A Model-Based Approach to Assess Unstable Creatinine Clearance in Critically Ill Patients

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Creatinine clearance is an important tool to describe the renal elimination of drugs in pharmacokinetic (PK) evaluations and clinical practice. In critically ill patients, unstable kidney function invalidates the steady-state assumption underlying equations, such as Cockcroft-Gault. Although measured creatinine clearance (mCrCL) is often used in nonsteady-state situations, it assumes that observed data are error-free, neglecting frequently occurring errors in urine collection. In contrast, compartmental nonlinear mixed effects models of creatinine allow to describe dynamic changes in kidney function while explicitly accounting for a residual error associated with observations. Based on 530 serum and 373 urine creatinine observations from 138 critically ill patients, a one-compartment creatinine model with zero-order creatinine generation rate (CGR) and first-order CrCL was evaluated. An autoregressive approach for interoccasion variability provided a distinct model improvement compared to a classical approach (Δ Akaike information criterion (AIC) −49.0). Fat-free mass, plasma urea concentration, age, and liver transplantation were significantly related to CrCL, whereas weight and sex were linked to CGR. The model-based CrCL estimates were superior to standard approaches to estimate CrCL (or glomerular filtration rate) including Cockcroft-Gault, mCrCL, four-variable modification of diet in renal disease (MDRD), six-variable MDRD, and chronic kidney disease epidemiology collaboration as a covariate to describe cefepime and meropenem PKs in terms of objective function value. In conclusion, a dynamic model of creatinine kinetics provides the means to estimate actual CrCL despite dynamic changes in kidney function, and it can easily be incorporated into population PK evaluations.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✓ Measured creatinine clearance (mCrCL) is considered a gold standard for the assessment of creatinine clearance/glomerular filtration rate in critically ill patients. However, urine collection is error-prone. Other approaches, such as Cockcroft-Gault, are commonly used in clinical settings, but are based on steady-state assumptions regarding creatinine formation and elimination and thus are less suitable in patients with unstable renal function.

WHAT QUESTION DID THIS STUDY ADDRESS?
✓ Is it feasible to appropriately assess unstable CrCL via a model-based approach?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
✓ This study provides a dynamic creatinine model, which can flexibly estimate CrCL in intensive care patients by allowing for dynamic changes in kidney function and accounting for measurement error.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
✓ The creatinine model developed in this study provides distinct advantages over commonly used equations and mCrCL. The use of the model is expected to provide more appropriate descriptions of kidney function and drug excretion in clinical trials and patient care.

The estimation of creatinine clearance (CrCL) and glomerular filtration rate (GFR) in critically ill patients is often complicated by an unstable and highly variable renal function. Commonly used equations are not suitable for this population since they are based on data from non-critically ill patients and assume steady-state creatinine concentrations.1–3 In addition, the creatinine generation rate (CGR) in critically ill patients might deviate from other populations.4 Measured CrCL (mCrCL)5 calculated using urinary excretion data is frequently regarded as a gold standard approach in unstable renal function. However, serum and urine

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Received March 15, 2021; accepted June 1, 2021. doi:10.1002/cpt.2341
measurements are subject to errors in bioanalytical quantification, blood sampling, and urine collection. Even in a controlled clinical trial setting, up to 50% of urine collections were erroneous. Further options are the Jelliffe, modified Jelliffe, Chiu, and kinetic GFR (kGFR) equations. However, despite their ability to handle nonsteady-state conditions, these equations depend on the formula-based estimation of CGR and allow neither to incorporate urine data nor to account for the residual error of measurements. A flexible extension of static approaches is compartmental nonlinear mixed-effects modeling. Compartmental models allow to incorporate all available data from a patient, including urine and serum data with arbitrary timings, to model time-dependent changes in kinetic parameters, and to describe the residual error associated with measurements. Furthermore, compartmental creatinine models naturally combine with population pharmacokinetics (PKs), allowing for an interplay of creatinine and drug data. In this study, a compartmental creatinine model in critically ill patients with unstable renal function was developed. Predictors of CrCL were evaluated, and the performance of the creatinine model was explored in a simulation study. Finally, the model-based approach was evaluated in the context of a population PK analysis of two renally excreted antibiotics.

METHODS

Study design and patients
This evaluation was based on data from a prospective observational study conducted at medical-surgical intensive care units (ICUs) in Germany (ClinicalTrials.gov number NCT01793012). The trial was carried out according to the principles of the Helsinki Declaration after approval by the Institutional Review Board of the Medical Faculty of the Ludwig-Maximilians-University (registration number 428–12). Written informed consent was obtained from all patients or legal representatives. Patients aged ≥ 18 years treated for severe infection and with an ICU stay of at least 4 days were included.

