Received: 29 September 2023 | Revised: 13 November 2023 | Accepted: 23 November 2023

DOI: 10.1111/bcp.15978

ORIGINAL ARTICLE

A physiological approach to renal clearance: From premature neonates to adults

Nick Holford[1] | Conor J. O'Hanlon[1] | Karel Allegaert[2,3,4] | Brian Anderson[5] | Amilcar Falcão[6] | Nicolas Simon[7] | Yoke-Lin Lo[8,9] | Alison H. Thomson[10] | Catherine M. Sherwin[11,12,13] | Evelyne Jacqz-Aigrain[14] | Carolina Llanos-Paez[15,17] | Stefanie Hennig[15,18] | Linas Mockus[19] | Carl Kirkpatrick[16]

Correspondence
Nick Holford, Department of Pharmacology & Clinical Pharmacology, University of Auckland, Auckland, New Zealand.
Email: n.holford@auckland.ac.nz

Funding information
No funding was provided for data compilation, data analysis or writing this paper.

[Correction added on 14 February 2024, after first online publication: Carolina Llanos-Paez and Stefanie Hennig's affiliations have been corrected in this version.]

Abstract

Aims: We propose using glomerular filtration rate (GFR) as the physiological basis for distinguishing components of renal clearance.

Methods: Gentamicin, amikacin and vancomycin are thought to be predominantly excreted by the kidneys. A mixed-effects joint model of the pharmacokinetics of these drugs was developed, with a wide dispersion of weight, age and serum creatinine. A dataset created from 18 sources resulted in 27,338 drug concentrations from 9,901 patients. Body size and composition, maturation and renal function were used to describe differences in drug clearance and volume of distribution.

Results: This study demonstrates that GFR is a predictor of two distinct components of renal elimination clearance: (1) GFR clearance associated with normal GFR and (2) non-GFR clearance not associated with normal GFR. All three drugs had GFR clearance estimated as a drug-specific percentage of normal GFR (gentamicin 39%, amikacin 90% and vancomycin 57%). The total clearance (sum of GFR and non-GFR clearance), standardized to 70 kg total body mass, 176 cm, male, renal function 1, was 5.58 L/h (95% confidence interval [CI] 5.50-5.69) (gentamicin), 7.77 L/h (95% CI 7.26-8.19) (amikacin) and 4.70 L/h (95% CI 4.61-4.80) (vancomycin).

Conclusions: GFR provides a physiological basis for renal drug elimination. It has been used to distinguish two elimination components. This physiological approach has been applied to describe clearance and volume of distribution from premature neonates to elderly adults with a wide dispersion of size, body composition and renal function. Dose individualization has been implemented using target concentration intervention.

The authors confirm that, where possible, the principal investigators for this paper are listed in Table S1 and that they had direct clinical responsibility for patients.

For affiliations refer to page 1078

KEYWORDS

amikacin, clinical pharmacology, gentamicin, infectious diseases, nephrology, paediatrics, pharmacometrics, vancomycin

1 | INTRODUCTION

The antibiotics gentamicin, amikacin and vancomycin are used extensively across the human age range, and renal clearance is thought to be the main process of elimination. There have been few attempts to describe the similarities and differences in the pharmacokinetic behaviour of these antibiotics across the full spectrum of clinical size, age and kidney function. Previous studies of renally eliminated antibiotics have focused on describing the maturation of glomerular filtration from neonates to adults.[1,2] We have extended this approach, using some of those same data, to examine elimination linked to glomerular filtration rate (GFR) as well as elimination not directly linked to GFR. A comprehensive consideration of the role of body size and composition in describing predictable differences in elimination and distribution clearances, and central and peripheral apparent volumes of distribution has been applied to all three antibiotics.

We have developed a pooled dataset including doses, concentrations and demographics collected in patients who were treated with gentamicin, amikacin or vancomycin (the GAVamycin dataset). The GAVamycin dataset has been used to develop a joint pharmacokinetic model for the three antibiotics with a focus on defining the link between normal GFR (nGFR)[3] and clearance, and the role of body size and composition as predictors of differences in pharmacokinetic parameters.[4]

What is already known about this subject

- The pharmacokinetics of gentamicin, amikacin and vancomycin have been described in cohorts of different ages.
- These antibiotics are thought to be almost entirely eliminated by renal excretion.

What this study adds

- Renal clearance has two components distinguished by GFR and renal function.
- Description of maturation of central and peripheral volumes of distribution.
- Consistent foundation for standardizing PK parameters and individual dose prediction in the clinical setting.

2 | METHODS

2.1 | Body size

Normal fat mass (NFM)[4] is an extension of the concept of predicted normal weight[5] used to incorporate a measure of body composition into body size. It is derived from total body mass (TBM), fat free mass (FFM) and theory based allometric concepts.[6] NFM is calculated from FFM and TBM with an additional parameter, F_{fat}, which is estimated for each relevant drug parameter and accounts for the contribution of fat mass (TBM − FFM) (Equation 1).

$$NFM = FFM + F_{fat} \times (TBM - FFM) \quad (1)$$

F_{fat} converts fat mass to its allometric equivalent in terms of FFM. A standard value for NFM (NFM_{std}) may be calculated based on an adult male with a TBM of 70 kg, an FFM of 56.1 kg, a height of 176 cm and a drug and pharmacokinetic parameter specific estimate of F_{fat} (Equation 2).

$$NFM_{std} = 56.1 + F_{fat} \times (70 - 56.1) \quad (2)$$

A size factor, F_{size}, can be obtained from NFM, NFM_{std} and a theory-based allometric exponent WBE (Equation 3). WBE is obtained from the West, Brown and Enquist theory, which predicts an allometric exponent of 1 for structural properties (eg, V) and ¾ for functional properties (eg, CL).[7] NFM allows for body composition to be included in the meaning of allometric size.

$$F_{size} = \left(\frac{NFM}{NFM_{std}}\right)^{WBE} \quad (3)$$

2.2 | FFM

The method developed by O'Hanlon et al,[8] based on data in neonates, infants and children, was used to predict faFFM across all age groups with the aid of an adult model for predicting FFM.[9]

2.3 | nGFR

nGFR is the glomerular filtration rate (GFR) predicted in an individual without kidney disease (Equation 4).

$$nGFR = GFR_{std} \times F_{size} \times F_{mat,PMA} \times F_{mat,PNA} \quad (4)$$

GFR_{std} is the standard GFR for a 70-kg TBM male with a height of 176 cm, originally reported in Rhodin et al,[3] and updated with new

models for FFM and maturation leading to a standard GFR estimate of 6.96 L/h.[8] F_{size} is a factor for size using NFM,[4] $F_{mat,PMA}$ is a factor for maturation based on post-menstrual age (PMA) and $F_{mat,PNA}$ is a factor for maturation based on post-natal age (PNA), which describes a post-natal transition component of maturation. $F_{mat,PMA}$ is defined in terms of TM_{50}, the maturation half time, ie the PMA at 50% of the fully mature adult value of 1, and Hill, a parameter that describes the steepness of the maturation curve (Equation 5).

$$F_{mat,PMA} = \frac{1}{1 + \left(\frac{PMA}{TM_{50}}\right)^{-Hill}} \quad (5)$$

$F_{mat,PNA}$ is defined in terms of PNA_{max}, the fractional increase relative to the end of the post-natal transition associated maturation, $PNAT_{50}$, the half time required to achieve 50% of this post-natal change, and PNAD, PNA in days (Equation 6).

$$F_{mat,PNA} = 1 - PNA_{max} + PNA_{max} \times \left(1 - e^{\frac{-\ln(2) \times PNAD}{PNAT_{50}}}\right) \quad (6)$$

$F_{mat,PMA}$ and $F_{mat,PNA}$ approach an asymptote of 1 signifying completion of these maturational processes.

