AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

A Population Pharmacokinetic Model of Gentamicin in Pediatric Oncology Patients To Facilitate Personalized Dosing

C. C. Llanos-Paez,[a] C. E. Staatz,[a] R. Lawson,[b] S. Hennig[a]

School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia[a]; The Lady Cilento Children's Hospital, Brisbane, Queensland, Australia[b]

ABSTRACT To ensure the safe and effective dosing of gentamicin in children, therapeutic drug monitoring (TDM) is recommended. TDM utilizing Bayesian forecasting software is recommended but is unavailable, as no population model that describes the pharmacokinetics of gentamicin in pediatric oncology patients exists. This study aimed to develop and externally evaluate a population pharmacokinetic model of gentamicin to support personalized dosing in pediatric oncology patients. A nonlinear mixed-effect population pharmacokinetic model was developed from retrospective data. Data were collected from 423 patients for model building and a further 52 patients for external evaluation. A two-compartment model with first-order elimination best described the gentamicin disposition. The final model included renal function (described by fat-free mass and postmenstrual age) and the serum creatinine concentration as covariates influencing gentamicin clearance (CL). Final parameter estimates were as follow CL, 5.77 liters/h/70 kg; central volume of distribution, 21.6 liters/70 kg; peripheral volume of distribution, 13.8 liters/70 kg; and intercompartmental clearance, 0.62 liter/h/70 kg. External evaluation suggested that current models developed in other pediatric cohorts may not be suitable for use in pediatric oncology patients, as they showed a tendency to overpredict the observations in this population. The final model developed in this study displayed good predictive performance during external evaluation (root mean square error, 46.0%; mean relative prediction error, −3.40%) and may therefore be useful for the personalization of gentamicin dosing in this cohort. Further investigations should focus on evaluating the clinical application of this model.

KEYWORDS pharmacokinetics, gentamicin, NONMEM, pediatrics, oncology, pharmacometrics, population pharmacokinetics

Received 3 February 2017 **Returned for modification** 11 April 2017 **Accepted** 13 May 2017

Accepted manuscript posted online 22 May 2017

Citation Llanos-Paez CC, Staatz CE, Lawson R, Hennig S. 2017. A population pharmacokinetic model of gentamicin in pediatric oncology patients to facilitate personalized dosing. Antimicrob Agents Chemother 61:e00205-17. https://doi.org/10.1128/AAC.00205-17.

Address correspondence to C. C. Llanos-Paez, c.llanospaez@uq.edu.au.

Febrile neutropenia induced by chemotherapy is a common complication in pediatric oncology patients. Neutropenic patients are more susceptible to the development of infections (1). Sepsis is the primary cause of mortality and morbidity in pediatric oncology patients with febrile neutropenia (2). The rate of mortality due to sepsis is 1.6-fold higher for oncology pediatric patients than it is for other pediatric patients (3). Aminoglycoside antibiotics, such as gentamicin, in combination with other broad-spectrum antibacterial agents play an important role in managing infectious complications in these individuals and are used as second-line therapies when treating Gram-negative bacterial infections and when resistance to first-line agents develops (4).

Gentamicin has a narrow therapeutic window and displays large pharmacokinetic variability. High levels of and prolonged exposure to gentamicin has been associated with nephro- and ototoxicity (5, 6). Pediatric oncology patients often receive long

courses of gentamicin on multiple occasions alongside chemotherapy, which further increases the risk of toxicity.

Physiological changes (e.g., the presence of fever, augmented renal clearance, decreased muscle mass, or malnutrition) in oncology patients and administration of chemotherapy can alter a patient's body composition and the pharmacokinetics of gentamicin, increasing the difficulty of identifying the optimal dose (7–9). Increased clearance (CL) and an increased volume of distribution (*V*) for gentamicin have been seen in adults (7) and pediatric patients (8, 10) with cancer. Augmented renal clearance, possibly due to systemic inflammation, has also been reported in febrile neutropenic patients (11). However, when the CL of gentamicin was normalized by body surface area, it decreased in those patients receiving prior nephrotoxic chemotherapy compared to those who did not receive nephrotoxic chemotherapy (8).

The Australian Therapeutic Guidelines (12) recommend that for safety and efficacy reasons, aminoglycoside antibiotic doses should be adjusted on the basis of a computerized method, such as Bayesian forecasting. While the log-linear regression method is more commonly used (13), it may be more invasive, tedious, and reactive in nature than Bayesian forecasting. The former requires at least 2 blood sample measurements for predictions (14), whereas Bayesian forecasting may require only 1 sample, and it is not able to give dosage predictions until a dose has first been administered. In adults with febrile neutropenia, a Bayesian approach has been shown to increase the number of patients achieving the desired target exposure to gentamicin compared to the number achieving the desired target obtained when the log-linear regression method is used (15).

To be able to perform dosage individualization through Bayesian forecasting, a population pharmacokinetic model which characterizes typical pharmacokinetic parameter values, between- and within-subject pharmacokinetic variability, and influential covariate factors associated with the drug of interest in the cohort receiving such therapy first needs to be developed. Few population pharmacokinetic models of gentamicin have been developed in children between 2 and 18 years of age (16–18), and to our knowledge, no models specifically characterizing pediatric oncology patients currently exist. Application of a relevant population model in a Bayesian forecasting program would likely improve the individualization of gentamicin dosing in pediatric oncology patients (15, 19).

This study aimed to describe the population pharmacokinetics of gentamicin in pediatric oncology patients with febrile neutropenia; evaluate the influences of covariates, such as concomitant chemotherapy treatment; characterize pharmacokinetic variability in this population; and externally evaluate the predictive performance of this model as well as previously published models in a separate patient cohort.

RESULTS

Patients and data. Data from a total of 423 pediatric oncology patients (219 males [52%]) with 2,422 gentamicin concentration-time data points were used for model development. Eighty-eight percent of these patients had febrile neutropenia, and 12% had fever-free neutropenia. The patients' median postnatal age was 5.18 years (range, 0.2 to 18.2 years), the patients' median weight was 19.4 kg (range, 4.8 to 102.8 kg), and the patients' median fat-free mass (FFM) was 15.7 kg (range, 3.4 to 72.6 kg). Seventy-three patients (17%) were younger than 2 years of age, 247 patients (59%) were 2 to 10 years old, and 103 patients (24%) were older than 10 years of age. Gentamicin concentration measurements ranged from 0.3 to 62.5 mg/liter, with sampling times after the end of the infusion ranging from 0.5 to 36.0 h. A total of 372 (15%) gentamicin measurements were below the lower limit of quantitation (LLOQ) at an average of 15 h after dosing. For model evaluation, data from 52 pediatric oncology patients (22 males [42%]) with 174 gentamicin concentration-time points were used. The patients' median postnatal age was 7.9 years (range, 0.7 to 16.8 years), the patients' median weight was 22.2 kg (range, 6.2 to 121.0 kg), and the patients' median FFM was 20.5 kg (range, 5.3 to 62.2 kg). Eight patients (15%) were younger than 2 years of age, 33