Clinical and laboratory parameters
Demographics (age, height, weight, and sex), laboratory tests (bilirubin, liver function tests, renal function tests, albumin, blood counts, sodium, potassium, glucose, and C-reactive protein), and clinical data (Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, extracorporeal membrane oxygenation (ECMO) use, type of sepsis, Acute Respiratory Distress Syndrome (ARDS), and liver and lung transplantation status (LiTX/LuTX)) were recorded. For the assessment of renal function, serum creatinine (Scr) as well as creatinine concentrations in urine (NPC; creatinine data) or visual predictive check (VPC; drug data). For the assessment of renal function in critically ill patients, with unstable renal function was developed. Predictors of CrCL were evaluated, and the performance of the creatinine model was explored in a simulation study. Finally, the model-based approach was evaluated in the context of a population PK analysis of two renally excreted antibiotics.

Computed tomography
Abdominal computed tomography (CT) scans measuring lean muscle mass area (LMA), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were obtained as part of routine clinical practice in 43 patients.

Pharmacokinetic data
Patients received one of five antibiotics (cefepime, meropenem, piperacillin/tazobactam, linezolid, and ciprofloxacin) for the treatment of a confirmed or suspected infection according to local guidelines. Serum samples were obtained at regular intervals (median, 29 per patient per drug), and concentrations were determined by liquid chromatography-tandem mass spectrometry.

Creatinine model
A nonlinear mixed-effects model of creatinine was developed using NONMEM 7.4.3. First-order conditional estimation with interaction (FOCE-I) was used. Missing covariate values were imputed by the median of available values of the relevant subject. Models were assessed based on the objective function value (OFV), goodness of fit (GOF) plots, individual plots, confidence intervals of parameter estimates from a non-parametric bootstrap (n = 1000), and numerical predictive check (NPC; creatinine data) or visual predictive check (VPC; drug data).

One-compartment creatinine model was assumed. The structural model was parameterized in terms of zero-order CrGR, first-order CrCL, and volume of distribution (V). The V was fixed to 60% of the total body weight, reflecting the total body water. Interindividual variability (IV) was modeled assuming log-normal distributions of CrGR and CrCL and proportional, additive, and combined error models were tested.

Implementation of interoccasion variability
Interoccasion variability (IOV) was evaluated using two approaches. As the classical approach, random effects corresponding to different occasions were assumed to be independent and identically (log)distributed (i.i.d). Alternatively, random effects corresponding to different occasions were allowed to be correlated via auto-regression. The classical approach can be considered a specific case of the auto-regressive model with auto-correlation parameter (AR) = 0. With the auto-regressive IOV approach, the random effect ηivt at the current occasion t comprised a fraction (AR) of the random effect associated with the previous occasion (ηivt-1) plus an additional, i.i.d random term (ηivt) (Eq. 1). Each day was defined as a new occasion for creatinine and PK data. Steady-state of CrCL was assumed at baseline.

\[ ηivt = AR \times ηivt-1 + ηivt \]  

Simulation-based study of the IOV model
To evaluate the impact of the IOV model on empirical Bayes estimates (EBEs), creatinine serum and urine data was simulated in 5000 virtual subjects over a period of 4 days based on the creatinine model. For each subject, CrGR and baseline CrCL were randomly sampled from a multivariate log-normal distribution. A single event with a reduction in CrCL was simulated, with a randomly sampled onset (T on) and relative extent of reduction (fLO) to 50% of baseline, e.g., from 4 L/h to 0–2 L/h; uniform distributions). The functional form (F1) of reduction (stepwise, linear, or exponential) was randomly chosen for each subject (Figure 1). For a linear / exponential reduction, the slope / rate constant was chosen such that fLO was attained after 4 days. EBEs were calculated using different IOV models and compared with simulated and therefore known CrCL and CrG values in terms of root mean squared error (RMSE) and bias. Finally, mCrCL was compared with model-based estimates.

Covariate analysis
Covariates for the creatinine model were preselected based on physiological plausibility. Age, body weight, and sex were evaluated as part of typical CrCL and GFR equations. Fat-free mass (FFM) was introduced because CrGR depends on muscle mass. Albumin levels represent nutritional status and liver function, which might be linked to CrGR and kidney function. Urea concentrations depend on kidney function. The SOFA score (after subtracting the score associated with Scr) was evaluated because it provides a measure of organ failure, which might be linked to CrGR and kidney function. Renal failure is a frequent
complication of lung and liver transplantation.\textsuperscript{23,24} Finally, a correlation of serum potassium and creatinine concentrations has been reported.\textsuperscript{25}