2.4 | Estimated GFR

GFR is hard to measure directly on a routine basis, therefore much effort has been put into developing methods for estimating GFR using endogenous solutes such as serum creatinine (Scr).[10] By multiplying paired measurements of GFR and Scr, and assuming steady state, it is possible to calculate GFR-linked values of creatinine production rate (CPR). We call this CPR_{GFR} to emphasize that CPR was obtained from GFR and not from creatinine clearance (CLcr)

$$CPR_{GFR} = GFR \times Scr \quad (7)$$

Before adulthood is reached (PNA < =20 years), a method for predicting CPR_{GFR} has been described.[8] CPR_{GFR} can be predicted in adults using a method based on the estimated renal component of aminoglycoside clearance.[11] The estimated GFR (eGFR) can then be predicted using CPR_{GFR} and Scr (Equation 8).

$$eGFR = \frac{CPR_{GFR}}{Scr} \quad (8)$$

A method that does not assume Scr is at steady state was used to calculate eGFR when more than one Scr measurement was available in an individual.[8] To evaluate this method of estimation of GFR we tried substituting eGFR with the values estimated by the CKD-EPI method.[12]

2.5 | Scr

Assays for Scr quantitation can have poor analytical specificity, for example the Jaffe colorimetric method.[13,14] Plasma proteins, immunoglobulins and other drugs (eg, cephalosporins) are known to interfere with the Jaffe assay.[15] Enzymatic methods used for Scr quantitation are more accurate, have greater specificity and are less affected by interfering substances.[14,16] The Jaffe method for Scr determination is still widely used, which can be challenging when CPR is based on a more specific method. A conversion factor of 0.748 was used to convert Jaffe Scr measurements to the more specific enzymatic equivalent.[8]

Scr is not reliable as a predictor of eGFR immediately after birth because most Scr in a neonate is derived from the mother. An estimate of creatinine half-life[8] can be used to predict how long it will take for most of the maternally derived creatinine to be eliminated from the neonate, for example after four neonatal creatinine half-lives. After that, it becomes reasonable to use measured Scr in neonates to estimate CLcr to obtain eGFR. When Scr was missing for this reason, renal function (RF) was imputed to be 1.

2.6 | Prediction of RF

The functional efficiency of the kidney can be described by comparison of GFR in an individual with that expected in a similar individual in the absence of kidney disease. A metric that we call RF[8] has been developed to make this comparison generalisable. RF is calculated from the ratio of eGFR to nGFR (Equation 9).

$$RF = \frac{eGFR}{nGFR} \quad (9)$$

An individual without kidney disease and eGFR equal to nGFR will have an RF value of 1 for all combinations of size, body composition and maturation. Typically, kidney disease will decrease RF but values greater than 1 are expected with disease associated hyperfiltration, which has been described in septic states[17] and a variety of other disease conditions.[18]

RF differs from the more general term "kidney function" by proposing a quantitative measure of the efficiency of all functions of the kidney that may be linked with renal solute elimination. RF is a quantity independent of size, body composition, maturation and post-natal transition effects when these factors are consistently accounted for in both eGFR and nGFR, as described in O'Hanlon et al.[8] This can be expressed as a continuous function to predict RF from premature neonates to adults.

2.7 | The GAVamycin dataset

Pooled data were obtained from 18 source studies (Supporting Information Table S1). Most of these sources have published

pharmacokinetic analyses of individual drugs (Supporting Information Table S3). Some of the data in the GAVamycin dataset were also used in a separate pooled analysis of vancomycin pharmacokinetics[19] (Supporting Information Table S4). The number of patients (Supporting Information Table S2) is based on those remaining after data plausibility and imputation criteria had been applied.

If height was missing, body surface area was predicted from the TBM[20] then height imputed from the body surface area and TBM. Patients without at least one SCr measurement were removed from the data. The RF value and ratio of FFM/TBM were used to identify plausible values because each of these quantities depends on several observed covariates. RF values greater than 2.5 were deemed physiologically implausible because they would necessitate an eGFR that was more than 2.5 times the nGFR. The selection of 2.5 itself incorporates high RF values that have not been observed in more meticulously monitored scenarios and, in our judgement, are at the limit of plausibility. A value of FFM/TBM greater than 0.95 was considered implausible and in that case a plausible value for FFM was imputed from TBM as follows: 0.8 × TBM when age was ≤20 years, 0.72 × TBM for adult females, 0.78 × TBM for adult males. Young patients (preterm and term) aged less than 197 post-natal days with TBM outside the 3rd and 97th percentiles for normal growth were thought to be implausible.[21] All patients with either implausible RF or TBM values were removed from the GAVamycin dataset used for analysis.

2.8 | Pharmacokinetic analysis

Drug input was described using a bolus or zero-order input. Infusion rate was calculated from amount and infusion duration. Missing infusion durations were estimated. Drug disposition was described using a two-compartment distribution model and first-order elimination. Elimination clearance (CL) was partitioned into a component, CLGFR, predicted as a fraction of nGFR, and a component not predictable from GFR (CLNGFR). This is an extension of using CLcr to distinguish a component of CL predictable from CLcr from CL not predictable from CLcr.[11] The use of CLcr in Matthews et al[11] assumed a linear relationship between CLcr and CL to estimate that about 76% of CL is predictable from CLcr. We have explored this linearity assumption using nGFR and RF applied to CLGFR and CLNGFR.

Equation 10 shows that CL_{grp}, the total elimination CL, is made up of $CLGFR_{grp}$, the GFR predictable component of CL_{grp}, and $CLNGFR_{grp}$ the non-GFR predictable component of CL_{grp}. The subscript "grp" is used to indicate that the parameter represents a group of people who share the same combination of covariates predicting the parameter.

$$CL_{grp} = CLGFR_{grp} + CLNGFR_{grp} \tag{10}$$

The fraction of nGFR that best predicted CLGFR was estimated as a drug-specific value, FGFR (Equation 11).

$$CLGFR_{grp} = RF \times FGFR \times nGFR \tag{11}$$

We initially used a linear function of RF to describe how CLGFR changes with RF (Equation 11) but quickly found that a nonlinear function of RF provided a better prediction (Equation 12).

$$CLGFR_{grp} = \frac{FGFR \times nGFR}{1 + \left(\frac{RF}{CLGFR_{RF50}}\right)^{\text{if } (RF < CLGFR_{RF50}) \text{ then } (-Hill_{LT}) \text{ else } (-Hill_{GE})}} \tag{12}$$

An asymmetrical sigmoid function was used to describe the relationship between RF and CLGFR using drug-specific parameters, $CLGFR_{RF50}$, $Hill_{LT}$ and $Hill_{GE}$. The sigmoidicity parameter in Equation (12) has a different value depending on whether RF is less than ($Hill_{LT}$) or greater than or equal ($Hill_{GE}$) to $CLGFR_{RF50}$.

The second component of clearance CLNGFR that is not linked to GFR is estimated as $CLNGFR_{grp}$ (Equation 13).

$$\begin{aligned} CLNGFR_{grp} = {} & CLNGFR_{pop} \times RF \times F_{size}NGFR \times F_{mat,PMA}NGFR \\ & \times F_{mat,PNA}NGFR \times F_{vent} \times F_{NSAID} \end{aligned} \tag{13}$$

$CLNGFR_{pop}$ is a drug-specific population parameter estimate for CLNGFR that is directly proportional to RF. Additional factors include allometric scaling for size (F_{size}NGFR, using NFM, and maturation, $F_{mat,PMA}$NGFR, with post-natal transition, $F_{mat,PNA}$NGFR), as described in Equations (4)-(6).

Fvent and FNSAID are factors to estimate the impact of positive pressure ventilation and concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen or indomethacin, which may affect a component of clearance.

The volume of distribution may be increased in neonates relative to TBM scaled values in adults.[22] The drug-specific fractional increase associated with post-natal transition, $F_{neovol,drug}$, and the half-life of an exponential loss of physiological neonatal excess volume, $POPT2_{neovol}$, were estimated. The effect of $FMATV_{neovol,drug}$ was applied to both central (V) and peripheral (VP) volumes of distribution (Equation 14).

$$\begin{aligned} FMATV_{neovol,drug} &= 1 + F_{neovol,drug} \times \exp\left(-\frac{\ln(2)}{POP_{T2_{neovol}}} \times PNA\right) \\ V_{grp,drug} &= POP_{V,drug} \times FMATV_{neovol,drug} \\ VP_{grp,drug} &= POP_{VP,drug} \times FMATV_{neovol,drug} \end{aligned} \tag{14}$$

2.9 | Computation

Data were analysed using NONMEM (ICON Development Solutions) version 7.5.1. Population parameter estimates were obtained using NONMEM's first-order conditional estimation method with the interaction and Laplacian options. The convergence criterion (NSIG) was 3 with tolerance SIGLEVEL = 9. Model selection was based on the minimum objective function value (OFV), calculated by NONMEM

from -2log-likelihood. A *P* value was calculated assuming a chi-square distribution with degrees of freedom determined by the number of additional parameters in the more complex model. A *P* value ≤.001 was used to aid model selection. Model evaluation was based on prediction corrected visual predictive checks (VPCs), parameter plausibility and parameter uncertainty. VPCs were used to compare the 5th, 50th and 95th percentiles of the observed and model predicted values.[23] The 95% confidence intervals were estimated from the replicates of each of the prediction percentiles. VPCs were performed using Wings for NONMEM 751 (WFN; http://wfn.sourceforge.net/) and R version 4.2.0. Parameter uncertainty was evaluated using an estimate of the relative standard error obtained from non-parametric bootstrapping.[24] Non-parametric bootstraps were performed using WFN and NONMEM. A total of 250 bootstrap replicates were used to describe the distribution of the parameter estimates and describe the uncertainty of the estimate.

