL_{CRCG_WT_adj}–CKD–EPI–MDRD–CL_{CRCG_mod}–CL_{CRJEL_adj}–CKD–EPI_{adj}–MDRD_{adj}, see Table S2). Formulas that considered the patients’ actual BSA (mL/min) were superior to their variants adjusted to standard BSA (mL/min/1.73 m²), both in terms of statistical significance (decrease in OFV) and explanation of BSV, with CL_{CRCG_WT} leading to the largest (55.8%) and MDRD causing

the lowest reduction (49.0%) in variability associated with meropenem clearance. Exchange of WT in the standard Cockcroft–Gault formula CL_{CRCG_WT} against alternative body size descriptors (IBW, LBW, etc.) did not result in improved prediction of meropenem clearance (indicated by a lower decrease in OFV compared with the base model).

Linear implementation of the parameter–covariate relationships performed similar to or better than power models. Therefore, owing to higher acceptability in routine clinical practice, CL_{CRCG_WT} was entered into the final model in a linear fashion despite a marginally lower drop in OFV (2.60) compared with the power function (for a more detailed explanation of the final model, see [Supplementary information](#)). The high impact of renal function on meropenem clearance resulted in a >3-fold increase in CL from 4.15 to 14.8 L/h given CL_{CRCG_WT} values ranging from 30 to 180 mL/min.

Similar parameter estimates were obtained when estimating model parameters with the complete dataset versus a subset only comprising the first observation of the patients. Neither unstable SCr values within individuals nor SCr measurements sampled during later independent meropenem treatments affected the estimated relationship between CL_{CRCG_WT} and clearance. Assumption of a smaller influence of renal function on meropenem CL for high $CL_{CRCG_WT} > 80$ and > 130 mL/min, respectively, did not improve the model.

A proportional residual unexplained variability model was most appropriate to describe meropenem concentrations. Inclusion of inter-occasion variability on clearance for different occasions of therapy was not supported by the data. Table 2 presents all parameter estimates for the final covariate model. None of the 95% bootstrap confidence intervals of the parameter estimates included zero, indicating their statistical significance. Goodness-of-fit plots (Figure 1) and the VPC (Figure 2) both revealed an adequate description of the observed data by the model.

External model evaluation

A total of 171 meropenem measurements from 73 patients constituted the validation dataset. Daily doses (mode 3000 mg/24 h, range 500–6000 mg/24 h), meropenem concentrations (median C_{SS} 13.7, range 3.0–47.6 mg/L) and patient characteristics of the external data largely resembled those of the model

development dataset, with a slightly higher proportion of male patients (Table 1). External evaluation confirmed the predictive performance of the model as demonstrated by goodness-of-fit plots, VPCs and normalized prediction distribution errors (Figure 3, Figure S2), confirming that the model was suitable for dosing simulations.

Dosing nomogram and PTA analysis

The dosing nomogram that was established based on the linear CL – CL_{CRCG_WT} relationship is depicted in Figure 4, together with a general function to calculate the daily doses required to attain any desired target concentration. For example, to reach an efficacy threshold of 8 mg/L (solid line in the nomogram) in 90% of patients with CL_{CRCG_WT} values of 20, 50, 80, 120 and 180 mL/min (x-axis), daily meropenem doses of 910, 1480, 2050, 2800 and 3940 mg (y-axis) would be required. PTA analysis (Figure 5) indicated a low probability of adverse drug reactions (<0.5%) associated with these doses.

Table 2. Parameter estimates for meropenem from the final population pharmacokinetic model

Parameter	Model estimate	RSE (%)	Bootstrap	
			median	95% CI
Structural model parameters				
θ_{CL} (L/h)	7.71	2.5	7.70	7.35–8.08
θ_{COV}^a (min/mL)	0.00924	4.0	0.00922	0.00851–0.00994
Between-subject variability				
ω_{CL} (%CV)	25.7	7.5	25.6	21.6–29.5
Residual unexplained variability				
σ (%CV)	23.2	6.7	23.0	20.3–26.3

RSE, percentage relative standard error (standard error/estimate \times 100; RSE of between-subject and residual unexplained variability estimates reported on approximate standard deviation scale); convergence rate of bootstrap: 100%; %CV, coefficient of variation; θ_{CL} , population clearance given a reference CL_{CRCG_WT} (creatinine clearance according to Cockcroft and Gault) of 80 mL/min as a lower limit of normal kidney function.

^a θ_{COV} , fractional change in CL per unit change of CL_{CRCG_WT} .