Initially, covariates known to be related to kidney function (weight, age, and sex) were incorporated into the base model. FFM was evaluated as an alternative to weight and sex. The best model including weight, age, sex, and/or FFM was chosen based on predictive OFV (OFVp). Then, the covariates albumin, urea, SOFA score, and lung and liver transplantation, were evaluated in a univariate fashion based on the best model identified in the previous step. Covariates providing a decrease in OFVp were kept in the full covariate model. Finally, covariates were removed one by one from the full model if removal was not linked to an increase in OFVp (backward elimination). All continuous covariates were centered to the respective median and parameterized in terms of a linear (Eq. 2) and power (Eq. 3) relationships. Categorical covariates were evaluated as linear relationship. Allometric scaling was also evaluated for the parameters related to body size (weight and FFM). The OFVp was obtained from cross-validation to assess the predictive performance. Thus, patients were randomly divided into two equally sized groups (G1 and G2), parameter estimation was carried out based on data from G1/G2, and the OFVp was obtained by calculating OFVs for the resulting model given data from G2/G1, respectively. Relationships between CT-based estimates of body composition (LMA, SAT, and VAT) and CGR were evaluated separately in an explorative manner because CT data were only available in a limited number of subjects.

\[
P = \theta_1 \times \left[ 1 + \theta_2 \times \left( \frac{\text{covariate} - \text{covariate}_{\text{median}}}{\text{covariate}_{\text{median}}} \right) \right] 
\]

\[
P = \theta_1 \times \left( \frac{\text{covariate}_{\text{median}}}{\text{covariate}_{\text{median}}} \right)^{\theta_2} 
\]

where \(\theta_1\) and \(\theta_2\) are typical value of the parameter (P) in an individual with median covariate and magnitude of covariate effect, respectively.

**Application of the creatinine model to pharmacokinetic data**

Among the studied antibiotics, cefepime, meropenem, and piperacillin/tazobactam are mainly eliminated by the kidneys. Piperacillin and tazobactam may relevantly interact with each other,\textsuperscript{26} therefore, PK data of cefepime and meropenem were selected for this evaluation. Two-compartment drug models were selected based on previous literature\textsuperscript{27,28} and parameters related to cefepime and meropenem kinetics were estimated. Elimination clearances of cefepime and meropenem were split into two fractions; clearance linked to renal function \(\text{CL}_{\text{LR}}\) and clearance not linked to renal function \(\text{CL}_{\text{NLR}}\), where \(\text{CL}_{\text{LR}}\) was considered to be related to CrCL and/or GFR (see below). \(\text{CL}_{\text{NLR}}\) does not strictly represent nonrenal clearance: because an estimate of kidney function might also be correlated with nonrenal clearance.

PK parameters were allometrically scaled.\textsuperscript{29} IIV was evaluated on all PK parameters, whereas IOV was only evaluated on elimination clearance and central volume of distribution using both classical and auto-regressive approaches.

**CrCL / GFR estimated as covariates for renal elimination of antibacterials**

The CrCL estimated by the creatinine model was compared to the CrCL / GFR estimated by the common equations, such as Cockcroft-Gault, mCrCL, four-variable modification of diet in renal disease (MDRD\textsuperscript{4}),\textsuperscript{21} six-variable MDRD (MDRD\textsuperscript{6})\textsuperscript{30} and chronic kidney disease epidemiology collaboration (CKD-EPI)\textsuperscript{31} using two approaches.

Using EBEs of CrCL from creatinine models. The model-based EBEs of CrCL from the creatinine model and estimated CrCL / GFR from common equations were introduced as clearance covariates in PK models of meropenem and cefepime using Eq. 4.\textsuperscript{32} OFVs and changes in random effects variance estimates were compared.

\[
\text{CL} = \text{CL}_{\text{NLR}} + \text{CL}_{\text{LR}} \times \text{RF} 
\]

where CL is the total clearance of a drug, \(\text{CL}_{\text{NLR}}\) is the clearance not linked to renal function (RF), \(\text{CL}_{\text{LR}}\) is the clearance linked to RF. RF was estimated by Eq. 5:

\[
\text{RF} = \frac{\text{CrCL (or GFR)}}{\text{CrCL (or GFR)}_{\text{STD}}} 
\]

CrCL (or GFR) is the creatinine clearance (or glomerular filtration rate) estimated by the model, Cockcroft-Gault, mCrCL, MDRD\textsuperscript{4}, MDRD\textsuperscript{6}, or CKD-EPI equation, respectively. CrCL (or GFR)\textsuperscript{STD} is the standard CrCL (or GFR) fixed to 5 L/h in this study.

