Optimizing Aminoglycoside Dosing Regimens for Critically Ill Pediatric Patients with Augmented Renal Clearance: a Convergence of Parametric and Nonparametric Population Approaches

Sean N. Avedissian,^a Roxane Rohani,^{b,c} John Bradley,^{d,e} Jennifer Le,^f Nathaniel J. Rhodes^{b,c}

^aDepartment of Pharmacy Practice and Science, UNMC College of Pharmacy, Omaha, Nebraska, USA

^bMidwestern University, College of Pharmacy Downers Grove Campus, Downers Grove, Illinois, USA

^cCenter of Pharmacometric Excellence, Midwestern University, Downers Grove, Illinois, USA

^dDivision of Infectious Diseases, University of California San Diego School of Medicine, La Jolla, California, USA

^eRady Children's Hospital San Diego, San Diego, California, USA

^fUniversity of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, California, USA

Sean N. Avedissian and Roxane Rohani contributed equally. They completed the modeling and drafted the manuscript; author order is alphabetical.

ABSTRACT Augmented renal clearance (ARC) can occur in critically ill pediatric patients receiving aminoglycosides such as gentamicin and tobramycin, yet optimal dosing strategies for ARC are undefined. We evaluated the probability of achieving efficacious or toxic exposures in pediatrics. Parallel population modeling of concentration strategies were pursued using *Pmetrics* v1.5.2 (nonparametric) and Monolix v2019R2 (parametric). Bayesian exposures were used to classify ARC based on total clearance (CL). The effects of serum creatinine (SCR), creatinine clearance (CRCL), total body weight (TBW), postnatal age (PNA), and ARC were explored as covariates. The probabilities of target attainment (PTA) (i.e., maximum concentration [C_{max}]/MIC, area under the concentration-time curve [AUC]/MIC) and of toxic exposure (PTE) (i.e., minimum concentration [C_{min}] > 2 μ g/ml) were calculated according to PNA and ARC. A total of 123 patients (1 to 21 years old, 56% female) contributed 304 concentrations. A two-compartment model was superior to a one-compartment model in both approaches. Bayesian posterior predicted concentrations from the nonparametric base model fit the data well ($R^2 = 0.96$) and classified 34 patients as having ARC (28%). Both the nonparametric and parametric approaches resulted in allometrically scaling of TBW on volume (V) and clearance (CL). ARC modified CL and central V. CRCL and a maturation function modified CL. ARC was associated with a 1.49- versus 1.66-fold increase in CL and a 1.56- versus 1.66-fold increase in the central V (nonparametric versus parametric). A high dose of 12 mg/kg of body weight/day was required to achieve adequate PTA when MICs were 1 to 2 μ g/ml; ARC lowered achievable MICs. When PNA was <2 years, PTE was increased. Aminoglycoside monotherapy should be avoided in critically ill pediatric patients with ARC when MICs exceed 1 μ g/ml, as optimal exposures are unachievable with standard dosing.

KEYWORDS augmented renal clearance, population-based pharmacokinetic modeling, aminoglycosides

Augmented renal clearance (ARC) is a hyperdynamic state of clearance that exists in contradistinction to acute kidney injury (AKI), which affects critically ill patients (1–7). Whereas AKI is characterized by reductions in organ function which can lead to accumulation of drugs and toxins (8), ARC is marked by rapid clearance which can lead

Citation Avedissian SN, Rohani R, Bradley J, Le J, Rhodes NJ. 2021. Optimizing aminoglycoside dosing regimens for critically ill pediatric patients with augmented renal clearance: a convergence of parametric and nonparametric population approaches. *Antimicrob Agents Chemother* 65:e02629-20. <https://doi.org/10.1128/AAC.02629-20>.

Copyright © 2021 American Society for Microbiology. All Rights Reserved.

Address correspondence to Jennifer Le, jenle@health.ucsd.edu, or Nathaniel J. Rhodes, nrhode@midwestern.edu.

Received 15 December 2020

Returned for modification 3 January 2021

Accepted 22 January 2021

Accepted manuscript posted online

1 February 2021

Published 18 March 2021

to suboptimal drug exposure (9, 10). Delays in effective antimicrobial therapy are particularly concerning in pediatric patients and can lead to increased morbidity and organ dysfunction (11). As such, to overcome the effect of ARC in pediatric sepsis, it is essential to understand the importance of ARC to antimicrobial clearance and distribution.