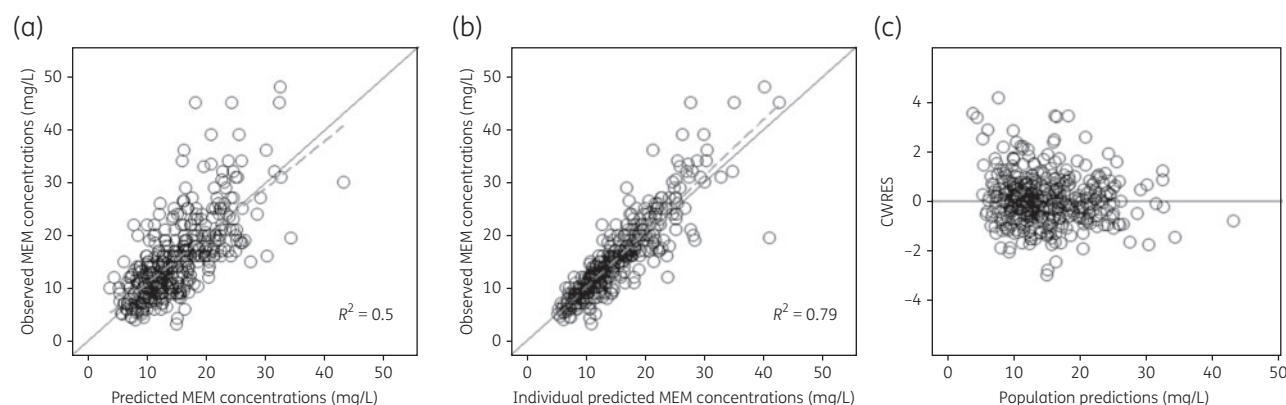


Figure 1. Goodness-of-fit plots for the final model: observed versus population predicted concentrations (a) and individual predicted concentrations (b) of meropenem (MEM) in plasma. (c) Conditional weighted residuals (CWRES) versus population predicted meropenem concentrations. Open circles represent MEM concentrations. The solid line represents the line of unity; the dashed line (a, b) depicts a linear regression line.

Discussion

The present study provided a nomogram for optimized continuous-infusion dosing of meropenem in a critically ill cohort based on a successfully validated population PK model. Of all routinely available SCr-based estimates of kidney function investigated, the Cockcroft–Gault equation was identified as best describing meropenem clearance and was therefore included in the nomogram.

Our results confirm previous PK studies of meropenem, which almost uniformly demonstrate a considerable impact of renal function on exposure; this can be anticipated for hydrophilic antibiotics such as carbapenems.^{16,34–41} Different markers of renal function have been related to meropenem clearance, including CL_{CR} measured by urine collections^{35,38,39,42} or estimation equations

such as CL_{CRCG} .^{16,34,36,37,43} However, to the best of our knowledge, no systematic comparison of various routinely available approximations of kidney function regarding their ability to predict meropenem clearance in ICU patients has yet been performed.

Similar to our findings, the superiority of the Cockcroft–Gault formula, even compared with equations containing newer biomarkers for renal function, has been described also in ICU patients treated with other β -lactams, e.g. cefepime.⁴⁴ In our work, CL_{CRCG_WT} accounted for more than half of the unexplained BSV associated with clearance, which is in agreement with a similar study.³⁷ The remaining variability might partly be due to disease-related factors potentially influencing meropenem clearance (e.g. disease severity) or to the non-renal contribution of meropenem elimination (e.g. metabolism to a microbiologically inactive compound or faecal elimination), which has been shown to exceed the renal pathway in individuals with renal impairment.^{36,45} Although significantly improving the meropenem model as well (ΔOFV 199.58), the MDRD equation was the marker least predictive of meropenem clearance, presumably also owing to its development based on patients with chronic renal dysfunction only, while our population spanned a wide range of renal functions which would predominantly be driven by acute pathology.

In our analysis, the good performance of the standard Cockcroft–Gault formula CL_{CRCG_WT} , which serves as the basis for dosing adaptations in the manufacturer's product label,²⁴ might be due to its weight component (total body weight), which is missing in all other investigated formulas. Predictability of meropenem clearance improved with anthropomorphic measures, i.e. formulas considering actual BSA (mL/min) performed better than their BSA-normalized versions (mL/min/1.73 m²). Similar to our work, a previous study by Pai et al.³⁷ in obese patients provided nomograms based on CL_{CRCG} rather than on BSA-normalized values of CL_{CRCG} .