**Simultaneous evaluation of creatinine and pharmacokinetic data.** Here, parameters related to creatinine, cefepime, and meropenem kinetics were estimated simultaneously to explore the use of PK data of the antibacterials to further inform parameter estimation of the creatinine model. The link between creatinine and the drug models is described by Eq. 4 and the creatinine model was compared to the common equations. Analytical solutions of differential equations corresponding to the one-compartment model were used in combination with PK data to decrease computation times.
RESULTS

Patients

One hundred eighty-six patients participated in the clinical study, of which 48 patients on dialysis were excluded from this evaluation. Median (range) of weight, age, baseline SCr concentration, and urinary creatinine excretion were 71 (44–140) kg, 58 (23–94) years, 1.0 (0.30–4.7) mg/dL, and 0.93 (0.065–3.25) g/24 h, respectively (Table 1). A total of 530 serum and 373 urine creatinine measurements were available. Covariate data was missing in 4% (serum potassium), 5% (urea), 6% (albumin), and 18% (mCrCL). CT data to assess adipose tissue distribution was available for 43 patients. Eight patients received cefepime (median dose, 2 g), whereas 41 patients received meropenem (median dose, 1 g) infusions over 30 minutes.

Base and IOV model of creatinine

A one-compartment model with zero-order creatinine generation and first-order elimination with proportional residual error described serum and urine measurements well. The auto-regressive IOV model performed distinctly better than the classical IOV model when applied to the measured data (AIC −1267.7 vs. −1237.8). This was confirmed by the simulation study, in which the auto-regressive model performed better than the classical IOV model in terms of RMSE of CrCL (14.8 vs. 16.7). Similarly, the compartmental creatinine model with either auto-regressive or classical IOV performed distinctively better than mCrCL (RMSE 28.7; Table S1).

Covariate analysis

In the first step, age (power relationship), weight (power), and sex were significant covariates on CGR, whereas age (linear) and FFM (power) were significant covariates on CrCL and were included in the base model. Plasma urea and LiTX further improved the prediction of CrCL. Addition of further covariates to CGR did not improve the prediction. In the backward elimination step, removal of age from CGR and fixing the exponent of FFm on CrCL to 0.75 further improved the predictive performance of the model (Table S2). In the separate analysis of CT data, none of the covariates (LMA, SAT, and VAT) provided a significant benefit over weight or FFm (Table S3). Parameter estimates of the creatinine model, including bootstrap results are presented in Table 2.

GOF plots of SCr (Figure 2, upper) and urine creatinine (Figure 2, lower) indicated a good model fit. NPCs indicated that SCr concentrations were described well by the model (Figure 3, left), with a slight underprediction for lower urine creatinine amounts excreted (Figure 3, right).

Application to PK data

Two compartments each described 204 cefepime and 1197 meropenem concentrations adequately (Figure S1, Figure S2). A proportional/combined error model provided the best fit for cefepime/meropenem. CLINLR of cefepime was not significantly different from zero. Therefore, it was fixed to zero which did not lead to increase in OFV. The AR approach also performed better than the classical approach to incorporate IOV for PK data (AIC 5825.1 vs. 5830.0).

CrCL / GFR estimated as covariates for renal elimination of antibacterials

EBEs of CrCL from creatinine model. The model in which the EBEs of CrCL from creatinine model were linked as a covariate to cefepime and meropenem clearances performed better than models with Cockcroft-Gault, mCrCL, MDRD4, MDRD6, and CKD-EPI covariates on clearances (OFV of 5761.1 vs. 5811.1, 5842.6, 5819.3, 5809.2, 5817.7, and 5821.4, respectively; Table 3). However, the explained random variability (IIV and IOV) was similar among models.

GOF plots of cefepime (Figure S1, upper) and meropenem (Figure S1, lower) indicated a good model fit. VPCs indicated that drug concentrations were described well by the model (Figure S2). Please refer to Table 3 for bootstrap results of all the PK models.

Simultaneous evaluation of creatinine and pharmacokinetic data.

The joint model in which the creatinine model was directly linked to cefepime and meropenem clearances also performed better than models with the Cockcroft-Gault, mCrCL, MDRD4, MDRD6, and CKD-EPI equation estimates as clearance covariates (AIC of 4551.4 vs. 4613.3, 4646.9, 4612.4, 4662.7; Table S1).
In this study, a compartmental creatinine model that allows for an unstable renal function in population PK evaluations has been developed and evaluated. The novel model-based approach explained the variability of elimination clearance of two renally excreted drugs distinctly better than models based on the commonly used equations to predict CrCL and/or GFR.

In the covariate evaluation, CrCL was linearly related to age, which corresponds to previous observations. As expected based on physiological considerations, FFM was significantly related to CrCL. Urea plasma concentrations explained a relevant fraction of random variability of CrCL. Because serum urea and SCr both are elevated in circumstances where renal clearance decreases (i.e., acute and chronic renal impairment), considering urea in the creatinine model seems plausible. Blood urea nitrogen is also part of the 6-variable MDRD equation. A decline in CrCL in liver transplant recipients also seems reasonable as these patients are generally at higher risk of renal function impairment after transplantation. Similarly, CGR was significantly related to weight and sex of the patients. CGR is clearly weight-related and the different body composition between sexes makes this result plausible. Finally, the removal of the age effect on CGR during the backward elimination step might be a result of muscle mass / body weight explaining the variability in creatinine generation rates sufficiently well.