TABLE 1 Demographic and clinical information for all patients included in model building and evaluation analysis

Patient characteristic	Values	
	Model-building data (n = 423)	Model evaluation data (n = 52)
Median (range):		
Total body wt (kg)	19.4 (4.8–102.8)	22.2 (6.22–121)
FFM (kg)	15.7 (3.4–72.6)	20.5 (5.25–62.2)
Postnatal age (yr)	5.18 (0.2–18.2)	7.86 (0.69–16.8)
Postmenstrual age (wk)	309 (50.9–985)	450 (76.0–916)
Ht (cm)	110.2 (48.8–182.3)	127 (67.5–175)
No. (%) of patients aged (yr):		
<2	73 (17.3)	8 (15.4)
2–10	247 (58.4)	33 (63.5)
>10	103 (24.3)	11 (21.1)
No. (%) male/female patients	219 (52)/204 (48)	22 (42)/30 (58)
Median (range):		
Serum creatinine concn (μmol/liter)		
Below the lowest reportable limit[a]	33.0 (21.0–204.0)	34.0 (21.5–359)
Above the lowest reportable limit	42.0 (30.0–204.0)	43.0 (30.0–359)
Creatinine clearance (ml/min/1.73 m^2)[b]	126 (11.5–225.2)	132 (9.08–186)
Gentamicin dosing regimen (mg/kg)	7.35 (0.80–15.0)	7.33 (1.98–10.8)
Time of sampling after dosing (h)	6.50 (0.5–36.0)	3.34 (0.75–34.4)
No. of gentamicin concn	2,422	174
No. (%) of gentamicin concn below limit of quantification	372 (15)	16 (9)
No. (%) of patients who received nephrotoxic drugs (cisplatin and carboplatin)	101 (24)	6 (11.5)

[a]Serum creatinine concentration below the lowest reportable limit set to an expected creatinine concentration physiological mean (42).
[b]Creatinine clearance calculated using the formula of Schwartz et al. (45), with the serum concentration below the lowest reportable limit being set to an expected physiological mean creatinine concentration (42).

patients (64%) were 2 to 10 years old, and 11 patients (21%) were older than 10 years of age. Gentamicin concentration measurements ranged from 0.5 to 30.8 mg/liter, with samples being taken from 0.75 to 34.3 h after the end of the infusion. A total of 16 (9%) gentamicin measurements were below the LLOQ. Key patient demographic characteristics, laboratory values, and gentamicin dosing information are summarized in Table 1.

Pharmacokinetic model. A two-compartmental model with first-order elimination best described the data (change in the objective function value [ΔOFV] = −332.7 compared to a one-compartmental model). The typical CL estimated was 5.77 liters/h/70 kg, and the apparent volume of distribution of the central compartment (V_1) was 17.4 liters/70 kg. Between-subject variability (BSV), including a correlation between CL and V_1 (ΔOFV = −156.5) and between-occasion variability (BOV) on CL (ΔOFV = −516.4), was estimated for CL, V_1, and the apparent volume of distribution of the peripheral compartment (V_2).

Inclusion of the effect of maturation of the glomerular filtration rate (GFR_{mat}) on CL and the effect of either FFM, body weight, or normal fat mass (NFM) on V_1, intercompartmental clearance (Q), and V_2 improved the fit and increased the explained variability. The use of any body size descriptor (body weight, NFM, or FFM) in the GFR_{mat} equation and for V_1, Q, and V_2 resulted in a significant drop in the OFV (ΔOFV = −406.6, ΔOFV = −403.1, and ΔOFV = −408.3, respectively) (see Table S1 in the supplemental material). However, according to the Akaike information criterion (AIC), FFM fit the data best compared to body weight and NFM. Addition of GFR_{mat} increased the explained parameter variability (EPV) on CL (change in EPV [ΔEPV] = 1.15 liters/h), as did inclusion of FFM on V_1 (ΔEPV = 12.67 liters) (Table S1). In addition to GFR_{mat}, inclusion of an association between the serum creatinine concentration (Scr) measurement and gentamicin CL using a power model (ΔOFV = −324.2) further significantly improved the fit. Inclusion of Scr increased EPV on CL compared to the previous model that included only GFR_{mat} (Table S1). In subsequent steps, inclusion of the effect of the use of

nephrotoxic drugs and body temperature on gentamicin CL resulted in nonsignificant improvements (ΔOFV = −2.80 and −1.30, respectively). Typical pharmacokinetic parameter estimates for the base and final models are shown in Table 2.

Model selection and internal model evaluation. Visual predictive check (VPC) plots associated with the final model indicated good agreement between the observed and predicted data (Fig. 1). VPC, normalized prediction distribution errors (npde), and goodness-of-fit plots associated with the final model are shown in Fig. 1.

Results from the nonparametric bootstrap were in agreement with the population pharmacokinetic parameters in the final model with narrow 95% confidence intervals (Table 2). As the eta shrinkage on CL, V_1, and V_2 was relatively high in the final model (43%, 58%, and 66%, respectively), the diagnostic use of goodness-of-fit plots has been limited (20), and these have not been presented.

External evaluation of the final model and models published in the literature. From the literature search, only three population pharmacokinetic models of gentamicin developed in pediatric populations were identified (Table 3) (16, 17, 21). These models, together with the final model from this study, were tested regarding their predictive performance with the external data set. Observed versus population predicted concentration-time plots and VPC plots obtained from all four models generated during external evaluation are displayed in Fig. S1 and 2, respectively. Of the four models evaluated, the final population model developed in this study was the least biased, with a mean relative prediction error (MRPE) of −3.40%, and the most precise, with a root mean square error (RMSE) of 46.0%, compared to the other models tested (Fig. 2).

DISCUSSION

This study developed and externally evaluated a population pharmacokinetic model of gentamicin in pediatric oncology patients that could be used to improve adjustment of the dosage of this drug in this cohort in the future. The final model included an effect of renal function on CL and an effect of FFM on all pharmacokinetic parameters. Prior use of nephrotoxic agents, cisplatin and carboplatin, was not identified as having a significant influence on the CL of gentamicin, after taking into consideration maturation changes in renal function and the potential function impairment observed given a patient's Scr. FFM was identified to be the best descriptor to model the influence of body size on gentamicin CL, V_1, Q, and V_2. The final model displayed good predictive performance, when it was applied to a new data set not used for model development.