The present patient cohort displayed meropenem clearance values in the range of those published previously for critically ill patients receiving continuous infusion [7.71 L/h (CL_{CRCG_WT} = 80 mL/min) versus 8.85 L/h (CL_{CRCG_WT} = 97 mL/min) in obese patients,³⁷ 9.2 L/h (CL_{CRCG_WT} = 80 mL/min) in surgical ICU

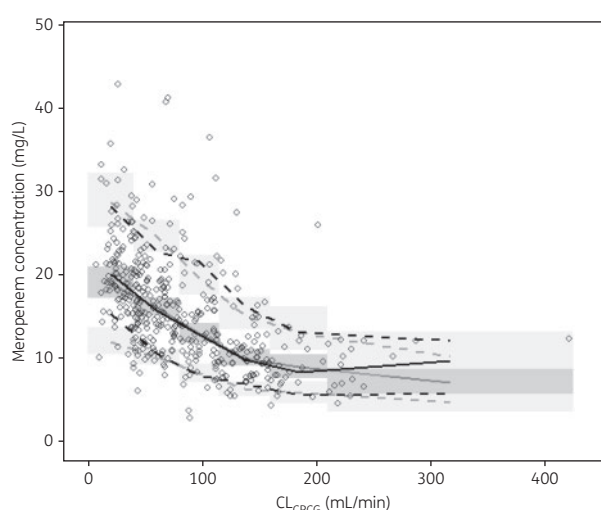


Figure 2. Visual predictive check (prediction corrected) for the observed meropenem concentrations (open circles). The grey solid line represents the median of the model predictions; the black line depicts the median of the observations. The dashed lines represent the 10th and 90th percentiles of the observed (black) and predicted (grey) data. The shaded areas represent the 90% CIs for the prediction lines.

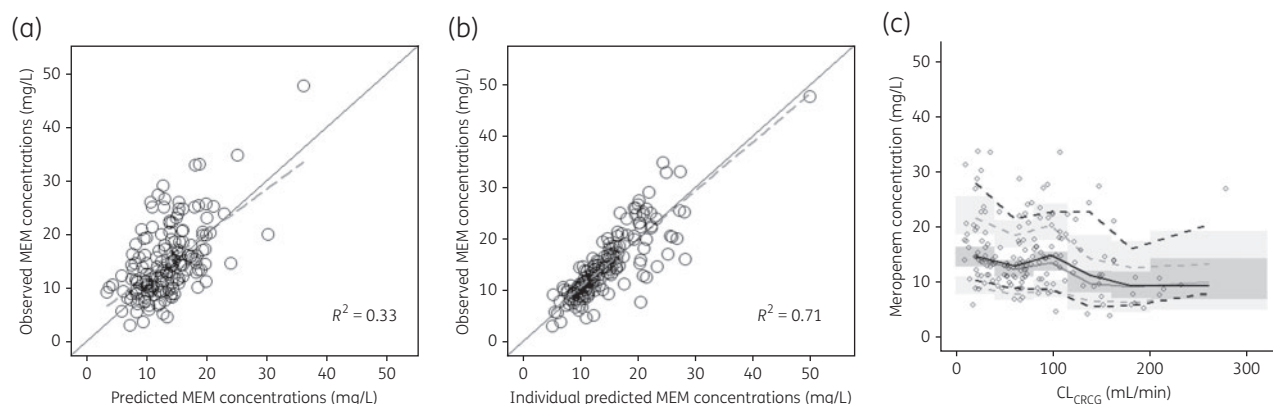


Figure 3. Diagnostic plots for the final model using the external validation dataset. Observed versus population predicted concentrations (a) and individual predicted concentrations (b) of meropenem (MEM) in plasma (open circles). (c) Visual predictive check (prediction corrected) for the observed meropenem concentrations (open circles). The grey solid line represents the median of the model predictions; the black line depicts the median of the observations. The dashed lines represent the 10th and 90th percentiles of the observed (black) and predicted (grey) data. The shaded areas represent the 90% CIs for the prediction lines.