Parameter variability was described by a mixed-effects approach with fixed and random effects. Fixed-effect variability was based on a population standard parameter $\theta_{POP,std}$ with a function of covariates such as TBM and RF to obtain the group parameter θ_{grp} (Equation 15).

$$\theta_{grp} = \theta_{POP,std} \times f(TBM, RF, \ldots) \quad (15)$$

where θ_{grp} is the group parameter after accounting for fixed effects due to covariates. Population parameter variability (PPV), between subject variability (BSV) and between occasion variability (BOV) were described using an exponential function of the random effect (Equation 16). The random effect, $\eta_{i,}$ describes variability assumed to be normally distributed with mean 0 and variance ω^2 Estimates of ω are shown as the square root of ω^2 and may be described as the apparent co-efficient of variation. θ_i is the individual parameter after accounting for random effects.

$$\theta_i = \theta_{grp} \times e^{\eta_i} \quad (16)$$

The residual unexplained variability (RUV) was described using a combined proportional and additive error model (Equation 17).

$$Y_i = Y_{Pred\,i} \times (1 + \varepsilon_{CV}) + \varepsilon_{SD} \quad (17)$$

where Y_i is the individual prediction of the observed value obtained from Y_{Predi} the model prediction and with proportional random effect ε_{CV} and additive random effect ε_{SD}. The random effects have mean zero and variance σ^2_{CV}. Estimates of σ are shown as the square root of σ^2.

2.10 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[25]

3 | RESULTS

The distribution by age group of primary covariates (PNA, TBM, height, Scr) and the derived covariate, RF, in relation to age are shown in Supporting Information Figures S1 to S5. Covariate counts include repeated individual values at the time of each new Scr measurement.

Key model selection steps (Table 1) were based on the likelihood ratio test using differences in NONMEM's OFV when comparing each model to the final Model 1. Estimation of common F_{fat} values for gentamicin, amikacin and vancomycin worsened the fit (Model 2). Using the FFM model proposed by Al-Sallami et al[26] instead of the FFM model that included premature neonates, neonates and infants[8] made the fit worse (Model 3). Using the same BSV with gentamicin, amikacin and vancomycin for CLGFR worsened the fit (Model 4). Substituting eGFR for the value estimated by the CKD-EPI 2021 method[12] had the same number of estimated parameters but the OFV indicated the model fit was much worse (Model 5). Fixing FGFR to 1 for gentamicin, amikacin and vancomycin made the fit much worse. When eGFR was used instead of CLcr in the Matthews model

TABLE 1 Major model component selection based on objective function value (OFV) compared with Model 1.

Model	Description	Obj	dOFV	Df	*P*
1	Final: different BSV CLGFR for G, A, V	81 742.91	.	.	.
2	Same F_{fat} for G, A and V	81 765.01	22.1	6	.0012
3	FFM using Al-Sallami 2015	81 951.69	208.8	7	.0000
4	Same BSV CLGFR for G, A, V	81 988.78	245.9	2	.0000
5	eGFR using CKDEPI2021	82 395.87	653.0	0	Different
6	FGFR fixed to 1 for G, A, V	83 433.59	1690.7	3	
7	Linear eGFR + constant CLNGFR (Matthews equivalent)	83 818.34	2075.4	9	.0000
8	Linear eGFR using CKDEPI + constant CLNGFR (Matthews equivalent)	84 186.17	2443.3	9	.0000

Note: A= amikacin; CKDEPI = CKD-EPI eGFR without race[12]; CLGFR = GFR clearance; CLNGFR = non-GFR clearance; Different = dOFV importantly different (chi-square not used because df the same as final model); df = degrees of freedom (number of parameters less than final model); dOFV = change in OFV from the final model; eGFR = estimated GFR (Equation 8); G = gentamicin; *P* = chi-square (dOFV,df); V = vancomycin.

linking CLcr to aminoglycoside clearance[11] the fit was significantly worse (Model 7). Using the CKD-EPI 2021 method for eGFR had an even worse fit (Model 8).

The parameter estimates from the GAVamycin data based on the final model are shown in Table 2. Wherever appropriate, parameters values are expressed as a standard value, identified by the "std" suffix. They are based on a 70 kg TBM, 176 cm adult male with RF equal to 1 and GFR of 6.96 L/h.[8,27]

The bootstrap 95% confidence intervals are generally quite narrow, as summarized in the relative standard error (RSE%). Based on these confidence intervals (Table 2), all parameters scaled using NFM with theory-based allometry had F_{fat} estimates different from either 1 or 0, except for amikacin intercompartmental clearance (Q_FFAT_AMIK). The Q_FFAT_AMIK estimate included 0, indicating it could be described by FFM.

The asymmetrical sigmoid function linking RF to the fraction of clearance explained by GFR showed a steep relationship (exponent >1) both below and above the midpoint CLGFR_RF50 (Figure 1). The linear function of RF linked to non-GFR clearance is shown in Figure 2.

The total clearance of each drug, obtained from the sum of GFR clearance and non-GFR clearance, is shown in Figure 3. GFR clearance accounted for 42% of gentamicin, 59% of amikacin and 64% of vancomycin total clearance.

The separate maturation and post-natal transition components for predicted nGFR are shown in Supporting Information Figure S6 and for non-GFR associated clearance (CLNGFR) in Supporting Information Figure S7. The combined components are shown in Supporting Information Figure S8. The maturation and post-natal transition changes of CLGFR were determined by nGFR. At birth CLGFR is 27% of the size-scaled adult value at birth, with post-natal transition 95% completed by 25 days PNA (Table 2) with subsequent maturation described by PMA. The large fraction (0.962) of maturation associated with post-natal transition (CLNGFR_PNAmax) means CLNGFR is less than 1% of the size-scaled adult value at birth but post-natal transition is rapid and 95% complete by 12 days PNA (Table 2), with subsequent maturation described by PMA.

The combined maturation and post-natal transition time course of GFR clearance, non-GFR clearance and total clearance are shown in Supporting Information Figure S9 (CLGFR), Supporting Information Figure S10 (CLNGFR) and Supporting Information Figure S11 (CLGFR + CLNGFR).

Administration of inotropes was associated with an increase in the total volume of distribution. There was no detectable effect of mechanical ventilation on total clearance. The use of NSAIDs is summarized by type and PMA in Supporting Information Figure S21. The fit was improved more by putting the effect of NSAIDs on non-GFR clearance than on GFR clearance. Treatment of patent ductus arteriosus with ibuprofen decreased CLNGFR. The indomethacin treatment effect bootstrap confidence interval included 1 and thus did not support a detectable effect of indomethacin on CLNGFR.

We report maturation of volumes of distribution with a drug-specific initial fractional increase in addition to size-scaled adult values. The subsequent volume decrease towards adult values was described by an exponential process with central and peripheral volume half-lives (Supporting Information Figure S12 and Table 2). The maturation of volume falls exponentially to just 5% above adult values by 3.17 years (central volume) and 2.94 years (peripheral volume).

The BOV for total clearance and for central volume was small relative to BSV.

A combined proportional and additive model described residual error of concentration predictions. The studies which contributed to the source datasets varied widely in duration of individual patient intensity of sampling and duration of follow up. These design factors were associated with variability in residual error of each concentration. The source of each contribution to the total GAVamycin dataset was used as an explanatory covariate to account for the relative magnitude of residual error variability.

VPCs as a function of days after the start of dosing (Figure 4), TBM all data (Figure 5), TBM less than or equal to 5 kg (Supporting Information Figure S13), PMA (Figure 6), RF (Figure 7) and PNA (Supporting Information Figure S14) show that median concentrations are well predicted and support the covariate models used to describe fixed-effect sources of variability. VPCs for each drug as a function of time and RF are shown in Supporting Information Figures S15 to S20.