Selection of a two-compartment model with first-order elimination to describe the disposition of gentamicin in this study is in agreement with the models selected in a number of studies performed in nononcology children, neonates, and adults included in a recent review (22). Only one population pharmacokinetic model of gentamicin has previously been developed in children who were of an age similar to that of the children included in this study (18). This previous study involved nononcology children (median age, 2.4 years) who received gentamicin intramuscularly (18). The typical gentamicin apparent CL (CL/F) in these children (7.21 liters/h/70 kg for a patient with an average Scr of 33.0 μmol/liter) was higher than that estimated in this study based on intravenous administration (5.77 liters/h/70 kg for a patient with an average Scr of 37.4 μmol/liter). Two studies have been performed in pediatric oncology patients, but they used noncompartmental analysis methods (8, 10). In the first study (8), typical CL values of 9.33 liters/h/70 kg and 10.3 liters/h/70 kg were reported in pediatric patients receiving and not receiving chemotherapy, respectively. In the second study (10), a typical CL of 8.10 liters/h/70 kg was reported. Comparison of the CL values of gentamicin obtained in this study with the values published in the literature is difficult because most previous studies were primarily based on neonates or infants and involved different analysis techniques. The typical V_1 estimated in this study (21.6 liters/70 kg) was similar to that described in other reports; however, it was lower than that reported previously in nononcology children (24.5 liters/70 kg) and preterm

TABLE 2 Population pharmacokinetic parameter estimates of base and final models and bootstrap results from final model[a]

Base model							Final model							Mean (95% CI) bootstrap value (n = 1,000)		
	Estimate		BSV		BOV			Estimate		BSV		BOV			CV (%)	
Parameter	Value	RSE (%)	CV (%)	RSE (%)	CV (%)	RSE (%)	Parameter	Value	RSE (%)	CV (%)	RSE (%)	CV (%)	RSE (%)	Estimate	BSV	BOV
No. of parameters	26						No. of parameters	27						27		
OFV	3,460						OFV	2,729						2,704 (2,239–3,219)		
CL (liters/h)	2.08	3.02	43.8	5.53	24.3	3.93	CL (liters/h/70 kg)	5.77	1.78	16.0	9.91	20.7	2.15	5.76 (5.59–5.93)	16.0 (12.9–18.5)	20.8 (19.2–22.1)
V_1 (liters)	5.16	4.26	50.3	6.55			V_1 (liters/70 kg)	21.6	2.86	21.5	17.8			21.5 (20.3–22.6)	21.3 (13.7–27.1)	
Q (liters/h)	0.22	6.76					Q (liters/h/70 kg)	0.62	4.98					0.63 (0.57–0.68)		
V_2 (liters)	3.34	15.7	73.5	15.4			V_2 (liters/70 kg)	13.8	10.5	62.4	7.34			13.5 (10.8–16.7)	60.9 (44.1–76.3)	
Covariate model θ_{Scr}								0.55	8.84					0.55 (0.47–0.63)		
Correlation (%) between CL and V_1	93.6	6.55						69.2	17.6					69.1 (53.9–75.5)		
Residual error model																
Proportional (%)	26.8	5.86						27.5	3.47					27.2 (24.8–30.1)		
Additive (mg/liter)	0.05	11.5						0.04	15.1					0.05 (0.03–0.06)		

[a]BOV, between-occasion variability; BSV, between-subject variability; CI, confidence interval; CL, clearance; CV, coefficient of variation; OFV, objective function value; RSE, relative standard error; Q, intercompartmental clearance; Scr, serum creatinine concentration; V_1, apparent volume of distribution of the central compartment; V_2, apparent volume of distribution of the peripheral compartment; θ_{Scr}, effect of serum creatinine on clearance. The final model was as follows: CL (in liters per hour) = $5.77 \times (GFR_{mat}/100) \times [Scr_{mean}/Scr_i)^{0.55}]$, V_1 (in liters) = $21.6 \times$ (FFM/70), Q (in liters per hour) = $0.62 \times (FFM/70)^{0.75}$, V_2 (in liters) = $13.8 \times$ (FFM/70), and GFR_{mat} (in milliliters per minute) = $(FFM/70)^{0.75} \times [PMA^{3.33}/(55.4^{3.33} + PMA^{3.33})] \times 112$, where GFR_{mat} is maturation of the glomerular filtration rate; Scr_{mean} is the mean serum creatinine concentration calculated using a formula described by Ceriotti et al. (42); Scr_i is the serum creatinine concentration for individual patient i; FFM (in kilograms) is the fat-free mass; and PMA (in weeks) is postmenstrual age considering 40 weeks of gestation.

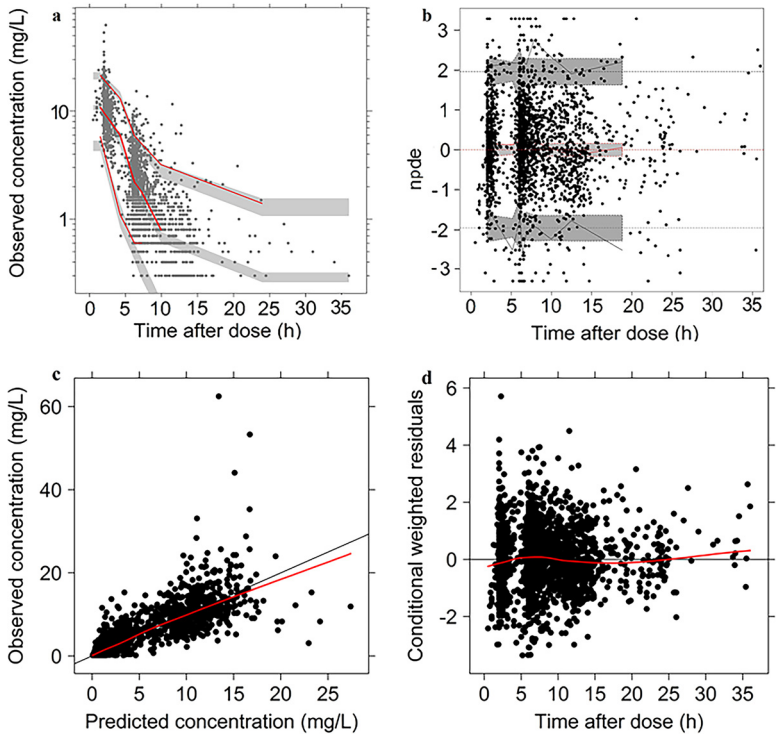

FIG 1 (a) Visual predictive check plot based on 500 simulations associated with the final population pharmacokinetic model. Gray dots, observed data; red line, the median and 95th and 5th percentiles of the observed data; black dashed line, median and 95th and 5th percentiles of the simulated data; gray areas, 95% confidence interval of the simulated data; (b) normalized prediction distribution errors based on 1,000 simulations associated with the final population pharmacokinetic model versus time after dose (black dots, observed data; gray area, 95% confidence interval of the simulated data); (c) observed versus population predicted gentamicin serum concentrations (black dots, observed data; black line is the line of identity and red line is a smooth); (d) conditional weighted residuals versus time after dose associated with the final population pharmacokinetic model (black dots, observed data; black line is the line of identity and red line is a smooth).

neonates (31.1 liters/70 kg) and higher than that reported in term neonates (19.3 liters/70 kg) (22).