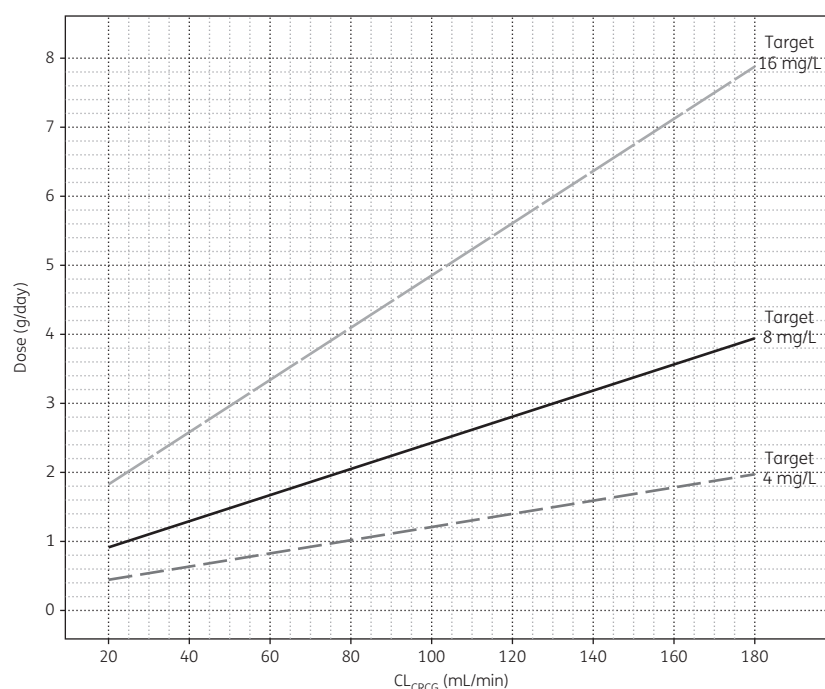


Figure 4. Nomogram depicting the daily doses of continuous-infusion meropenem required to achieve specific target steady-state concentrations (4, 8 and 16 mg/L) in 90% of the critically ill cohort given different creatinine clearance values (CL_{CRG_WT} , calculated according to Cockcroft and Gault). Relationships between daily dose (DD) and CL_{CRG_WT} for specific target steady-state concentrations (C_{SS}) were as follows: (a) target 4 mg/L: $DD_{CSS_4} = 0.00945 \cdot CL_{CRG_WT} + 0.267$; (b) target 8 mg/L: $DD_{CSS_8} = 0.0189 \cdot CL_{CRG_WT} + 0.534$; (c) target 16 mg/L: $DD_{CSS_16} = 0.0378 \cdot CL_{CRG_WT} + 1.07$; (d) general target $DD_{CSS_TARGET} = C_{SS_TARGET} \cdot (0.00236 \cdot CL_{CRG_WT} + 0.0665)$.

patients, 7.7 L/h (CL_{CR} 83.7 mL/min) in patients with pneumonia or sepsis⁴⁶ and 13.6 L/h (CL_{CR} = 100 mL/min) in septic patients].¹² The higher values of clearance reported in the literature might be partly due to better renal function or younger age in the studied population or determination based on a renal function marker other than CL_{CRG_WT} .^{12,38,47,48} As distinct markers of renal function differ in magnitude for the same population, deviating clearance values are obtained when estimated relative to the same reference kidney function, e.g. 80 mL/min (Table S2).

Apart from (patho)physiological aspects, drug degradation might influence the apparent plasma clearance of a drug; however, this scenario was deemed unlikely in the present investigation as indicated by previous evidence of meropenem stability at 25°C as well as by internal stability tests at 23°C (see Supplementary information).^{20,21,49}

The established nomogram showed the antibiotic doses required to achieve plasma concentrations of 4/8/16 mg/L, thus $4 \times MIC = 1/2/4$ mg/L and $>4 \times MIC \leq 0.5$ mg/L. The selected magnitudes originated from findings associating β -lactam concentrations $>4-6 \times MIC$ with higher microbiological and clinical response or suppression of resistance.^{47,50,51} If administered as continuous instead of intermittent infusions, standard daily doses of 3000 mg for patients with intact renal function (1000 mg q8h²⁴) would lead to meropenem $C_{SS} = 8$ mg/L in $\geq 90\%$ of patients with $CL_{CRG_WT} \leq 130$ mL/min.

In patients with augmented renal function, higher than licensed daily doses would be necessary to maintain $C_{SS} \geq 8$ mg/L; given a target of $C_{SS} = 16$ mg/L, higher than standard daily doses of 3000 mg were suggested by the nomogram even for a renal

function of $CL_{CRG_WT} > 50$ mL/min. According to the PTA analysis, higher than standard doses suggested by the nomogram for the target $C_{SS} = 8$ mg/L (4000 mg, for $CL_{CRG_WT} = 180$ mL/min) did not lead to meropenem concentrations higher than $C_{SS} = 32$ mg/L, putting patients unnecessarily at higher risk of adverse drug reactions, which is supported by a recent study that did not find a higher incidence of adverse events after administration of doses beyond those approved.⁵² Regarding concentration-toxicity relationships of meropenem, Imani *et al.*⁵³ recently reported that meropenem threshold concentrations of $C_{min} = 64.2$ mg/L and $C_{min} = 44.5$ mg/L in plasma were associated with a 50% increased risk of a neurotoxic or nephrotoxic event during intermittent dosing, respectively. A previous study in septic ICU patients suggested that the risk of neurotoxicity increases with higher meropenem concentrations; more precisely, a $C_{min}/MIC_{2mg/L}$ ratio of ≥ 8 mg/L during intermittent administration was associated with worsening neurological status in $\sim 65\%$ of the treated patients.³³ Thus, the upper threshold of $C_{SS} = 32$ mg/L (representing $4 \times$ the EUCAST PK/PD resistant breakpoint) investigated in the present work represents a concentration for which higher values will not result in increased efficacy but for which toxicity is more likely and so seems a reasonable limit.