The scatter distribution of concentration observations according to different covariates is quite dense, except as shown in Supporting Information Figure S5, where the RF values approaching the upper cut-off of 2.5 become quite sparse. This may be considered an a posteriori justification for the 2.5 cut-off and helps explain the overlap of the percentiles, unlike other VPCs with clearly separated percentiles. All the VPCs show that upper 95% percentiles of observed concentrations are commonly higher than the predicted 95% percentile. This indicates there may be factors associated with a small number of high concentration measurements, for example due to sampling from veins used for drug administration.

4 | DISCUSSION

Renal drug elimination, like hepatic drug elimination,[28] is necessarily limited by organ blood flow but the limiting role of GFR for renal drug elimination has not been widely recognized. We describe a model for renal drug clearance with a component limited by GFR and a second component not directly linked to GFR based on readily available demographic and pharmacokinetic data.

Gentamicin, amikacin and vancomycin are widely believed to be extensively, if not completely, eliminated from the body by the renal route. We have investigated pharmacokinetic models assuming that the underlying processes described by the models are the same for all these drugs and differences between them would be revealed in the parameters defining the processes.

Our joint analysis of gentamicin, amikacin and vancomycin data across a wide dispersion of body size, age and RF has been able to describe drug concentrations as a function of dose, time, TBM, PNA, PMA, nGFR and RF. This description used commonly applied models

TABLE 2 Parameter estimates for the GAVamycin model

Parameter	Description	Units	Original	Bootstrap average	Bootstrap 2.5%ile	Bootstrap 97.5%ile	RSE
CLGFR_GENT	GFR CL gentamicin	L/h std	2.33	2.34	2.29	2.38	1%
CLGFR_AMIK	GFR CL amikacin	L/h std	4.56	4.55	4.15	4.93	3%
CLGFR_VANC	GFR CL vancomycin	L/h std	3.03	3.02	2.94	3.10	1%
CLNGFR_GENT	Non-GFR CL gentamicin	L/h std	3.25	3.25	3.17	3.33	1%
CLNGFR_AMIK	Non-GFR CL amikacin	L/h std	3.21	3.20	2.83	3.47	5%
CLNGFR_VANC	Non-GFR CL vancomycin	L/h std	1.67	1.67	1.61	1.73	1%
CLTOT_GENT	GFR CL + non-GFR CL gentamicin	L/h std	5.58	5.59	5.50	5.69	1%
CLTOT_AMIK	GFR CL + non-GFR CL amikacin	L/h std	7.77	7.74	7.26	8.19	3%
CLTOT_VANC	GFR CL + non-GFR CL vancomycin	L/h std	4.70	4.69	4.61	4.80	1%
FGFR_GENT	Gentamicin clearance fraction of GFR	–	0.390	0.390	0.386	0.396	1%
FGFR_AMIK	Amikacin clearance fraction of GFR	–	0.900	0.900	0.886	0.909	0.8%
FGFR_VANC	Vancomycin clearance fraction of GFR	–	0.567	0.567	0.557	0.575	1%
CLGFR_RF50_GENT	RF at 50% of GFR CL vancomycin	–	0.476	0.473	0.425	0.490	3%
CLGFR_RF50_AMIK	RF at 50% of GFR CL amikacin	–	0.628	0.632	0.604	0.684	3%
CLGFR_RF50_VANC	RF at 50% of GFR CL gentamicin	–	0.531	0.533	0.517	0.557	2%
CLGFR_HILL_LT_GENT	Gentamicin Hill less than RF50	–	2.44	2.43	2.38	2.48	2%
CLGFR_HILL_LT_AMIK	Amikacin Hill less than RF50	–	2.12	2.13	1.86	2.68	10%
CLGFR_HILL_LT_VANC	Vancomycin Hill less than RF50	–	1.88	1.89	1.84	2.00	3%
CLGFR_HILL_GE_GENT	Gentamicin Hill greater than or = RF50	–	6.03	6.03	5.91	6.08	1%
CLGFR_HILL_GE_AMIK	Amikacin Hill greater than or = RF50	–	1.73	1.75	1.61	2.08	6%
CLGFR_HILL_GE_VANC	Vancomycin Hill greater than or = RF50	–	5.08	5.08	4.94	5.15	1%
CLNGFR_TM50	Time to 50% maturation of non-GFR CL	PMA week	57.8	57.8	57.2	58.3	0.5%
CLNGFR_HILL	Hill parameter for maturation of non-GFR CL	–	3.24	3.26	3.21	3.42	2%
CLNGFR_PNAMAX	Post-natal max non-GFR CL	–	0.962	0.962	0.962	0.964	0.1%
CLNGFR_PNAT50	Post-natal half-life non-GFR CL	PNA day	2.84	2.83	2.69	2.90	3%
CLNGFR_FFAT_GENT	Gentamicin F_{fat} for allometric size for non-GFR CL	–	2.43	2.44	2.27	2.59	3%
CLNGFR_FFAT_AMIK	Amikacin F_{fat} for allometric size for non-GFR CL	–	6.53	7.26	6.47	18.02	50%
CLNGFR_FFAT_VANC	Vancomycin F_{fat} for allometric size for non-GFR CL	–	0.324	0.319	0.223	0.409	22%
V_GENT	Gentamicin central volume of distribution (V)	L std	19.0	19.1	18.8	19.5	1%
V_AMIK	Amikacin central volume of distribution (V)	L std	22.9	22.9	22.3	23.6	1%
V_VANC	Vancomycin central volume of distribution (V)	L std	32.5	32.6	31.8	33.3	1%
V_FFAT_GENT	Gentamicin F_{fat} for allometric size for V	–	1.19	1.20	1.12	1.29	3%
V_FFAT_AMIK	Amikacin F_{fat} for allometric size for V	–	1.38	1.40	1.17	1.78	10%

TABLE 2 (Continued)

Parameter	Description	Units	Original	Bootstrap average	Bootstrap 2.5%ile	Bootstrap 97.5%ile	RSE
V_FFAT_VANC	Vancomycin F_{fat} for allometric size for V	—	0.337	0.351	0.271	0.489	14%
VP_GENT	Gentamicin peripheral volume of distribution (VP)	L std	37.2	37.3	36.2	39.2	2%
VP_AMIK	Amikacin peripheral volume of distribution (VP)	L std	28.6	27.5	20.9	28.6	8%
VP_VANC	Vancomycin peripheral volume of distribution (VP)	L std	27.4	27.5	26.1	28.8	2%
VP_FFAT_GENT	Gentamicin F_{fat} for allometric size for VP	—	5.11	5.13	4.94	5.35	3%
VP_FFAT_AMIK	Amikacin F_{fat} for allometric size for VP	—	2.60	2.67	1.86	3.74	25%
VP_FFAT_VANC	Vancomycin F_{fat} for allometric size for VP	—	11.7	11.7	11.2	12.1	2%
Q_GENT	Gentamicin intercompartmental clearance (Q)	L/h std	1.72	1.72	1.64	1.75	2%
Q_AMIK	Amikacin intercompartmental clearance (Q)	L/h std	1.53	1.51	1.19	1.58	7%
Q_VANC	Vancomycin intercompartmental clearance (Q)	L/h std	1.33	1.33	1.29	1.37	2%
Q_FFAT_GENT	Gentamicin F_{fat} for allometric size for Q	—	0.804	0.814	0.753	0.926	6%
Q_FFAT_AMIK	Amikacin F_{fat} for allometric size for Q	—	0.634	0.517	−0.566	0.643	65%
Q_FFAT_VANC	Vancomycin F_{fat} for allometric size for Q	—	4.02	4.04	3.83	4.25	3%
FNEOV_GENT	Gentamicin fractional increase of V at birth	—	0.590	0.590	0.577	0.607	1%
FNEOV_AMIK	Amikacin fractional increase of V at birth	—	0.398	0.398	0.382	0.415	3%
FNEOV_VANC	Vancomycin fractional increase of V at birth	—	0.109	0.109	0.103	0.111	2%
T2NEOV_VANC	Half-life of loss of neonatal V	PNA week	38.0	38.0	37.9	38.1	0.1%
FNEOVP_GENT	Gentamicin fractional increase of VP at birth	—	0.0136	0.0136	0.0131	0.0137	1%
FNEOVP_AMIK	Amikacin fractional increase of VP at birth	—	0.0171	0.0170	0.0140	0.0175	7%
FNEOVP_VANC	Vancomycin fractional increase of VP at birth	—	0.0156	0.0156	0.0154	0.0162	1%
T2NEOVP_VANC	Half-life of loss of neonatal VP	PNA week	35.3	35.3	35.1	35.3	0.2%
F1_SDY10	Bioavailability of gentamicin not flushed (source 9) relative to other studies		0.884	0.886	0.864	0.915	1%
TK0	Duration of IV infusion (source 9)	h	0.994	0.995	0.986	0.999	1%
FINO	Inotrope effect on V + VP	—	1.15	1.16	1.11	1.22	2%
FVNT	Mechanical ventilation effect on non-GFR CL + GFR CL	—	1.00	1.00	1.00	1.00	0%
FINDO	Indomethacin effect on CLNGFR	—	1.00	1.00	0.84	1.16	8%
FIBU	Ibuprofen effect on CLNGFR	—	0.744	0.724	0.754	0.754	1%
RUV_CV_G	Gentamicin concentration proportional residual error	—	0.140	0.140	0.135	0.146	2%
RUV_SD_G	Gentamicin concentration additive residual error	mg/L	0.155	0.155	0.145	0.164	3%
RUV_CV_A	Amikacin concentration proportional residual error	—	0.245	0.247	0.230	0.276	5%
RUV_SD_A	Amikacin concentration additive residual error	mg/L	0.992	0.989	0.858	1.09	4%