A surprising result was the lack of benefit of CT-based data on body composition in estimating CGR, which has previously been shown to be superior compared to demographic variables. One reason for this finding might be that CT measurements represented the pelvic body composition, which might be only weakly correlated with the whole-body composition. Furthermore, pathological-physiological conditions in critically ill patients may have a pronounced impact on creatinine kinetics, which might be uncoupled from LMA, SAT, and VAT. Finally, CT measurements were only available for a small number of patients. A general limitation of covariate evaluations regarding creatinine kinetics is the limited capability to distinguish between covariate effects related to CGR and CrCL. At steady-state, covariate effects related to CGR and CrCL are indistinguishable, and information might still be insufficient to separate covariate effects in presence of a nonsteady-state situation. Therefore, the use of PK data to inform the creatinine model appears to be helpful because it provides additional information about CrCL while being independent of creatinine generation.

Auto-regressive approaches have been previously implemented in PK evaluations and their use has been advocated in modeling PK data. However, applying auto-regression to IOV is a rather novel approach. The classical assumption of statistical independence of IOV for PK parameters on subsequent occasions is not plausible from a physiological perspective because parameters on subsequent treatment days are likely to be correlated. For example, CrCL might gradually increase or decrease, resulting in a systematic trend over time, and therefore in correlated IOV estimates. To describe such phenomena, more sophisticated auto-regressive structures might be beneficial. For example, one might describe the extent, pattern, and time of change of a PK parameter via random effects, allowing to circumvent arbitrary occasion definitions. However, we decided to implement a simplified auto-regressive approach because it does not require dense creatinine data and therefore seems to provide a reasonable trade-off.

When adjusting dosing regimens based on kidney function, the application of the renal function index that best describes PK data

Table 2 Parameter estimates of the creatinine model obtained from bootstrap statistics (n = 1000)

| Parameter | Median (95% CI) |
|-----------|----------------|
| CrCL (L/h) = θ1 × \left(\frac{\text{weight}}{100}\right)^{0.75} × \frac{\text{FFM}}{\text{weight}} × \frac{\text{LITX}}{55 \times \text{SEX}} | 2.64 (2.32–3.96) |
| θ2 | −0.16 (−0.27 to −0.06) |
| θ3 | −0.25 (−0.38 to −0.10) |
| CGR (mg/h) = θ4 × \left(\frac{\text{weight}}{100}\right)^{0.75} × (1 + θ6 × \text{SEX}) | 43.83 (39.7–48.1) |
| θ4 | 41.53 (34.7–47) |
| θ6 | −0.30 (−0.37 to −0.22) |
| Vd(L) = 0.6 × total body weight (fixed) | 1.00 (1.00–1.00) |
| θ1 | 60 (48–73) |
| θ5 | 41 (34–47) |
| Correlation θ1, θ2, θ3, θ4, θ5, θ6 | 75 (64–83) |
| IOV CrCL (CV%) | 15 (12–19) |
| Proportional error SCr (SD) | 0.08 (0.07–0.10) |
| Proportional error UCr (SD) | 0.29 (0.26–0.33) |
| AR creatinine | 1.00 (1.00–1.00) |
| IV CrCL (CV%) | 60 (48–73) |
| IV CGR (CV%) | 41 (34–47) |
| Correlation IV CrCL and CGR (%) | 75 (64–83) |
| IOV CrCL (CV%) | 15 (12–19) |
| Proportional error SCr (SD) | 0.08 (0.07–0.10) |
| Proportional error UCr (SD) | 0.29 (0.26–0.33) |

AR, auto-correlation parameter; CI, confidence interval; CrCL, creatinine clearance; CGR, creatinine generation rate; CV%, coefficient of variation and was calculated as √(CV × 100); FFM, fat-free mass; IV, interindividual variability; IOV, interoccasion variability; LITX, liver transplant status; SCr, serum creatinine; UCr, urine creatinine; Vd, volume of distribution of creatinine. CV is where ω is IV or IOV. Sex was coded as 1 for women and 0 for men in the dataset. LITX was coded as 0 for non-transplant patients and 1 for patients who had undergone liver transplantation.

The creatinine model and MDRD6 explained the highest fraction of IV on cefepime clearance.

Computation times were excessive (5–6 days) when combining compartmental drug models with the creatinine model using different equations. Combining analytical solutions for the two-compartment drug models (ADVAN 3) with manually coded analytical solutions for creatinine kinetics reduced runtimes drastically (20–60 minutes). A portion of the dataset (Table S5) and model code are provided in the supplement.