There are a few limitations to our study we would like to acknowledge. Our analysis was retrospective and based on data gathered during routine clinical practice. The investigated population was heterogeneous and details on patient outcomes and actual MIC values were lacking; thus, the present work focused on the PK of meropenem and on the attainment of clinical MIC breakpoints as targets rather than clinical outcomes. As meropenem

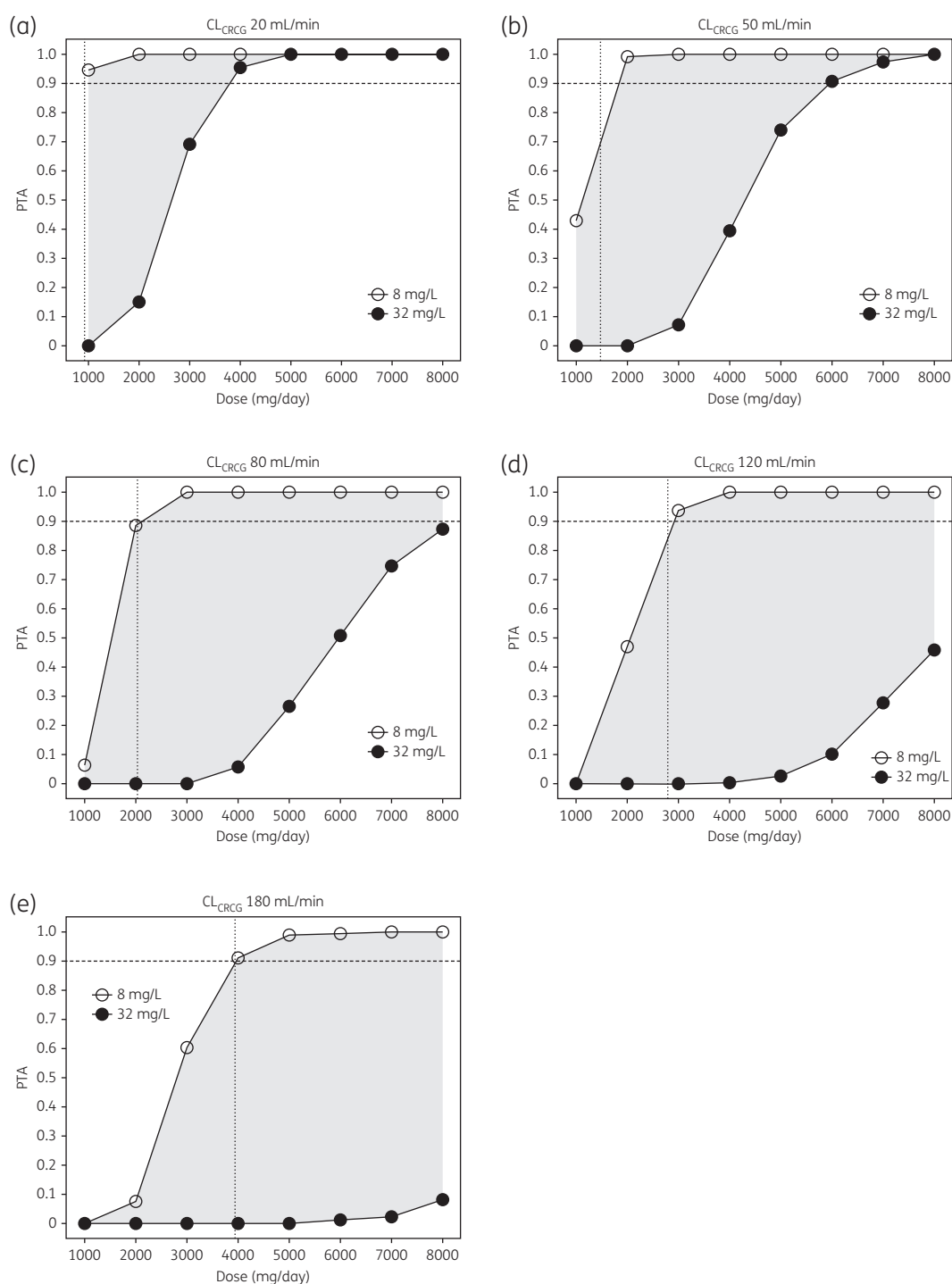


Figure 5. Probability of target attainment (PTA) for meropenem efficacy ($C_{SS} \geq 8$ mg/L, open circles) and potentially increased likelihood of adverse drug reactions ($C_{SS} > 32$ mg/L, filled circles) in patients with CL_{CRG_WT} of (a) 20 mL/min, (b) 50 mL/min, (c) 80 mL/min, (d) 120 mL/min and (e) 180 mL/min. Vertical dotted lines represent the daily doses as suggested by the nomogram to achieve $C_{SS} = 8$ mg/L in 90% of the patients.