The final model included an effect of body size in terms of FFM on all pharmacokinetic parameters. When the final model was applied to an external data set, it predicted gentamicin concentrations more accurately and precisely than a model using NFM on all pharmacokinetic parameters. A recent review of population pharmacokinetic models of gentamicin found that total body weight was the most common covariate included as a body size descriptor on CL and V_1 (22). Considering that before 2015 no FFM equation for pediatrics was available (23), the inclusion of FFM in models for pediatric populations was limited. This study found that FFM explained more variability between subjects than other body size descriptors, possibly due to the fact that gentamicin is highly hydrophilic and mainly distributes into muscle mass or lean body weight rather than fat. One study of gentamicin in elderly patients included the effect of FFM on V_1 (24), and another reported that FFM improved the prediction of GFR in pediatric patients (25).

An equation describing changes in renal function over time due to organ maturation (GFR_{mat}) was utilized here. This equation was originally developed from a large study involving 923 patients ranging from premature neonates to young adults, of which most had normal renal function and only 5% were known oncology patients (25). We found that additional inclusion of the effect of Scr on CL after consideration of renal function maturation through GFR_{mat} further improved the model fit. An accurate bedside estimate of renal function does not exist for young children, and Scr is not generally considered to be a good marker to describe renal function maturation in

TABLE 3 Summary of published population pharmacokinetic models of gentamicin identified for external evaluation[a]

Model (reference)	No. of patients (no. of samples)	Mean ± SD or median (range)			Structural model	Parameter value and covariate relationships included	BSV (%)	Residual unexplained variability
		Age[b]	Body wt (kg)	CL_{CR} (ml/min)				
Final model	423 pediatric oncology patients (2,422)	5.18 (0.2–18.2)	19.4 ± 16.5 (4.8–102.8)	114.4 (11.5–206.5)	2 CMT	CL (liters/h) = 5.77 × (GFR_{mat}/100) × (Scr_{mean}/Scr_i)$^{0.55}$; V_1 (liters) = 21.6 × (FFM/70); V_2 (liters) = 13.8 × (FFM/70); Q (liters/h) = 0.62 × (FFM/70)$^{0.75}$	CL, 16.0 [20.7][c]; V_1, 21.5; V_2, 62.4	Prop, 27.5%; Add, 0.04 mg/liter
Model 1 (16)	26 children with malnutrition (96)	1.72 ± 1.33 (0.25–5)	7.10 ± 2.40	NR	1 CMT	CL (liters/h) = 1.15 × (PNA/median PNA)$^{0.321}$; V (liters) = 2.33 × (wt/median wt)$^{0.743}$	CL, 47.2; V, 35.6	Prop, 24%
Model 2 (21)	208 infants (335)	0.46 ± 0.40	6.4 ± 2.2	76.7 ± 36.9	2 CMT	CL (liters/h) = 0.12 × wt + 0.06 × (CL_{CR}/75); V_1 (liters) = 0.35 × wt; V_2 (liters) = 2.3; Q (liters/h) = 0.23	CL, 26.4; V_1, 26.5	Prop, 11.2%
Model 3 (17)	50 neonates, infants, and children (238)	0.44 (1 day–15 yr)	4.8 (2–80)	NR	2 CMT	CL (liters/h) = 2.09 × (PNA/162)$^{0.14}$ × (wt/70)$^{0.75}$; V_1 (liters/kg) = 0.35 × wt; V_2 (liters) = 3.78; Q (liters/h) = 0.18	CL, 52; V_1, 10.3	Add, 0.76 mg/liter

[a]Add, additive error; BSV, between-subject variability; CL, clearance of gentamicin; CL_{CR}, creatinine clearance; CMT, compartmental model with the indicated number of compartments; GFR_{mat}, maturation of glomerular filtration rate using the formula of Rhodin et al. (25); FFM, fat-free mass (in kilograms); NR, not reported; PNA, postnatal age (in years); Prop, proportional error; Q, intercompartmental clearance; Scr, serum creatinine concentration; Scr_i, serum creatinine concentration for individual patient i; Scr_{mean}, Scr standardized to an expected physiological mean creatinine concentration (42); V_1, apparent volume of distribution of the central compartment; V_2, apparent volume of distribution of the peripheral compartment; wt, body weight (in kilograms).

[b]Units for age are years, unless indicated otherwise.

[c]Value in brackets indicates between-occasion variability [BOV (%)].