R Shiny application for estimation of CrCL

Based on the creatinine model, an R shiny application was developed for the estimation of CrCL in critically ill patients. For this application, the R packages mvtnorm, shinydashboard, DT, ggplot2, and gridExtra were used. Based on entered patient data and given the creatinine model, EBEs of CrCL are provided by the app (Figure S3, https://taubertm.shinyapps.io/ICU_CrCL/).

DISCUSSION

In this study, a compartmental creatinine model that allows for an improved description of unstable renal function in population PK evaluations has been developed and evaluated. The novel model-based approach explained the variability of elimination clearance...
Figure 2. Combined goodness of fit plot of serum creatinine (left) and urine creatinine (right) concentrations. CWRES, conditionally weighted residuals. [Colour figure can be viewed at wileyonlinelibrary.com]
has been suggested.\textsuperscript{40} This index does not necessarily coincide with the best estimator of actual renal function, because it might also reflect nonrenal processes. Cockcroft-Gault is the most widely used method for this purpose and has shown to provide a superior or equivalent predictive performance as compared to MDRD, modified MDRD, Jelliffe, and CKD-EPI equations.\textsuperscript{40,41} However, if an equation, such as Cockcroft-Gault, is intentionally applied to reflect both renal and nonrenal processes, considering the components of the Cockcroft-Gault equations separately (weight, sex, SCr concentrations, and age) might provide a better and easier way to interpret description of the PKs of a drug.\textsuperscript{42} In this sense, the presented creatinine model seems preferable because it allows to distinguish between renal function-related and other covariates while providing the best description of PK data among the evaluated approaches. The potential usefulness of a model-based approach is highlighted by the population PK evaluation of cefepime. For cefepime, clearance variability is a major concern due to an association between overexposure and potentially severe neurotoxicity. Jonckheere et al.\textsuperscript{27} evaluated the usefulness of a number of kidney function predictors to identify the best dose of cefepime in critically ill patients. Cockcroft-Gault performed similarly compared with mCrCL, although the latter was principally expected to provide a better estimate of CrCL. This finding might be a consequence of relationships between cefepime PKs and single components of the Cockcroft-Gault equation (age, weight, and sex) rather than kidney function itself. Similar observations were made with ciprofloxacin\textsuperscript{42} and meropenem\textsuperscript{38} where Cockcroft-Gault was found to be related to clearance, whereas no significant relationship between clearance and SCr or mCrCL could be identified. In a classical covariate evaluation, distinguishing between effects related to kidney function and demographics included in the Cockcroft-Gault equation is not feasible. Thus, a covariate evaluation is likely to result in the rejection of mCrCL, although it contains valuable information on urinary excretion of creatinine. Furthermore, Cockcroft-Gault overestimates CGR in critically ill patients,\textsuperscript{43} resulting in flawed and difficult to interpret models. In contrast, compartmental creatinine models enable to independently evaluate covariate effects on parameters of the creatinine model and on those of the drug model. Finally, by associating serum and urine creatinine measurements with a residual error, the model can weigh the impact of a certain observation type. For example, error-prone urine measurements have less impact on clearance estimates if the associated residual error is larger than for SCr. Indeed, the model confirmed the uncertainty associated with urine measurements via a pronounced residual error variance. Other options include approaches such as the kGFR equation, which has provided heterogeneous results when applied to drug dosing.\textsuperscript{44–46} Potential limitations of kGFR include the use of baseline clearance and maximum change in SCr, which are subjective and might not be suitable in a clinical trial setting, and the inability to consider urine data. Again, a model-based approach seems preferable.

Finally, in a joint model, creatinine data might not only improve the PK model of a drug, but the PK data of a renally excreted drug also provides valuable information that can be used to estimate kidney function parameters via a creatinine model. This particularly includes information that might be beneficial to distinguish between CGR and CrCL. If the primary aim of CrCL estimation is to assess the severity or progress of a kidney disease, drug data might be incorporated to obtain more precise estimates. However, the administration of a substance, such as iohexol, might be preferable if the main aim is to quantify kidney function. Furthermore, the use of drug data to inform CrCL estimation might also have adverse effects. For the joint model, certain assumptions must be made on the functional relationship between drug clearance and CrCL. In our evaluation, elimination clearances of drugs were split into Cl\textsubscript{LR} and a Cl\textsubscript{NLR}, where Cl\textsubscript{LR} was considered to be related to CrCL and/or GFR. This parametrization reflects physiological conditions appropriately, and the parameters of the creatinine model changed only very slightly after inclusion of drug data (Table 2, S3).