(Continues)

TABLE 2 (Continued)

Parameter	Description	Units	Original	Bootstrap average	Bootstrap 2.5%ile	Bootstrap 97.5%ile	RSE
RUV_CV_V	Vancomycin concentration proportional residual error	–	0.150	0.150	0.144	0.157	2%
RUV_SD_V	Vancomycin concentration additive residual error	mg/L	2.14	2.14	2.04	2.25	2%
FRUV_SDY2	Source 2 fraction of source 1 residual error	–	1.95	1.94	1.53	2.42	10%
FRUV_SDY3	Source 3 fraction of source 1 residual error	–	1.20	1.20	1.09	1.35	5%
FRUV_SDY5	Source 5 fraction of source 1 residual error		1.22	1.23	1.13	1.35	4%
FRUV_SDY6	Source 6 fraction of source 1 residual error	–	1.18	1.17	1.06	1.30	4%
FRUV_SDY8	Source 8 fraction of source 1 residual error	–	1.02	1.01	0.79	1.23	9%
FRUV_SDY9	Source 9 fraction of source 1 residual error	–	0.61	0.62	0.58	0.66	3%
FRUV_SDY10	Source 10 fraction of source 1 residual error	–	1.50	1.51	1.43	1.64	3%
FRUV_SDY11	Source 11 fraction of source 1 residual error	–	1.49	1.49	1.26	1.73	6%
FRUV_SDY12	Source 12 fraction of source 1 residual error	–	2.34	2.35	2.08	2.69	5%
FRUV_SDY13	Source 13 fraction of source 1 residual error	–	1.11	1.11	0.99	1.24	5%
FRUV_SDY14	Source 14 fraction of source 1 residual error	–	3.57	3.57	3.52	3.62	1%
FRUV_SDY15	Source 15 fraction of source 1 residual error	–	1.17	1.17	1.14	1.20	1%
FRUV_SDY16	Source 16 fraction of source 1 residual error	–	3.09	3.08	1.99	4.03	14%
FRUV_SDY17	Source 17 fraction of source 1 residual error	–	2.08	2.07	1.93	2.14	4%
FRUV_SDY18	Source 18 fraction of source 1 residual error	–	2.45	2.45	2.41	2.49	1%
FRUV_SDY19	Source 19 fraction of source 1 residual error	–	1.75	1.74	1.38	2.17	10%
FRUV_SDY20	Source 20 fraction of source 1 residual error	–	1.86	1.86	1.81	1.88	1%
BSV_CLGFR_GENT	Between subject variability of GFR CL gentamicin	–	0.191	0.193	0.190	0.222	4%
BSV_CLGFR_AMIK	Between subject variability of GFR CL amikacin	–	0.068	0.067	0.050	0.078	8%
BSV_CLGFR_VANC	Between subject variability of GFR CL vancomycin	–	0.221	0.221	0.208	0.231	2%
BSV_CLNGFR	Between subject variability of non-GFR CL		0.366	0.369	0.355	0.386	2%
BSV_V	Between subject variability of VC	–	0.020	0.020	0.019	0.020	1%
PPV_Q	Population parameter variability of Q	–	0.254	0.255	0.247	0.269	3%
PPV_VP	Population parameter variability of VP	–	0.427	0.425	0.400	0.442	2%
BSV_TK0	Between subject variability of source 9 input duration	–	0.016	0.016	0.016	0.017	2%
PPV_RUV_CP	PPV of residual error of GAV concentrations	–	0.793	0.797	0.787	0.821	1%
BOVCL1	Between occasion variability for CL	–	0.0140	0.0140	0.0140	0.0140	1%
BOVV1	Between occasion variability for V1	–	0.0030	0.0030	0.0030	0.0030	4%

Note: Parameter names correspond to those used in NM-TRAN code (Supporting Information Data S1). Population parameter variability (PPV), between subject variability (BSV) and between occasion variability (BOV) values are shown as the square root of the variance estimate reported by NONMEM. Random unidentified variability (RUV) values are THETA. estimates reported by NONMEM. Relative standard error (RSE%) was calculated by dividing the original parameter estimate by the bootstrap standard deviation.
Description Column: CL = clearance; FGFR = drug specific fraction of nGFR; GAV = gentamicin, amikacin, vancomycin; GFR = glomerular filtration rate; nGFR = normal GFR; PNA = post-natal age; Q = inter-compartmental clearance; RF = renal function; RF50 = RF at 50% of FGFR x nGFR; VC = central volume of distribution; VP = peripheral volume of distribution.

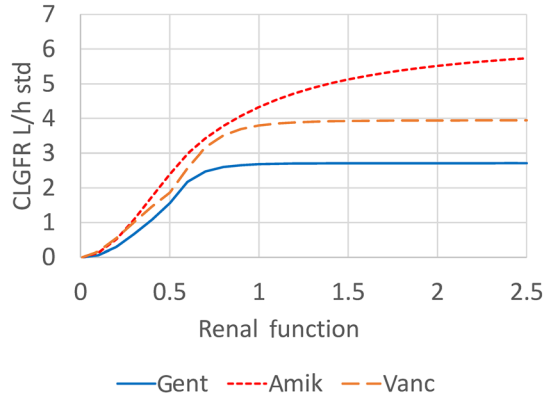

FIGURE 1 Renal function and glomerular filtration rate (GFR) associated clearance (CLGFR). Gent, gentamicin; Amik, amikacin; Vanc, vancomycin.

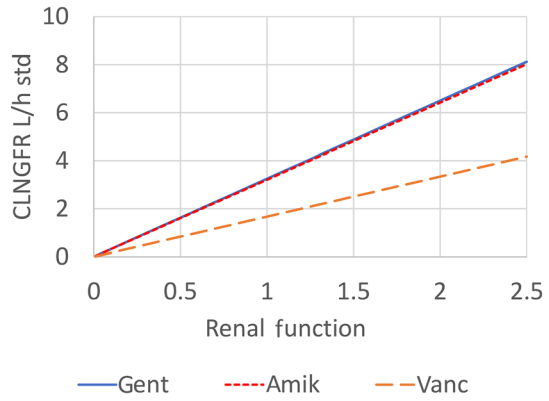

FIGURE 2 Renal function and non-glomerular filtration rate (GFR) associated clearance (CLNGFR) (amikacin and gentamicin lines are overlapping). Gent, gentamicin; Amik, amikacin; Vanc, vancomycin.

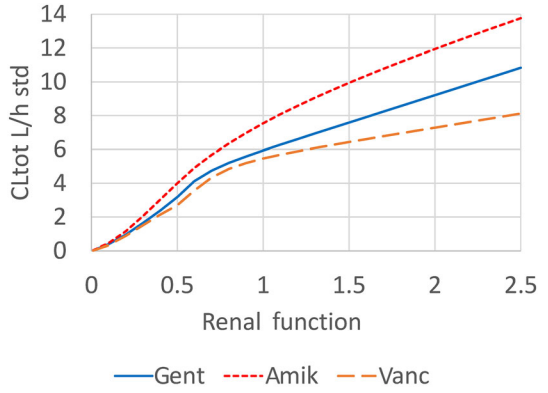

FIGURE 3 Renal function and total clearance (CLGFR + CLNGFR). CLtot, total clearance; Gent, gentamicin; Amik, amikacin; Vanc, vancomycin.

to describe drug distribution (central and peripheral volumes and intercompartment clearance) but describing drug elimination was more complex.