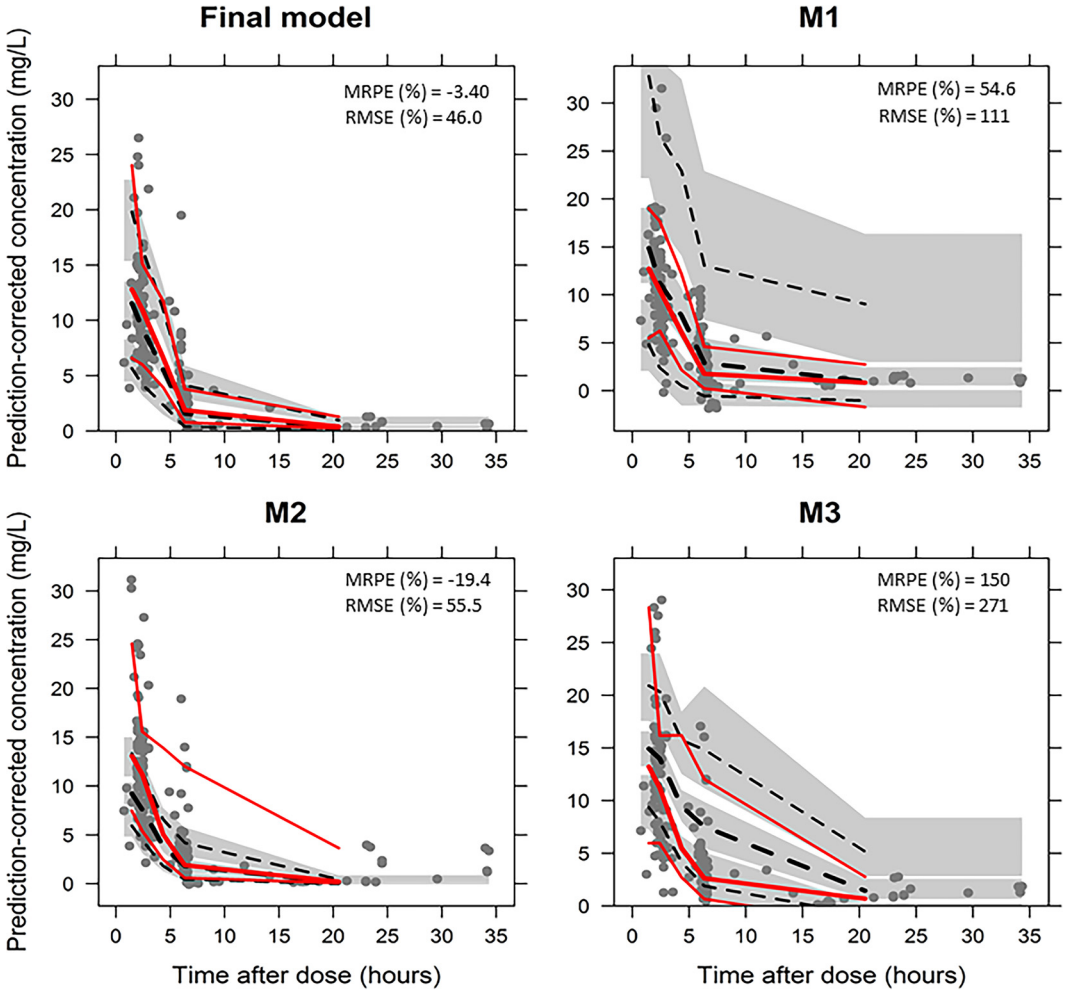

FIG 2 Visual predictive check plot based on 500 simulations associated with this study's final population pharmacokinetic model and three other published population pharmacokinetic models of gentamicin in children generated during external evaluation. Gray dots, observed data; red lines, median and 95th and 5th percentiles of the observed data; black dashed lines, median and 95th and 5th percentiles of simulated data; gray areas, 95% confidence interval of simulated data. The predictive performance for each model is presented numerically with the relative root mean square error (RMSE; in percent) and the mean relative prediction error (MRPE; in percent). M1 to M3, models 1 to 3 from previous studies (see references 16, 21, and 17 respectively).

pediatric patients, especially in oncology patients, due to the lack of muscle mass (26), though in this study, for patients with an Scr of >30 μmol/liter, Scr appeared to be a marker of renal dysfunction, which is not accounted for in the GFR renal maturation equation. According to our final model, a 2-fold increase in Scr in patients with an Scr of >30 μmol/liter led to a 32% decrease in gentamicin CL. Inclusion of Scr in the model was further supported by an increase in EPV and a significant drop in OFV. A limitation of using Scr in this study was that 52% of Scr measurements were <30 μmol/liter; thus, the model does not account for renal dysfunction in patients with an Scr of <30 μmol/liter. Inclusion of covariates resulted in a large decrease in BSV in CL and V_1 between the base model and the final model, namely, 28% and 29%, respectively (Table 2). Both BSV and BOV were below 21% for CL; however, BOV was slighter higher than BSV, which may have been due to underlying changes in the patient's physiological condition with cancer treatment over time.

The usage of cisplatin and carboplatin was not found to have a significant effect on gentamicin CL. It should be noted, however, that only 24% of patients received these drugs in the 6-month period prior to gentamicin administration, the window considered during modeling. This window may be too wide or narrow for examination (27,

28), and cumulative lifetime use was not assessed. Moreover, inclusion of patient Scr values within the model may already account for any potential nephrotoxicity caused by these agents. Further attempts were made to assess the influence of cumulative doses of cisplatin and carboplatin and the timing of their coadministration on gentamicin CL, but no significant relationships were identified.

One previous study reported that body temperature can influence gentamicin CL in pediatric patients (18). Here, the influence of body temperature on gentamicin CL did not show significance. Body temperature may not have been a suitable marker for critically ill patients here, possibly due to the potential use of antipyretics, resulting in a median body temperature of 36.6°C during gentamicin therapy. Information on antipyretic usage was not collected in this study; however, antipyretics are part of the standard treatment for febrile neutropenia.

Previous pharmacokinetic studies using noncompartmental pharmacokinetic analysis suggested gentamicin starting doses of between 7.5 and 10.8 mg/kg of body weight for pediatric oncology patients (8, 10, 29). While exposure targets have not been fully elucidated in this population, guidelines typically recommend that an area under the concentration-time curve from time zero to 24 h (AUC_{24})-to-bacterial MIC ratio (AUC_{24}/MIC) of between 80 and 100 and/or a maximum concentration (C_{max})-to-MIC ratio (C_{max}/MIC) of greater than 10 be targeted (30, 31). These targets were obtained from clinical studies performed in adults and consider several different microorganisms (32, 33). Given these targets and the estimated population CL in this study, an initial dose of 8.0 mg/kg would be required for a typical patient in this study to achieve this target, which is in agreement with previous dose recommendations in this population.

External model evaluation showed that previously published pediatric models overpredicted exposure compared to that predicted by our model. This is not unexpected, as the previous models, even though only models including pediatric patients were considered, were based on different patient cohorts in terms of age, disease state, and medication usage. In addition, two out of three previous models evaluated in this study (16, 21) did not scale CL using an allometric weight with an exponent of 0.75. This may partly explain the poor performance of these models in predicting gentamicin concentrations in our pediatric oncology patients (34). This reinforces the suggestion that a population pharmacokinetic model should not be applied to individuals with characteristics too far beyond the characteristics of the cohort in which it was developed.

On the basis of a visual and numerical assessment, the final model presented in this study displayed good predictive performance and should be clinically useful in the pediatric oncology setting. In addition, all PK parameters were estimated with relative standard errors (RSE) of less than 20%.

This study had limitations in terms of the sparse number of samples per patient per dose collected from the therapeutic drug monitoring (TDM) data available. This is common in special populations, such as pediatric populations (35), and may have led to the higher eta shrinkage and limited the use of diagnostic plots of individual parameter estimates and covariates (20). Furthermore, this study involved retrospective data collection, which relies on the accuracy of written medical charts.

After implementation of the model in a Bayesian forecasting program, future studies should focus on evaluating its clinical applicability to personalize gentamicin dosing regimens, ability to reduce the frequency of blood sampling during TDM, and capacity to improve target attainment compared to current practice in pediatric oncology patients (10).