Several limitations of this study apply. One- and two-compartment models of creatinine have been previously described in the literature.\textsuperscript{47–49} Whereas two-compartment models require a more extensive collection of serum and urine samples compared to one-compartment models to allow for parameter estimation, the difference between the two is expected to be negligible in terms of clinical decision making.\textsuperscript{48,49} The volume of distribution of creatinine was fixed to 60% of the total body weight. Obviously, this is only a rough approximation and neglected variability in volume of distribution might result in biased estimates of other kinetic parameters. However, estimating the volume of distribution demands for more extensive serum and urine sampling. Lack of a gold standard measure of renal function for comparison (e.g.,

![Figure 3](https://example.com/figure3.png)

**Figure 3** Numerical predictive checks of serum creatinine concentrations (left) and urine creatinine amounts (right). The solid line and the grey area represent the median and 95% interval of simulated data, respectively. The dashed line (overlapping with the solid line in the left plot) represents the empirical distribution of serum concentrations. [Colour figure can be viewed at wileyonlinelibrary.com]
Table 3 Parameter estimates of the PK models using EBEs for CrCL estimated by the creatinine model and common methods to assess CrCL and/or GFR equations as covariates to describe renal function

| Parameter                     | Creatinine model | Cockcroft-Gault | mCrCL | MDRD4 | MDRD6 | CKD-EPI |
|-------------------------------|------------------|-----------------|-------|-------|-------|---------|
| Δ OFV                         | −102.1           | −52.1           | −20.6 | −43.9 | −53.6 | −45.5   |

Cefepime PK model

| Parameter | Creatinine model | Cockcroft-Gault | mCrCL | MDRD4 | MDRD6 | CKD-EPI |
|-----------|------------------|-----------------|-------|-------|-------|---------|
| CL (L/h)  | = CL_{NLR} + 0.5 \times RF |                |       |       |       |         |
| CL_{NLR} (L/h) | 0 FIX | 0 FIX | 3.64 (1.58–5.84) | 0 FIX | 0 FIX | 0 FIX |
| θ5       | 4.99 (4.08–6.34) | 4.29 (3.32–5.40) | 0.13 (−0.37–1.52) | 3.91 (3.28–4.86) | 4.93 (4.10–5.98) | 4.48 (3.70–5.44) |
| V1 (L)   | 11.5 (5.95–13.0) | 11.6 (6.11–12.9) | 11.5 (5.98–12.9) | 11.5 (5.79–12.6) | 11.6 (5.75–12.8) | 11.1 (5.78–12.8) |
| Q (L/h)  | 11.3 (8.25–51.8) | 10.3 (7.73–51.3) | 11.1 (8.12–51.4) | 11.0 (7.82–52.2) | 10.3 (7.37–52.3) | 11.4 (8.38–51.0) |
| V2 (L)   | 13.7 (11.7–21.6) | 13.1 (11.2–21.6) | 13.2 (11.4–20.8) | 12.6 (11.1–21.9) | 13.2 (11.1–22.0) | 12.8 (11.2–22.5) |
| IV CL (CV%) | 21 (0.33–34) | 25 (5.0–44) | 71 (18–91) | 18 (0.33–28) | 0 FIX | 18 (0.28–31) |
| IOV CL (CV%) | 21 (8.8–33) | 26 (11–39) | 25 (9.4–41) | 24 (12–37) | 25 (11–36) | 22 (9.0–35) |
| Proportional error (SD) | 0.32 (0.25–0.37) | 0.33 (0.25–0.37) | 0.33 (0.25–0.37) | 0.33 (0.25–0.37) | 0.32 (0.23–0.37) | 0.33 (0.26–0.38) |