Drugs that are renally eliminated are commonly described by empirical linear or power functions linking Scr or estimated creatinine clearance to elimination CL, for example gentamicin,[29] amikacin[30] and vancomycin.[19] Matthews et al described the clearance of aminoglycosides with a component that was a linear function of estimated creatinine clearance and a seemingly independent component.[11] This was the starting point for the two-component clearance model described here. We have used GFR as a physiological variable to distinguish between two components of clearance: a component linked to GFR and a component not linked to GFR. It may be noted that the seemingly complex distinction between GFR and non-GFR clearance using a function of RF to describe total clearance is analogous to using saturable and non-saturable binding as a function of unbound concentration to describe total plasma protein binding. The maximum binding capacity is analogous to nGFR and non-specific binding is analogous to CLNGFR.

GFR clearance is linked directly to the predicted GFR for an individual using nGFR. nGFR provides a reference value for this clearance component in an individual to describe elimination occurring by glomerular filtration without re-absorption or tubular secretion. The individual upper limit on GFR clearance enforced by nGFR when RF = 1 required an asymptote (Figure 1) described by an asymmetrical sigmoid function of RF (Equation 12).

The drug-specific fraction of GFR (FGFR, Equation 11) was estimated to be less than 1 for all three drugs (Tables 1 and 2). This may be explained by plasma protein binding. Glomerular filtrate is assumed to contain only unbound drug, thus clearance will be unbound clearance. Clearance estimated from total (bound + unbound) concentration will be less than unbound clearance so FGFR will be less than 1.

Non-GFR clearance (CLNGFR) accounts for elimination not described by GFR clearance. Relative to total clearance, CLNGFR is 34% for gentamicin, 33% for amikacin and 55% for vancomycin. The inclusion of RF as a directly proportional predictor of non-GFR clearance provided a major improvement in fit (Table 1 and Figure 2). It is therefore likely that CLNGFR is describing renal excretion that is not explained simply by CLGFR but the renal elimination process associated with the non-GFR clearance component is not clear. It should also be noted that the developmental biology of CLNGFR is different from CLGFR, with very little contribution to total clearance at birth (1% compared with 27%) but more rapid completion of post-natal transition (95% at 12 days compared with 25 days) (Supporting Information Figure S9).

If CLcr is actually greater than GFR, for example by 10%,[31] then the method described in O'Hanlon et al[8] to estimate CPR_{GFR} will underestimate total CPR, for example by a factor of 100/110, because the CPR_{GFR} estimating equation is derived from GFR not CLcr. When calculating RF, care should be taken to avoid the use of equations developed to estimate CLcr, for example Cockcroft and Gault,[32] and preference given to equations developed to estimate GFR, for example O'Hanlon et al and Delanaye et al.[8,10] We note that the CKD-EPI 2021 eGFR method is not a suitable method for estimating GFR across the wide range of body size, age and kidney function that we

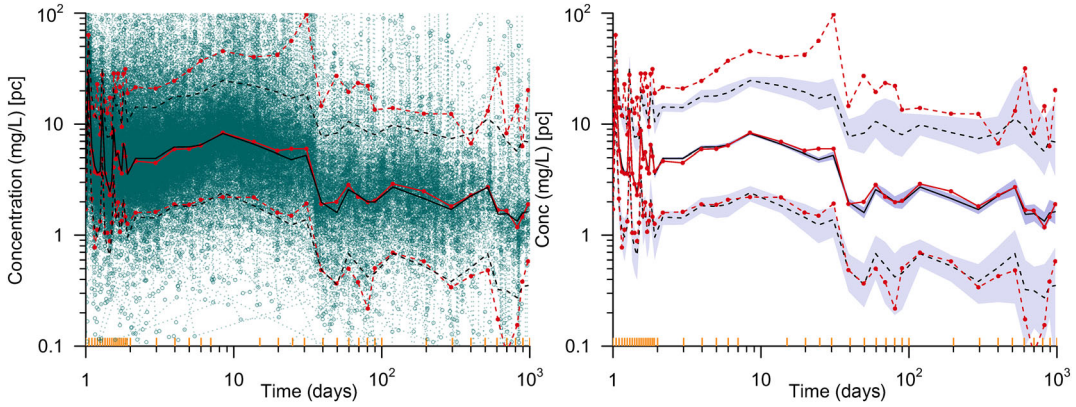

FIGURE 4 Prediction corrected [pc] visual predictive check (VPC) for all concentrations of gentamicin, amikacin and vancomycin as a function of days after the start of dosing (log scale). The 5%, median and 95% percentiles of the distribution of the observations (red lines) and predictions (black lines) compare the distributions. The open circles and dashed lines in the left-side plot link observations in the same individual. The 95% confidence intervals for the prediction percentiles are shown by the purple-shaded areas in the right-side plot. The yellow lines on the *x* axis show the data bins used in the construction of the VPC.

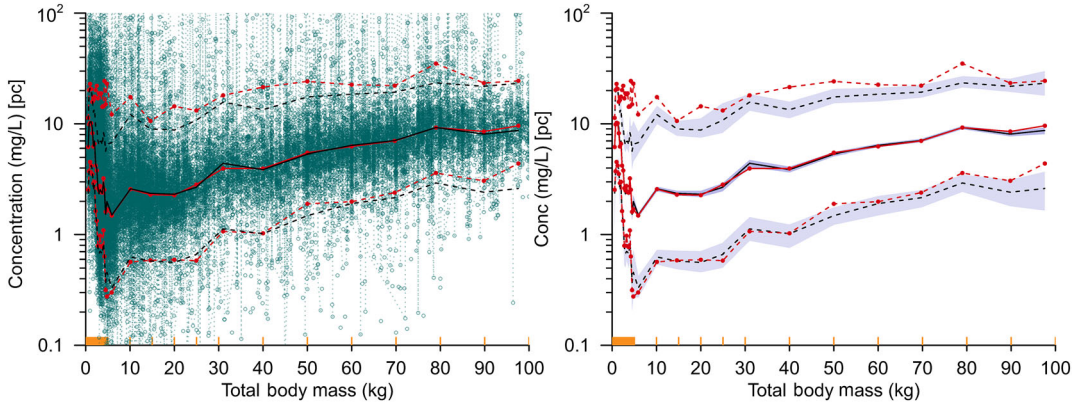

FIGURE 5 Visual predictive check as a function of total body mass (log scale). See Figure 4 legend for other details.

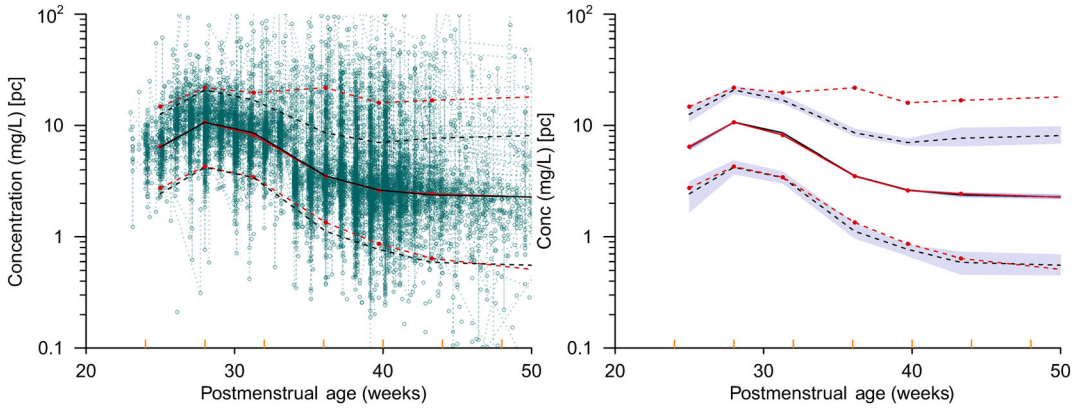

FIGURE 6 Visual predictive check as a function of post-menstrual age (log scale). See Figure 4 legend for other details.

studied, as demonstrated by a much worse goodness of fit (Table 1). This may be explained by the limited number of covariates (Scr, age and sex) included in this empirical model for GFR.[12]

Gentamicin, amikacin and vancomycin have different patterns of tubular re-absorption, with gentamicin having the highest fraction of net re-absorption (21%), followed by amikacin (17%)[33,34] and

vancomycin having minimal tubular re-absorption.[35] Golper et al[36] reported vancomycin renal clearance as 80% of creatinine clearance whereas our estimate indicates that CLGFR accounted for 64% of total clearance of vancomycin. We have confirmed the observation of GFR clearance being less than nGFR for gentamicin, amikacin and vancomycin using FGFR. While non-GFR clearance might be construed as indicative of renal tubular secretion, existing evidence suggests that tubular secretion for gentamicin and amikacin is negligible.[34] Golper et al[36] found no evidence for net tubular secretion of vancomycin because unbound vancomycin renal clearance was essentially the same as inulin clearance. Published physiologically based pharmacokinetic (PBPK) models have often relied on assumptions, attributing non-GFR clearance to biliary excretion independent of RF,[37] omitting mention of the role of GFR[38] or neglecting to account for increased clearance associated with high RF.[39] It is anticipated that PBPK models would yield more accurate predictions if grounded on the clearance components we have identified rather than relying on assumptions.