samples had exclusively been taken during continuous infusion and at steady-state, no volume of distribution could be estimated. However, total meropenem clearance and its relationship with renal function constitute the basis for steady-state dose calculations and were well captured by our model.

Next, no gold standard marker of kidney function (e.g. measured CL_{CR}) was available for the present analysis, which allowed conclusions regarding the relevance of different SCr-based renal function markers only for predicting meropenem clearance. Although some previous studies attributed limited accuracy to

SCr-based surrogates of renal function in ICU patients, who did not represent the original target population of these formulas, or suggested measured CL_{CR} to predict meropenem clearance in a small cohort of critically ill patients,³⁶ urine collection is usually not practicable in routine clinical practice and SCr commonly still represents the sole cost-effective marker of renal function readily available to optimize meropenem dosing. The impact of unstable SCr values on the $CL-CL_{CR_{CG_WT}}$ relationship was found to be marginal in our study, which corresponds to previous findings.³⁷ Last, apart from successful external validation of the developed model, additional prospective validation of the nomogram should be performed in the future to further confirm its reliability and evaluate its efficiency in clinical practice. Caution is advised against extrapolation of the nomogram to any patients falling outside the characteristics of the studied cohort (e.g. with highly augmented renal function or undergoing dialysis). It should also be noted that the developed nomogram was based on steady-state data; prior to continuous infusion at therapy initiation, a loading dose is imperative to ensure rapid achievement of therapeutic exposure in critically ill patients.

The present work adds value in comparison with previously developed nomograms for continuous-infusion meropenem^{37,43} in that it was established based on a population PK model, which quantified the PK variability associated with meropenem elimination and distinguished between interpatient variability and residual, e.g. drug assay-related, variability; only the relevant interpatient variability was considered in the nomogram. Furthermore, the nomogram was built on the data of a large patient cohort spanning broad ranges of renal function and weight. Hence, owing to consideration of variability in the developed nomogram, the proposed daily doses, which were associated with 90% of the patients attaining the target concentrations, were naturally slightly higher compared with those by Pea *et al.*⁴³

Overall, nomograms should not preclude the use of TDM coupled with Bayesian forecasting, considering both clinical covariates and measured antibiotic serum concentrations for individual dose adjustments.^{54,55} However, according to a recent study, TDM for carbapenems has not been implemented in >90% of ICUs⁵⁶ and in these settings, nomograms could provide hints about patients at risk of not attaining effective antibiotic concentrations during continuous infusion of standard doses, e.g. challenging patients with unimpaired renal clearance or infected with less susceptible pathogens.

In conclusion, we successfully developed and externally validated a population PK model for continuous-infusion meropenem based on a large cohort of critically ill patients exhibiting a wide range of renal function. We identified standard Cockcroft–Gault CL_{CR} to be the most adequate predictor of meropenem clearance and generated a nomogram translating renal function into the daily maintenance doses needed to reliably attain target concentrations.

Acknowledgements

Parts of the present work have previously been presented as a poster (Abstract 4619, Poster EP0356) at the 27th European Congress of Clinical Microbiology and Infectious Diseases (22–25 April 2017).

Funding

This study was supported by internal funding. J. A. R. received funding from the Australian National Health and Medical Research Council for a Practitioner Fellowship (APP1048652) and a Centre of Research Excellence (APP1099452).

Transparency declarations

J. A. R. has consulted for or has received grant funding for investigator-initiated studies to his institution from bioMérieux, Infectopharm, MSD, Astellas, The Medicines Company, Bayer and Achaogen. C. K. reports research grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann–La Roche Ltd, Merck KGaA and SANOFI), the Innovative Medicines Initiative–Joint Undertaking ('DDMoRe'), Diurnal Ltd and the Federal Ministry of Education and Research within the Joint Programming Initiative on Antimicrobial Resistance Initiative (JPIAMR). All other authors: none to declare.

Supplementary data

Supplementary information, Tables S1 and S2 and Figures S1 and S2 appear as Supplementary data at JAC Online.