Meropenem PK model

| Parameter | Creatinine model | Cockcroft-Gault | mCrCL | MDRD4 | MDRD6 | CKD-EPI |
|-----------|------------------|-----------------|-------|-------|-------|---------|
| CL (L/h)  | = CL_{NLR} + 0.6 \times RF |                |       |       |       |         |
| CL_{NLR} (L/h) | 2.25 (1.43–3.53) | 4.83 (3.01–6.95) | 6.33 (3.84–8.23) | 6.45 (4.09–8.26) | 5.87 (3.92–8.02) | 6.30 (4.05–8.39) |
| θ6       | 8.07 (6.45–9.79) | 4.32 (2.28–6.60) | 2.77 (1.30–5.48) | 2.69 (1.13–5.02) | 3.93 (1.61–6.39) | 2.81 (1.04–5.22) |
| V1 (L)   | 8.58 (6.97–11.5) | 8.61 (6.98–11.9) | 8.71 (7.10–11.7) | 8.42 (6.87–11.8) | 8.55 (7.14–11.8) | 8.47 (6.92–11.8) |
| Q (L/h)  | 25.9 (11.1–33.8) | 25.6 (11.1–34.0) | 26.4 (11.3–33.4) | 26.3 (10.9–34.3) | 26.1 (10.8–33.1) | 26.7 (11.1–33.8) |
| V2 (L)   | 15.1 (11.6–17.7) | 15.1 (11.6–17.5) | 15.3 (11.6–17.7) | 15.3 (11.5–17.8) | 15.2 (11.4–17.6) | 15.4 (11.5–17.7) |
| IV CL (CV%) | 26 (12–40) | 32 (22–42) | 24 (11–34) | 33 (23–42) | 31 (20–42) | 33 (23–42) |
| IOV CL (CV%) | 29 (18–39) | 38 (16–39) | 28 (16–39) | 28 (16–39) | 28 (16–39) | 28 (16–39) |
| Correlation IV CL and V1 (%) | 77 (42–98) | 64 (18–95) | 51 (−13–91) | 52 (7.7–89) | 57 (11–94) | 50 (5.8–90) |
| IV V2 (CV%) | 29 (18–39) | 30 (22–39) | 29 (21–37) | 29 (22–37) | 29 (22–37) | 29 (22–37) |
| IOV CL (CV%) | 14 (11–17) | 16 (12–20) | 16 (13–20) | 16 (12–20) | 16 (12–20) | 16 (12–20) |
| IOV V1 (CV%) | 15 (7.2–25) | 16 (6.7–24) | 16 (5.6–25) | 16 (7.5–24) | 16 (6.4–25) | 16 (6.4–25) |
| Proportional error (SD) | 0.17 (0.15–0.20) | 0.17 (0.14–0.20) | 0.18 (0.15–0.20) | 0.18 (0.15–0.20) | 0.17 (0.15–0.20) | 0.18 (0.15–0.20) |
| Additive error (SD) | 0.27 (0.12–0.40) | 0.27 (0.03–0.39) | 0.25 (0.03–0.37) | 0.28 (0.04–0.41) | 0.28 (0.04–0.41) | 0.27 (0.03–0.40) |
| AR drugs | 0.82 (0.41–0.97) | 0.79 (0.38–0.96) | 0.82 (0.52–1.00) | 0.80 (0.42–0.99) | 0.80 (0.45–0.98) | 0.83 (0.37–1.00) |

Values are given as median (95% confidence interval) obtained from bootstrap analysis (n = 1000).

CKD-EPI, chronic kidney disease epidemiology collaboration; CL, clearance; CL_{NLR}, clearance of the drug not related to renal function; CrCL, creatinine clearance; CV%, coefficient of variation; EBE, empirical Bayes estimate; FFM, fat-free mass; GFR, glomerular filtration rate; IV, interindividual variability; IOV, interoccasion variability; mCrCL, measured creatinine clearance; MDRD, modification of diet in renal disease; Δ OFV, change in objective function values as compared to the base model; PK, pharmacokinetic; RF, renal function; V_d, is the volume of distribution of creatinine.

RF is calculated by CrCL or GFR/CrCL or GFR_{STD} where CrCL (or GFR) estimated by the creatinine model, Cockcroft-Gault, measured CrCL, four-variable MDRD4, six-variable MDRD (MDRD6) and CKD-EPI, respectively, CrCL (or GFR)_{STD} is the CrCL (or GFR) standardized to the median CrCL; fixed to 5 L/h in this study. CV was calculated as $\sqrt{\theta^2} \times 100\%$ where $\theta$ is IV or IOV. CL_{NLR} and IV on various parameters were fixed to zero in cases where estimates were close to zero. This did not lead to an increase in OFV.
inulin clearance) is also a limitation in this study. Finally, occasions were defined arbitrarily based on urine collection intervals of 24 hours. However, as shown by the simulation study, the model still provided sufficiently precise estimates even if the time points of actual changes in kinetic parameters deviated significantly from occasion definitions. An increased number of occasions might be considered if serum and urine sampling is done more frequently or PK data are available. Other limitations include arbitrary selection of simulation study conditions and lack of external evaluation.

In conclusion, this study provides a model-based approach that can be useful to estimate CrCL in critically ill patients with unstable renal function. The dynamic model quantified the relationship between CrCL and the clearance of renally excreted drugs better than conventional methods.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

ACKNOWLEDGMENTS
Higher Education Commission of Pakistan and German Academic Exchange Service (DAAD) are highly acknowledged for providing PhD scholarship to Mr. Sami Ullah. The Higher Education Commission and DAAD had no role in the design, collection, analysis and interpretation of data, or writing and publication of the manuscript. Open Access funding enabled and organized by Projekt DEAL.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The authors declare no competing interests for this work.

AUTHOR CONTRIBUTIONS
S.U. and M.T. wrote the manuscript. M.Z., U.F., and U.J. designed the research. J.Z., T.W., and M.H.Z. performed the research. S.U., M.T., and U.A. analyzed the data.

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