Conclusions. To the best of our knowledge, the model described in this study presents the first population pharmacokinetic model for gentamicin in pediatric oncology patients with febrile neutropenia. This model was developed on the basis of physiologically plausible covariate parameterization informed by principles of allometric scaling, maturation of the glomerular filtration rate, and standardization for the age-expected serum creatinine concentration. The serum creatinine concentration measurement in this model accounted for renal dysfunction not explained by maturation. The model developed displayed a predictive performance superior to that of a

very limited number of models currently describing gentamicin pharmacokinetics in pediatric patients. This model is now available to be implemented in a Bayesian forecasting program, such as TDMx (http://www.tdmx.eu/) (36), for initial dose individualization and adaptive dose adjustment of gentamicin in pediatric oncology patients, to improve achievement of individualized exposure targets.

MATERIALS AND METHODS

Patients and data. Data for model building and model evaluation were collected retrospectively from the medical records of pediatric oncology patients at The Lady Cilento Children's Hospital (formerly known as the Royal Children's Hospital), Brisbane, Australia. These patients received gentamicin and had drug concentrations measured during routine therapeutic drug monitoring (TDM) between 2008 and 2013 (model-building data set) and 2014 and 2015 (model evaluation data set). Ethics approval for this study was obtained from the University of Queensland Human Research Ethics Unit (approval number: 2012001308) and the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (approval number HREC/12/QRCH/162).

Information on gentamicin dosing regimens, the timing of dose administration, gentamicin serum drug concentrations, and the times of sample collection for drug measurement, along with the patients' age, sex, total body weight, height, Scr, and body temperature readings, were recorded. In addition, information on the date, administration time, and dose of specific nephrotoxic drugs (cisplatin and carboplatin) that the patients had received within the 6 months preceding gentamicin usage were collected.

Gentamicin treatment and blood sampling. Pediatric oncology patients with a neutrophil count of $<$1.0 cells/mm^3 who developed a fever (a temperature of $\geq$38.5°C for at least 1 h or $\geq$38.0°C for at least 2 h) and who were considered critically ill or at high risk received gentamicin, in addition to empirical broad-spectrum penicillin-based therapy. Gentamicin was also added as directed treatment if cultures were confirmed to be positive for Gram-negative bacteria. Gentamicin was given as a 30-min infusion once daily and was initiated at a dose of 7.5 mg/kg for patients under 10 years of age and 6 mg/kg for patients over 10 years of age according to local hospital guidelines. Blood samples for measurement of gentamicin serum concentrations during TDM were generally taken at 2 h and 6 to 12 h postinfusion. In addition, on the basis of clinical judgment, samples were sometimes taken before a subsequent dose (for determination of trough levels).

Gentamicin assay. The gentamicin concentration in serum was measured using a fluorescence polarization immunoassay method at the Pathology Queensland Central Laboratory, Brisbane, Australia. Different immunoassays were applied over time. From 2008 to August 2011, a Beckman Coulter particle-enhanced turbidimetric inhibition immunoassay (PETINIA) run on a Beckman Coulter DXC800 analyzer was used. From August 2011 to November 2011, an Abbott chemiluminescent magnetic microparticle immunoassay run on an Abbot Architect i1000 immunoassay analyzer was used. From November 2011 to December 2012, a Beckman Coulter cloned enzyme donor immunoassay run on a Beckman Coulter DXC800 analyzer was used. From December 2012 onwards, a Beckman Coulter PETINIA run on a Beckman Coulter DXC800 analyzer was used. The lower limit of quantification (LLOQ) varied from 0.3 to 0.6 mg/liter across the immunoassay methods. Within- and between-assay coefficients of variation were below 10% for all immunoassays employed.

Population pharmacokinetic analysis. (i) Software. Population modeling was performed using NONMEM software (version 7.3; Icon Development Solutions, Ellicott City, MD, USA) (37) with an Intel FORTRAN compiler and Perl-speaks-NONMEM (PsN; version 3.5.3) (38). Typical population pharmacokinetic parameters of gentamicin as well as between-subject variability (BSV), between-occasion variability (BOV), and residual unexplained variability (RUV) were estimated via the first-order conditional estimation method with interaction (FOCE+I). Xpose (version 4.4.0; http://xpose.sourceforge.net) and R studio (version 3.1; http://www.r-project.org./) software were used for data exploration and visualization.

(ii) Model development. First, a base model was developed by testing one-, two-, and three-compartment structural disposition models with first-order elimination. Pharmacokinetic parameter values were assumed to be log-normally distributed. BSV was modeled using an exponential model (equation 1) and was initially applied to all pharmacokinetic parameters, and the parameters were removed if they were not supported. BOV was modeled using an additional random effects parameter (equation 2), which was tested one by one on CL and *V*.

$$P_i = \mathrm{TVP} \times e^{\eta_{i,P}} \quad (1)$$

$$P_{ij} = \mathrm{TVP} \times e^{(\eta_{i,P}+\kappa_{i,P})} \quad (2)$$

where TVP is the typical population parameter estimate and P_i is the parameter estimate for individual *i*; $\eta_{i,P}$ is a symmetrically distributed random variable with a mean of zero and a variance of $\omega^2_{\mathrm{BSV\_}P}$, where the square root of the variance represents the reported BSV; and P_{ij} is the parameter value for individual *i* on the *j*th occasion, $\kappa_{i,P}$ is the within-patient random effect, which is independent and normally distributed with a mean of zero and a variance of $\omega^2_{\mathrm{BOV\_}P}$. Proportional, additive, and combined models and different error models for the concentrations measured using different assays were compared during model building to describe RUV. Gentamicin drug concentrations reported as being below the LLOQ were replaced by LLOQ/2 values (39).

Clinical factors investigated for an influence on the pharmacokinetics of gentamicin included the patient's renal function (described by body size and age), Scr measurements, sex, use of nephrotoxic

drugs, and body temperature. After a structural base model was established, potential covariates were screened initially via graphical exploration, considering shrinkage (20). Covariate model building was in the first instance based on physiologically plausible covariate parameterization informed by principles of allometric scaling, maturation of the glomerular filtration rate, and standardization for the age-expected serum creatinine concentration.

The impact of changes in renal function due to maturation on gentamicin clearance was included using the glomerular filtration rate prediction model developed by Rhodin et al. (GFR_{mat}; in milliliters per minute; see equation 3) (25). Three descriptors of body size were tested in the GFR_{mat} equation: total body weight, normal fat mass (NFM) (40), and fat-free mass (FFM) (23). Both, FFM and the fraction of fat mass were used within the NFM calculation, with the fraction of fat mass being estimated. Allometric scaling (34, 41) using each of these three descriptors of body size (total body weight, NFM, and FFM) was applied to all other clearance and distribution parameters according to equation 4.

$$\mathrm{GFR_{mat}} = \left(\frac{\text{size descriptor}_i}{70}\right)^{0.75} \times \frac{\mathrm{PMA}^{3.33}}{55.4^{3.33} + \mathrm{PMA}^{3.33}} \times 112 \tag{3}$$

$$P_i = \mathrm{TVP} \times \left(\frac{\text{size descriptor}_i}{70}\right)^{\text{allometric exponent}} \tag{4}$$

where P_i is the parameter of interest, TVP is the typical population parameter value, and size descriptor$_i$ represents either body weight, FFM, or NFM (in kilograms) for individual *i*, which was standardized to 70 kg, to ease comparison to adult values. PMA is postmenstrual age (in weeks), calculated for each child by addition of 40 weeks, representing a typical gestation period, to their postnatal age.