The relationship between each clearance component, separately and combined as a function of key covariates, reveals the distinctly different patterns of predictable variation (Figures 1 to 3). Despite the difficulties in assigning a specific mechanism to GFR clearance and non-GFR clearance, the combination of these two components with component-specific covariate effects (NFM, PNA, PMA and RF) adequately describes the time course of observed concentrations as shown in the VPCs (Figures 4 to 7 and Supporting Information Figures S14 to S20). In Figure 7, when RF values are above 1.6 there are relatively few patients with a large degree of variability in associated concentrations. Nevertheless, the predicted percentiles agree well with the observed percentiles and support the use of RF even at these high values.

Using a model for FFM applicable across the full range of size and age, we have been able to use the concept of NFM to describe all the key PK parameters, including both components of clearance. This should help describe the PK parameters in patients who may be thin or obese. The F_{fat} parameters appear to be independent of maturation. Attempts to identify maturation changes of F_{fat} associated with PMA did not improve the fit.

An increase in the central volume of distribution in neonates and infants has been described previously and was thought to be due to increased total body water.[22] We describe an increase in central and peripheral volumes of distribution followed by maturation to approach adult values (Supporting Information Figure S12). We do not have an obvious explanation for the differences between the three drugs in the magnitude of the increase estimated at birth. It could be due to differences in blood sampling time, which would affect the estimation of central volume. The maturation of volume falls to just 5% above adult values by 3.18 years (central volume) and 2.94 years (peripheral volume). The time course was initially slower than that described for both total body water and extracellular fluid but agreed overall with previous observations.[40] Body fat content increases from 12% at 40 weeks PMA to 30% at 75 weeks PMA.[41] This may also affect the time course of central and peripheral volume changes. The maturation half-lives of central and peripheral volumes (38.0 and 35.3 weeks) were similar to the GFR maturation half-life of 33.7 weeks[8] that determines the maturation of GFR clearance but shorter than the non-GFR clearance maturation half-life of 57.2 weeks. Thus our description may reflect not only loss of total body water but also developmental changes in body structure that are not captured by changes in body size and composition.

This study describes the differences in the PK of gentamicin, amikacin and vancomycin from premature neonates to adults using data from a large number of patients from different locations and different underlying medical conditions (Supporting Information Table S1). A previous study (data from sources 15 and 16 in this pooled analysis)[42] reported differences in the PK of gentamicin between oncology and non-oncology paediatric patients by including NFM as a body size descriptor. NFM was applied[42] to describe the differences in the percentage of body fat between paediatric oncology (30.4%) and non-oncology (14.9%). An updated FFM method has been developed including data from neonates.[8] Utilizing this improved FFM predictor, which is applicable across the entire spectrum of size and age,[8] enables a more comprehensive description of FFM and facilitates the elucidation of variations in body composition across all ages, including alterations attributed to underlying cancer. We therefore believe that the model presented here implicitly

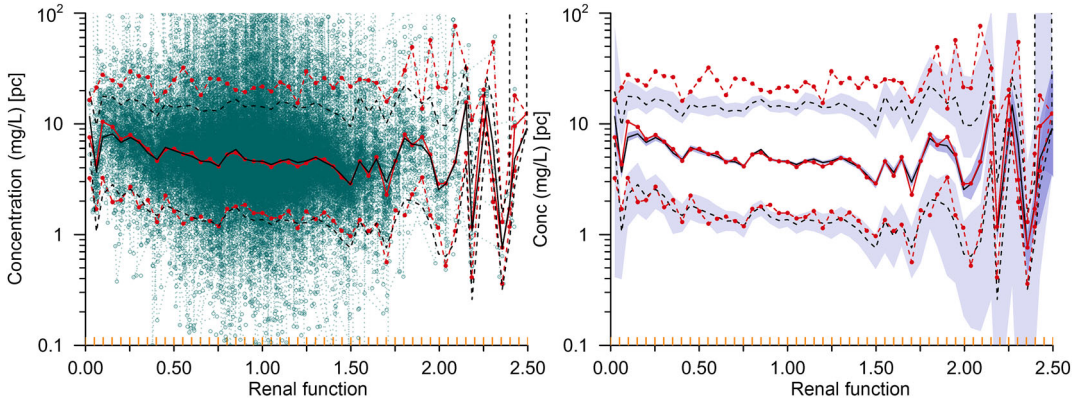

FIGURE 7 Visual predictive check as a function of renal function (log scale). See Figure 4 legend for other details.

considers the impact of the patient's underlying medical condition by considering patient kidney function, body size and body composition to describe individual differences in PK. It has been implemented for gentamicin, amikacin and vancomycin in NextDose, a freely available web-based tool.[43]

There was a high proportion of paediatric patients in the dataset, which facilitated examination of the influence of maturation. However, the relative paucity of data from elderly patients and from adult patients with renal impairment may have limited the ability to fully characterize the relationship between renal impairment and clearance in older patients.

With these three insights (GFR defined clearance components, NFM, and understanding the magnitude and time course of the development of volume of distribution) we expect the model to improve the ability to predict individual dosing both for initiation and monitoring of treatment using a target concentration intervention approach.[44]

AUTHOR CONTRIBUTIONS

NH designed the research, wrote the manuscript and conducted the analysis. CJO'H developed methods for checking consistency of the GAVamycin dataset and describing distributions of covariates. Other authors provided patient data, were given the opportunity to verify the final PK model and contributed to the manuscript.

AFFILIATIONS

[1]Department of Pharmacology & Clinical Pharmacology, University of Auckland, Auckland, New Zealand
[2]Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[3]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
[4]Department of Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands
[5]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand
[6]Faculty of Pharmacy, Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, Coimbra, Portugal
[7]Aix Marseille Univ, Hop Sainte Marguerite, Service de Pharmacologie clinique, Marseille, France
[8]Department of Pharmacy Practice, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia
[9]Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[10]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK
[11]University of Otago, Dunedin, New Zealand
[12]University of Utah, Salt Lake City, Utah, USA
[13]Department of Pediatrics, Wright State University Boonshoft School of Medicine/Dayton Children's Hospital, Dayton, Ohio, USA.
[14]Paediatric Pharmacology and Pharmacogenetics, APHP Hôpital Saint-Louis – University Paris Cité, Paris, France
[15]University of Queensland, Brisbane, Australia
[16]Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia
[17]Pharmetheus AB, Uppsala, Sweden.
[18]Certara, Inc., Princeton, New Jersey, USA
[19]Chemical Engineering Department, Purdue University, West Lafayette, Indiana, USA

ACKNOWLEDGEMENTS

This work used a licence for NONMEM granted by ICON to the Australian Centre for Pharmacometrics. The Australian Centre for Pharmacometrics is an initiative of the Australian Government as part of the National Collaborative Research Infrastructure Strategy. Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare.

DATA AVAILABILITY STATEMENT

The full data supporting our findings are not publicly available due to privacy and ethical considerations which vary across different sources.