Aminoglycosides, in combination with beta-lactams, are frequently used in the empirical treatment of sepsis in critically ill pediatric patients (12). Achieving adequate pharmacokinetic/pharmacodynamic (PK/PD) exposures is associated with improved clinical outcomes in patients receiving aminoglycoside who have Gram-negative bacterial infections, like bacteremia, urinary tract infections, and pneumonia (13). Aminoglycosides are concentration-dependent bactericidal agents with a long postantibiotic effect (14). Prior research has associated both the ratio of the peak or maximum concentration ($C_{\max}$) to the pathogen MIC (i.e., $C_{\max}/\text{MIC}$) as well as the ratio of the area under the concentration-time curve (AUC) to the pathogen MIC (i.e., AUC/MIC) with improved outcomes for aminoglycosides (15, 16). As a result, increasing the $C_{\max}/\text{MIC}$ or AUC/MIC for a given patient and infection is expected to increase the odds of clinical cure. Critically ill patients are well-known to exhibit alterations in organ function (e.g., dynamic renal function) (17) and volume of distribution (e.g., burn patients) (18, 19) which can substantially impact the effectiveness of aminoglycoside therapy. Optimizing aminoglycoside dosing for patients with ARC can be expected to be particularly challenging due to the dynamic nature of ARC, the narrow therapeutic window of aminoglycosides, and the relative degree of change in renal drug elimination in critical illness.

Acutely ill pediatric patients are a population at high risk for clinical failure due to the underdosing of antibiotic therapy caused by ARC (5–7, 9, 20). We previously observed that ARC occurs in at least 20% of pediatric intensive care unit (PICU) patients receiving aminoglycoside therapy (6) and that ARC can be classified using Bayesian estimates of drug clearance (CL) (6, 20). However, optimal empirical aminoglycoside dosing regimens that are both safe and effective in this population remain unclear. Importantly, both parametric and nonparametric population PK models can be used to predict the range of PK exposures in patients. Whereas parametric models attempt to describe the population mean parameter estimates and variability, nonparametric approaches seek to identify the most informative set of parameter estimates and their corresponding probabilities within the sample. These divergent approaches could yield very different answers with respect to the effect of ARC on drug distribution and clearance in the critically ill pediatric population. Yet, to date, no study has systematically compared these approaches in pediatric patients with ARC. The current study sought to identify physiologically relevant PK models that describe aminoglycoside CL and evaluate PK/PD exposures in patients with and without ARC utilizing both parametric and nonparametric PK approaches.

RESULTS

Demographics. A total of 123 patients (median [range] postnatal age [PNA], 12 [1 to 21] years) contributed 304 concentrations (mean [range] per patient, 2.5 [1 to 10]). There were 28% peaks, 24% random levels, and 48% trough levels observed. A summary of demographics is included in Table 1. There were 54 (44%) males. The patient sample had a median (interquartile range [IQR]) weight of 36.1 (18.4 to 57.33) kg, a body surface area (BSA) of 1.19 (0.74 to 1.61) m², and a creatinine clearance (CRCL) of 132 (95.7 to 185) ml/min/1.73 m². The median serum creatinine (SCR) was 0.41 mg/dl.

Structural PK model selection. A plot of the observed concentration-time profiles is displayed in Fig. S1 in the supplemental material. Both one- and two-compartment structural models were considered in the parametric and nonparametric model building procedures. In the nonparametric approach, the two-compartment model was found to have improved fitness versus the one-compartment model (Akaike's information criterion [AIC] = 840.7 versus 857.5). In the parametric approach, the two-compartment model also produced improved fitness versus the one-compartment model (change in the objective function value [ΔOFV] = −134.9).

Classification of ARC using Bayesian estimates. The nonparametric method was used to generate individual Bayesian posterior predicted concentrations for all patients.