Afterwards, Scr and body temperature were subsequently tested using a linear, exponential, and/or power model. An inverse relationship between Scr and CL was examined, with Scr being standardized to the mean expected creatinine concentration for a person of the relevant age and sex (42). For patients who had an Scr measurement below the lowest reportable limit ($<$30 μmol/liter), this value was fixed to the mean expected physiological creatinine concentration for a person of the relevant age and sex (42). The categorical covariates sex and use of cisplatin and/or carboplatin within 6 months prior to the gentamicin observation were tested by estimating the typical parameter value for the most common category and then obtaining the fractional difference in the parameter value for the second category compared to that for the first category.

(iii) Model selection and internal model evaluation. For nested models, the difference between a pair of objective function values (OFV) for two models approximates the chi-square (χ^2) statistic, which can be tested for significance ($\chi^2_{1,\,0.05} = 3.84$). The Akaike information criterion (AIC) was used for nonnested models. Further support for model selection was obtained by evaluating the difference in the magnitude of the change in the explained parameter variability (ΔEPV) after covariate inclusion compared to that in the base model (43). Basic goodness-of-fit plots for observations versus population predictions and conditional weighted residuals versus time after dose were examined for internal model evaluation. Model predictive performance was assessed by generating visual predictive check (VPC) plots based on 500 simulations. Plot of normalized prediction distribution errors (npde) versus time after dosing based on 1,000 simulations were also generated and evaluated. The precision of the model parameters was obtained from the relative standard errors and confirmed through nonparametric bootstrapping of the final model with 1,000 replicates.

(iv) External evaluation of the final model and models published in the literature. The model evaluation data set was used to externally evaluate the predictive performance of the final model as well as any previous population models of gentamicin published in the literature that were based on pediatric patients. A literature search was conducted in September 2016 using the PubMed and EMBASE databases with a restriction to English language publications to identify previously published population pharmacokinetic models. The following keywords were used during the search: gentamicin, pediatric, pharmacokinetics, and population pharmacokinetics. Models were included if they were developed in a pediatric population with a postnatal age of ≥5 months using a compartmental approach and were excluded if they did not provide enough information to be fully reproducible.

Each selected population pharmacokinetic model was implemented using NONMEM software, as stated above. Gentamicin concentrations were predicted using information on the gentamicin dosing regimen, time of sample collection for drug measurement, and relevant patient covariate values recorded for the evaluation data set, with pharmacokinetic parameter values and covariate relationships set being those determined in the final model and in the previous publications. The predictive performance of each selected population pharmacokinetic model was assessed visually (predicted concentration [C_{pred}] versus observed concentration [C_{obs}] plots and VPC plots) and numerically. Bias and precision were calculated using the relative root mean square error (RMSE; in percent) (equation 5) and mean relative prediction error (MRPE; in percent) (equation 6) (44):

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{C_{\mathrm{pred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right)_i^2} \times 100 \tag{5}$$

$$\mathrm{MRPE} = \frac{1}{N}\sum_{i=1}^{N}\left(\frac{C_{\mathrm{pred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right)_i \times 100 \tag{6}$$

where *N* is the number of concentration measurements in the sample.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00205-17.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

ACKNOWLEDGMENTS

We acknowledge the Australian Centre of Pharmacometrics for the hardware and NONMEM software licenses. C.C.L.-P. was supported by Becas Chile (CONICYT) through a scholarship and the University of Queensland Graduate School International Travel Award. No external funding supported this study.

C.C.L.-P. collected and analyzed the data and wrote the manuscript. C.E.S., R.L., and S.H. applied for the ethical approval, supported data collection, and provided a critical review of the manuscript. C.E.S. and S.H. supported and reviewed the data analysis and contributed to the writing of the manuscript.