References

- Roberts JA, Paul SK, Akova M *et al.* DALI: defining antibiotic levels in intensive care unit patients: are current β -lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; **58**: 1072–83.
- Muller AE, Punt N, Mouton JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. *Antimicrob Agents Chemother* 2014; **58**: 2512–9.
- Rhodes A, Evans LE, Alhazzani W *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017; **43**: 304–77.
- Roberts JA, Abdul-Aziz MH, Lipman J *et al.* Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14**: 498–509.
- Bassetti M, De Waele JJ, Eggimann P *et al.* Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. *Intensive Care Med* 2015; **41**: 776–95.
- Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. *Ann Intern Med* 2001; **134**: 298–314.
- Cohen J. Confronting the threat of multidrug-resistant Gram-negative bacteria in critically ill patients. *J Antimicrob Chemother* 2013; **68**: 490–1.
- Roberts JA, Kwa A, Montakantikul P *et al.* Pharmacodynamic profiling of intravenous antibiotics against prevalent gram-negative organisms across the globe: the PASSPORT program—Asia-Pacific region. *Int J Antimicrob Agents* 2011; **37**: 225–9.
- Minichmayr IK, Schaefflein A, Kuti JL *et al.* Clinical determinants of target non-attainment of linezolid in plasma and interstitial space fluid: a pooled population pharmacokinetic analysis with focus on critically ill patients. *Clin Pharmacokinet* 2017; **56**: 617–33.
- De Waele JJ, Lipman J, Akova M *et al.* Risk factors for target non-attainment during empirical treatment with β -lactam antibiotics in critically ill patients. *Intensive Care Med* 2014; **40**: 1340–51.
- Roberts JA, Roberts MS, Robertson TA *et al.* Piperacillin penetration into tissue of critically ill patients with sepsis–bolus versus continuous administration? *Crit Care Med* 2009; **37**: 926–33.