ORCID

Nick Holford https://orcid.org/0000-0002-4031-2514
Conor J. O'Hanlon https://orcid.org/0000-0003-2369-2858
Yoke-Lin Lo https://orcid.org/0000-0001-5521-2543
Alison H. Thomson https://orcid.org/0000-0002-2354-6116
Catherine M. Sherwin https://orcid.org/0000-0002-0844-3207
Evelyne Jacqz-Aigrain https://orcid.org/0000-0002-4285-7067
Stefanie Hennig https://orcid.org/0000-0001-5972-3711
Carl Kirkpatrick https://orcid.org/0000-0002-5715-1534

REFERENCES

1. De Cock RF, Allegaert K, Brussee JM, et al. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm Res*. 2014;31(10):2643-2654. doi:10.1007/s11095-014-1361-z
2. De Cock RFW, Allegaert K, Sherwin CMT, et al. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm Res*. 2014;31(3):754-767. doi:10.1007/s11095-013-1197-y
3. Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol*. 2009;24(1):67-76. doi:10.1007/s00467-008-0997-5
4. Holford NH, Anderson BJ. Allometric size: the scientific theory and extension to normal fat mass. *Eur J Pharm Sci*. 2017;109:S59-S64. doi:10.1016/j.ejps.2017.05.056
5. Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM. A standard weight descriptor for dose adjustment in the obese patient. *Clin Pharmacokinet*. 2004;43(15):1167-1178. doi:10.2165/00003088-200443150-00007

6. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science*. 1999; 284(5420):1677-1679. doi:10.1126/science.284.5420.1677
7. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science*. 1997;276(5309):122-126. doi:10.1126/science.276.5309.122
8. O'Hanlon CJ, Holford N, Sumpter A, Al-Sallami HS. Consistent methods for fat free mass, creatinine clearance and glomerular filtration rate to describe renal function from neonates to adults. *CPT Pharmacometrics Syst Pharmacol*. 2023;12(3):401-412. doi:10.1002/psp4.12924
9. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005;44(10): 1051-1065. doi:10.2165/00003088-200544100-00004
10. Delanaye P, Björk J, Courbebaisse M, et al. Performance of creatinine-based equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment. *Br J Clin Pharmacol*. 2022;88(5):2118-2127. doi:10.1111/bcp.15132
11. Matthews I, Kirkpatrick C, Holford N. Quantitative justification for target concentration intervention-parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. *Br J Clin Pharmacol*. 2004;58(1):8-19. doi:10.1111/j.1365-2125.2004.02114.x
12. 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(19):1737-1749. doi:10.1056/NEJMoa2102953
13. Boutten A, Bargnoux AS, Carlier MC, Delanaye P, Rozet E, Delatour V. Enzymatic but not compensated Jaffe methods reach the desirable specifications of NKDEP at normal levels of creatinine. Results of the French multicentric evaluation. *Clin Chim Acta*. 2013; 419:132-135. doi:10.1016/j.cca.2013.01.021
14. Drion I, Cobbaert C, Groenier KH, et al. Clinical evaluation of analytical variations in serum creatinine measurements: why laboratories should abandon Jaffe techniques. *BMC Nephrol*. 2012;13(1):133. doi:10.1186/1471-2369-13-133
15. Miller WG, Myers GL, Ashwood ER, et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. *Arch Pathol Lab Med*. 2005;129(3):297-304. doi:10.5858/2005-129-297-CMSOTA
16. Panteghini M. Enzymatic assays for creatinine: time for action. *Clin Chem Lab Med*. 2008;46(4):567-572. doi:10.1515/CCLM.2008.113
17. De Lange DW. Glomerular hyperfiltration of antibiotics. *Netherlands J Crit Care*. 2013;17:1-14.
18. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. *Nat Rev Nephrol*. 2012;8(5):293-300. doi:10.1038/nrneph.2012.19
19. Colin PJ, Allegaert K, Thomson AH, et al. Vancomycin pharmacokinetics throughout life: results from a pooled population analysis and evaluation of current dosing recommendations. *Clin Pharmacokinet*. 2019;58(6):767-780. doi:10.1007/s40262-018-0727-5
20. Boyd E. *The Growth of the Surface Area of the Human Body*. University of Minnesota Press; 1935.
21. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013; 13(1):59. doi:10.1186/1471-2431-13-59
22. Fuchs A, Guidi M, Giannoni E, et al. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates. *Br J Clin Pharmacol*. 2014;78(5):1090-1101. doi:10.1111/bcp.12444
23. Holford NH. The visual predictive check—superiority to standard diagnostic (Rorschach) plots. Page 14 Abstr 738 [www.page-meeting.org/?abstract=738 accessed 21 Dec 2023] Pamplona, Spain, 2005.
24. Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. *Comput Methods Programs Biomed*. 1999;59(1):19-29. doi:10.1016/S0169-2607(98)00098-4
25. Alexander SPH, Kelly E, Mathie A, et al. The concise guide to pharmacology 2019/20: introduction and other protein targets. *Br J Pharmacol*. 2019;176(Suppl 1):S1-S20. doi:10.1111/bph.14747
26. Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. Prediction of fat-free mass in children. *Clin Pharmacokinet*. 2015; 54(11):1169-1178. doi:10.1007/s40262-015-0277-z
27. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013;102(9):2941-2952. doi:10.1002/jps.23574
28. Wilkinson GR, Shand DG. Commentary: a physiological approach to hepatic drug clearance. *Clin Pharmacol Ther*. 1975;18(4):377-390. doi:10.1002/cpt1975184377
29. Pai MP, Sitaruno S, Abdelnabi M. Removing race and body surface area indexation for estimated kidney function based drug dosing: aminoglycosides as justification of these principles. *Pharmacotherapy*. 2023;43(1):35-42. doi:10.1002/phar.2746
30. Severino N, Urzua S, Ibocache M, et al. Population pharmacokinetics of amikacin in suspected cases of neonatal sepsis. *Br J Clin Pharmacol*. 2023;89(7):2254-2262.
31. Valentin J (Ed). Basic anatomical and physiological data for use in radiological protection: reference values. *Ann ICRP*. 2002;32(3-4):1-277. doi:10.1016/S0146-6453(03)00002-2
32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41. doi:10.1159/000180580
33. Brion N, Barge J, Godefroy I, et al. Gentamicin, netilmicin, dibekacin, and amikacin nephrotoxicity and its relationship to tubular reabsorption in rabbits. *Antimicrob Agents Chemother*. 1984;25(2):168-172. doi:10.1128/AAC.25.2.168
34. Contrepois A, Brion N, Garaud JJ, et al. Renal disposition of gentamicin, dibekacin, tobramycin, netilmicin, and amikacin in humans. *Antimicrob Agents Chemother*. 1985;27(4):520-524. doi:10.1128/AAC.27.4.520
35. Kan W-C, Chen Y-C, Wu V-C, Shiao C-C. Vancomycin-associated acute kidney injury: a narrative review from pathophysiology to clinical application. *Int J Mol Sci*. 2022;23(4):2052. doi:10.3390/ijms23042052
36. Golper TA, Noonan HM, Elzinga L, et al. Vancomycin pharmacokinetics, renal handling, and nonrenal clearances in normal human subjects. *Clin Pharmacol Ther*. 1988;43(5):565-570. doi:10.1038/clpt.1988.74
37. Emoto C, Johnson TN, McPhail BT, Vinks AA, Fukuda T. Using a vancomycin PBPK model in special populations to elucidate case-based clinical PK observations. *CPT Pharmacometrics Syst Pharmacol*. 2018; 7(4):237-250. doi:10.1002/psp4.12279
38. Ferreira A, Martins H, Oliveira JC, Lapa R, Vale N. In silico pharmacokinetic study of vancomycin using PBPK modeling and therapeutic drug monitoring. *Curr Drug Metab*. 2021;22(2):150-162. doi:10.2174/1389200221999210101232417
39. Maruyama T, Kimura T, Ebihara F, Kasai H, Matsunaga N, Hamada Y. Comparison of the predictive accuracy of the physiologically based pharmacokinetic (PBPK) model and population pharmacokinetic (PPK) model of vancomycin in Japanese patients with MRSA infection. *J Infect Chemother*. 2023;29(12):1152-1159. doi:10.1016/j.jiac.2023.08.017
40. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics*. 1961; 28(2):169-181. doi:10.1542/peds.28.2.169

41. Friis-Hansen B. Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. *Pediatrics*. 1971;47(Supplement_1):264-274. doi:10.1542/pedsv47is1fullP
42. Llanos-Paez CC, Staatz CE, Lawson R, Hennig S. Differences in the pharmacokinetics of gentamicin between oncology and nononcology pediatric patients. *Antimicrob Agents Chemother*. 2020;64(2):e01730-e01719. doi:10.1128/AAC.01730-19
43. Holford N, Holford SD. NextDose (www.nextdose.org) a web-based collaborative tool for target concentration intervention. 2021.
44. Holford NH, Ma G, Metz D. TDM is dead. Long live TCI! *Br J Clin Pharmacol*. 2022;88(4):1406-1413. doi:10.1111/bcp.14434

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Holford N, O'Hanlon CJ, Allegaert K, et al. A physiological approach to renal clearance: From premature neonates to adults. *Br J Clin Pharmacol*. 2024;90(4):1066-1080. doi:10.1111/bcp.15978