REFERENCES

1. Pizzo PA, Poplack DG, Ovid Technologies Inc. 2011. Principles and practice of pediatric oncology, vol 6th, Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia, PA.
2. Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, Aitken JF. 2012. Childhood cancer mortality in Australia. Cancer Epidemiol 36:476–480. https://doi.org/10.1016/j.canep.2012.06.001.
3. Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. 1997. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). Br J Haematol 99:580–588.
4. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. 2011. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56–e93. https://doi.org/10.1093/cid/cir073.
5. Dahlgren JG, Anderson ET, Hewitt WL. 1975. Gentamicin blood levels: a guide to nephrotoxicity. Antimicrob Agents Chemother 8:58–62. https://doi.org/10.1128/AAC.8.1.58.
6. Paterson DL, Robson JM, Wagener MM. 1998. Risk factors for toxicity in elderly patients given aminoglycosides once daily. J Gen Intern Med 13:735–739. https://doi.org/10.1046/j.1525-1497.1998.00224.x.
7. Higa GM, Murray WE. 1987. Alterations in aminoglycoside pharmacokinetics in patients with cancer. Clin Pharm 6:963–966.
8. Ho KK, Bryson SM, Thiessen JJ, Greenberg ML, Einarson TR, Leson CL. 1995. The effects of age and chemotherapy on gentamicin pharmacokinetics and dosing in pediatric oncology patients. Pharmacotherapy 15:754–764.
9. Rosario MC, Thomson AH, Jodrell DI, Sharp CA, Elliott HL. 1998. Population pharmacokinetics of gentamicin in patients with cancer. Br J Clin Pharmacol 46:229–236.
10. Bialkowski S, Staatz CE, Clark J, Lawson R, Hennig S. 16 September 2016. Gentamicin pharmacokinetics and monitoring in pediatric febrile neutropenic patients. Ther Drug Monit. https://doi.org/10.1097/ftd.0000000000000341.
11. Udy AA, Roberts JA, Lipman J. 2011. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 7:539–543. https://doi.org/10.1038/nrneurol.2011.141.
12. Antibiotic Expert Group. 2014. Therapeutic guidelines: antibiotic, version 15. Therapeutic Guidelines Limited, Melbourne, Australia.
13. Paviour S, Hennig S, Staatz CE. 2016. Usage and monitoring of intravenous tobramycin in cystic fibrosis in Australia and the UK. J Pharm Pract Res 46:15–21. https://doi.org/10.1002/jppr.1145.
14. Barras MA, Serisier D, Hennig S, Jess K, Norris RL. 2016. Bayesian estimation of tobramycin exposure in cystic fibrosis. Antimicrob Agents Chemother 60:6698–6702. https://doi.org/10.1128/AAC.01131-16.
15. Avent ML, Teoh J, Lees J, Eckert KA, Kirkpatrick CM. 2011. Comparing 3 methods of monitoring gentamicin concentrations in patients with febrile neutropenia. Ther Drug Monit 33:592–601. https://doi.org/10.1097/FTD.0b013e31822c78e9.
16. Lares-Asseff I, Perz-Guille MG, Camacho Vieyra GA, Perez AG, Peregrina NB, Lugo Goytia G. 2016. Population pharmacokinetics of gentamicin in Mexican children with severe malnutrition. Pediatr Infect Dis J 35:872–878. https://doi.org/10.1097/INF.0000000000001204.
17. Lopez SA, Mulla H, Durward A, Tibby SM. 2010. Extended-interval gentamicin: population pharmacokinetics in pediatric critical illness. Pediatr Crit Care Med 11:267–274. https://doi.org/10.1097/PCC.0b013e3181b80693.
18. Seaton C, Ignas J, Muchohi S, Kokwaro G, Maitland K, Thomson AH. 2007. Population pharmacokinetics of a single daily intramuscular dose of gentamicin in children with severe malnutrition. J Antimicrob Chemother 59:681–689. https://doi.org/10.1093/jac/dkl561.
19. Fernandez de Gatta MM, Garcia MJ, Lanao JM, Dominguez-Gil A. 1996. Bayesian forecasting in paediatric populations. Clin Pharmacokinet 31:325–330. https://doi.org/10.2165/00003088-199631050-00001.
20. Savic RM, Karlsson MO. 2009. Importance of shrinkage in empirical Bayes estimates for diagnostics: problems and solutions. AAPS J 11:558–569. https://doi.org/10.1208/s12248-009-9133-0.
21. Medellin-Garibay SE, Rueda-Naharro A, Pena-Cabia S, Garcia B, Romano-Moreno S, Barcia E. 2015. Population pharmacokinetics of gentamicin and dosing optimization for infants. Antimicrob Agents Chemother 59:482–489. https://doi.org/10.1128/AAC.03464-14.
22. Llanos-Paez CC, Hennig S, Staatz CE. 2017. Population pharmacokinetic modelling, Monte Carlo simulation and semi-mechanistic pharmacodynamic modeling as tools to personalize gentamicin therapy. 72:639–667. J Antimicrob Chemother https://doi.org/10.1093/jac/dkw461.
23. Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. 2015. Prediction of fat-free mass in children. Clin Pharmacokinet 54:1169–1178. https://doi.org/10.1007/s40262-015-0277-z.
24. Johnston C, Hilmer SN, McLachlan AJ, Matthews ST, Carroll PR, Kirkpatrick CM. 2014. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol 70:549–555. https://doi.org/10.1007/s00228-014-1652-7.
25. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. 2009. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol 24:67–76. https://doi.org/10.1007/s00467-008-0997-5.
26. Skinner R, Cole M, Pearson AD, Keir MJ, Price L, Wyllie RA, Coulthard MG, Craft AW. 1994. Inaccuracy of glomerular filtration rate estimation from height/plasma creatinine ratio. Arch Dis Child 70:387–390. https://doi.org/10.1136/adc.70.5.387.
27. English MW, Skinner R, Pearson AD, Price L, Wyllie R, Craft AW. 1999. Dose-related nephrotoxicity of carboplatin in children. Br J Cancer 81:336–341. https://doi.org/10.1038/sj.bjc.6690697.
28. Skinner R, Parry A, Price L, Cole M, Craft AW, Pearson AD. 2009. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. Eur J Cancer 45:3213–3219. https://doi.org/10.1016/j.ejca.2009.06.032.
29. Inparajah M, Wong C, Sibbald C, Boodhan S, Atenafu EG, Naqvi A, Dupuis LL. 2010. Once-daily gentamicin dosing in children with febrile neutro-

penia resulting from antineoplastic therapy. Pharmacotherapy 30:43–51. https://doi.org/10.1592/phco.30.1.43.
30. Queensland Government. 2016. Tobramycin/gentamicin therapeutic drug monitoring. http://www.childrens.health.qld.gov.au/wp-content/uploads/2016/03/658202.pdf. Accessed 24 November 2016.
31. The Children's Hospital at Westmead. 2015. Aminoglycoside dosing and monitoring. http://www.schn.health.nsw.gov.au/_policies/pdf/2011-8018.pdf. Accessed 24 November 2016.
32. Moore RD, Lietman PS, Smith CR. 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 155:93–99. https://doi.org/10.1093/infdis/155.1.93.
33. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS, Jr. 1999. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 43:623–629.
34. Germovsek E, Barker CI, Sharland M, Standing JF. 2017. Scaling clearance in paediatric pharmacokinetics: all models are wrong, which are useful? Br J Clin Pharmacol 83:777–790. https://doi.org/10.1111/bcp.13160.
35. Jones CD, Sun H, Ette EI. 1996. Designing cross-sectional population pharmacokinetic studies: implications for pediatric and animal studies. Clin Res Regul Aff 13:133–165. https://doi.org/10.3109/10601339609035949.
36. Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C. 2015. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents 45:442–444. https://doi.org/10.1016/j.ijantimicag.2014.12.010.
37. Beal S, Sheiner LB, Boeckmann A, Bauer RJ. 2009. NONMEM user's guides (1989-2009). Icon Development Solutions, Ellicott City, MD.
38. Lindbom L, Pihlgren P, Jonsson EN. 2005. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 79:241–257. https://doi.org/10.1016/j.cmpb.2005.04.005.
39. Beal SL. 2001. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 28:481–504. https://doi.org/10.1023/A:1012299115260.
40. Anderson BJ, Holford NH. 2008. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 48:303–332. https://doi.org/10.1146/annurev.pharmtox.48.113006.094708.
41. Holford NH. 1996. A size standard for pharmacokinetics. Clin Pharmacokinet 30:329–332. https://doi.org/10.2165/00003088-199630050-00001.
42. Ceriotti F, Boyd JC, Klein G, Henny J, Queralto J, Kairisto V, Panteghini M. 2008. Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem 54:559–566. https://doi.org/10.1373/clinchem.2007.099648.
43. Hennig S, Karlsson MO. 2014. Concordance between criteria for covariate model building. J Pharmacokinet Pharmacodyn 41:109–125. https://doi.org/10.1007/s10928-014-9350-8.
44. Sheiner LB, Beal SL. 1981. Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503–512. https://doi.org/10.1007/BF01060893.
45. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. 2009. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637. https://doi.org/10.1681/ASN.2008030287.