- 12 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**: 142–50.
- 13 Abdul-Aziz MH, Sulaiman H, Mat-Nor MB et al. β -Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent β -lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med* 2016; **42**: 1535–45.
- 14 Dulhunty JM, Roberts JA, Davis JS et al. Continuous infusion of β -lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013; **56**: 236–44.
- 15 Lorente L, Jiménez A, Palmero S et al. Comparison of clinical cure rates in adults with ventilator-associated pneumonia treated with intravenous ceftazidime administered by continuous or intermittent infusion: a retrospective, nonrandomized, open-label, historical chart review. *Clin Ther* 2007; **29**: 2433–9.
- 16 Abdul-Aziz MH, Lipman J, Akova M et al. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the defining antibiotic levels in intensive care unit patients (DALI) cohort. *J Antimicrob Chemother* 2016; **71**: 196–207.
- 17 Roberts JA, Abdul-Aziz M-H, Davis JS et al. Continuous versus intermittent β -lactam infusion in severe sepsis: a meta-analysis of individual patient data from randomized trials. *Am J Respir Crit Care Med* 2016; **194**: 681–91.
- 18 Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis* 2008; **47**: S32–40.
- 19 Crandon JL, Luyt C, Aubry A et al. Pharmacodynamics of carbapenems for the treatment of *Pseudomonas aeruginosa* ventilator-associated pneumonia: associations with clinical outcome and recurrence. *J Antimicrob Chemother* 2016; **71**: 2534–7.
- 20 Franceschi L, Cojutti P, Baraldo M et al. Stability of generic meropenem solutions for administration by continuous infusion at normal and elevated temperatures. *Ther Drug Monit* 2014; **36**: 674–6.
- 21 Carlier M, Stove V, Verstraete AG et al. Stability of generic brands of meropenem reconstituted in isotonic saline. *Minerva Anesthesiol* 2015; **81**: 283–7.
- 22 Jaruratanasirikul S, Thengyai S, Wongpoowarak W et al. 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* 2015; **59**: 2995–3001.
- 23 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**: 263.
- 24 AstraZeneca. MERREM® IV (Meropenem for Injection, for Intravenous Use)—Prescribing Information. 2016. https://www.accessdata.fda.gov/drug_satfda_docs/label/2016/050706s037lbl.pdf.
- 25 Carlier M, Dumoulin A, Janssen A et al. Comparison of different equations to assess glomerular filtration in critically ill patients. *Intensive Care Med* 2015; **41**: 427–35.
- 26 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
- 27 Jelliffe RW. Creatinine clearance: bedside estimate. *Ann Intern Med* 1973; **79**: 604–5.
- 28 Levey AS, Coresh J, Greene T et al. Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766–72.
- 29 Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–12.
- 30 D'Avolio A, Baietto L, De Rosa FG et al. A simple and fast method for quantification of ertapenem using meropenem as internal standard in human plasma in a clinical setting. *Ther Drug Monit* 2008; **30**: 90–4.
- 31 The European Committee on Antimicrobial Susceptibility Testing. *Breakpoint Tables for Interpretation of MICs and Zone Diameters*. Version 7.0, 2017. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.0_Breakpoint_Tables.pdf.
- 32 Wong G, Brinkman A, Benefield RJ et al. An international, multicentre survey of β -lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother* 2014; **69**: 1416–23.
- 33 Beumier M, Casu GS, Hites M et al. Elevated β -lactam concentrations associated with neurological deterioration in ICU septic patients. *Minerva Anesthesiol* 2015; **81**: 497–506.
- 34 Li C, Kuti JL, Nightingale CH et al. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. *J Clin Pharmacol* 2006; **46**: 1171–8.
- 35 Goncalves-Pereira J, Silva NE, Mateus A et al. Assessment of pharmacokinetic changes of meropenem during therapy in septic critically ill patients. *BMC Pharmacol Toxicol* 2014; **15**: 21.
- 36 Kees MG, Minichmayr IK, Moritz S et al. Population pharmacokinetics of meropenem during continuous infusion in surgical ICU patients. *J Clin Pharmacol* 2016; **56**: 307–15.
- 37 Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: a step toward dose optimization for the treatment of severe gram-negative bacterial infections. *Clin Pharmacokinet* 2015; **54**: 933–41.
- 38 Tsai D, Stewart P, Goud R et al. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. *Int J Antimicrob Agents* 2016; **48**: 542–6.
- 39 Doh K, Woo H, Hur J et al. Population pharmacokinetics of meropenem in burn patients. *J Antimicrob Chemother* 2010; **65**: 2428–35.
- 40 Huttner A, Von Dach E, Renzoni A et al. Augmented renal clearance, low β -lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. *Int J Antimicrob Agents* 2015; **45**: 385–92.
- 41 Udy AA, Varghese JM, Altukroni M et al. Subtherapeutic initial β -lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest* 2012; **142**: 30–9.
- 42 Casu GS, Hites M, Jacobs F et al. Can changes in renal function predict variations in β -lactam concentrations in septic patients? *Int J Antimicrob Agents* 2013; **42**: 422–8.
- 43 Pea F, Viale P, Cojutti P et al. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. *Antimicrob Agents Chemother* 2012; **56**: 6343–8.
- 44 Jonckheere S, De Neve N, De Beenhouwer H et al. A model-based analysis of the predictive performance of different renal function markers for cefepime clearance in the ICU. *J Antimicrob Chemother* 2016; **71**: 2538–46.
- 45 Christensson BA, Nilsson-Ehle I, Hutchison M et al. Pharmacokinetics of meropenem in subjects with various degrees of renal impairment. *Antimicrob Agents Chemother* 1992; **36**: 1532.
- 46 Thalhammer F, Traunmüller F, El Menyawi I et al. Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* 1999; **43**: 523–7.
- 47 Li C, Du X, Kuti JL et al. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob Agents Chemother* 2007; **51**: 1725–30.
- 48 Crandon JL, Ariano RE, Zelenitsky SA et al. Optimization of meropenem dosage in the critically ill population based on renal function. *Intensive Care Med* 2011; **37**: 632–8.

- 49** Berthoin K, Le Duff CS, Marchand-Brynaert J *et al*. Stability of meropenem and doripenem solutions for administration by continuous infusion. *J Antimicrob Chemother* 2010; **65**: 1073–5.
- 50** Tam VH, McKinnon PS, Akins RL *et al*. Pharmacodynamics of cefepime in patients with gram-negative infections. *J Antimicrob Chemother* 2002; **50**: 425–8.
- 51** Tam VH, Schilling AN, Neshat S *et al*. Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2005; **49**: 4920–7.
- 52** McDonald C, Cotta MO, Little PJ *et al*. Is high-dose β -lactam therapy associated with excessive drug toxicity in critically ill patients? *Minerva Anestesiol* 2016; **82**: 957–65.
- 53** 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**: 2891–7.
- 54** Sime FB, Roberts MS, Roberts JA. Optimization of dosing regimens and dosing in special populations. *Clin Microbiol Infect* 2015; **21**: 886–93.
- 55** Wicha SG, Kees MG, Solms A *et al*. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. *Int J Antimicrob Agents* 2015; **45**: 442–4.
- 56** Tabah A, De Waele J, Lipman J *et al*. The ADMIN-ICU survey: a survey on antimicrobial dosing and monitoring in ICUs. *J Antimicrob Chemother* 2015; **70**: 2671–7.