TABLE 1 Demographics of 123 pediatric patients included in the PK cohort^a

Variable	Unit	Value for variable for the following patients:			
		Not showing ARC based on drug CL (n = 89)		Showing ARC based on drug CL (n = 34)	
		Median	Range	Median	Range
PNA	yr	12	1–21	10	1.25–19
TBW	kg	40.5	5.23–98	26.75	8.1–89.5
CRCL	ml/min/1.73 m ²	126.5	10.9–568.2	165	78.5–545.2
SCR	mg/dl	0.5	0.12–4.8	0.335	0.1–0.71

^aOf the 123 pediatric patients, 45% without augmented renal clearance (ARC) based on drug clearance (CL) were male, and 41% with ARC based on drug CL were male. Abbreviations: PNA, postnatal age; TBW, total body weight; CRCL, creatinine clearance; SCR, serum creatinine.

The unadjusted two-compartment model base consisted of 29 support points, and this model was used to estimate each patient's concentration-time profile for the first 24 h of therapy. The R^2 of the posterior model for the observed data was 0.96 (bias, $-0.162 \mu\text{g/ml}$; imprecision, $0.0831 \mu\text{g}^2/\text{ml}^2$). The estimated median (IQR) area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was 54.2 (36.9 to 64.6) $\text{mg} \cdot \text{h/liter}$, and the estimated median (IQR) posterior clearance from 0 to 24 h (CL_{0-24}) was 106 (81.2 to 136) ml/min/1.73 m^2 . Using the definition of $>130 \text{ ml/min/1.73 m}^2$ of drug clearance and the non-parametric posterior estimates, 34 patients (28%) were classified as having augmented renal clearance (ARC). Using the same definition for ARC substituting creatinine clearance (CRCL) for drug clearance, 63 patients (51%) would have been classified as having ARC.

ROC analyses of CRCL for correct classification of ARC. A visual display of the predictive performance of CRCL (versus drug clearance) is shown in Fig. 1. The area under the receiver operating characteristic (ROC) curve for CRCL versus ARC was 0.6471. A CRCL threshold of $\geq 162.1 \text{ ml/min/1.73 m}^2$ yielded moderate sensitivity, moderately high specificity, and a modest correct classification rate (52.94%, 75.28%, and 69.11%, respectively). A CRCL threshold of $\geq 250.6 \text{ ml/min/1.73 m}^2$ yielded poor sensitivity, high specificity, and improved correct classification (20.59%, 94.38%, and 73.98%, respectively). A summary of various CRCL cutoff points for ARC can also be found in

FIG 1 Predictive performance via ROC comparative analyses at various CRCL cutoff points for ARC. See Table 2.

TABLE 2 CRCL ROC analysis of the data in Fig. 1

Cutoff point ^a	CRCL ROC analysis				
	ml/min/1.73 m ²	Sensitivity (%)	Specificity (%)	% correctly classified	Maximizes
D	≥78.47	100	11.24	35.77	Sensitivity
C	≥162.1	52.94	75.28	69.11	Mean accuracy
B	≥250.6	20.59	94.38	73.98	Overall accuracy
A	≥568.2	0	100	72.36	Specificity

^aCutoff points shown in Fig. 1.

Fig. 1 and Table 2. CRCL was unable to meaningfully discriminate between patients with ARC according to the posterior estimates of drug CL at an *a priori* threshold of 130 ml/min/1.73 m². Table 3 shows that when using a definition of ≥130 ml/min/1.73 m² to classify ARC, CRCL had 65% sensitivity and 54% specificity for ARC based on drug CL. As a result, only the Bayesian drug CL estimates were utilized to classify ARC in covariate screening and model building procedures.

Covariate screening and model selection. A summary of the parametric covariate screening and model building is provided in Table S1 in the supplemental material. A visual summary of the correlations between unadjusted PK parameters and covariates from the nonparametric base model is shown in Fig. S2. Visual inspection of the covariate plot shown in Fig. 2 of the nonparametric unadjusted CL estimates versus PNA suggested potential nonlinearity; therefore, a maturation Hill-type model was considered in both approaches. In both the parametric and nonparametric methods, standardizing CL and volume (V) (i.e., central volume [Vc] plus peripheral volume [Vp]) to total body weight (TBW) using a fixed allometric scaling factor for CL (power of 3/4) and V (power of 1) yielded significant improvements in model fitness. Modification of CL and Vc (individually and in tandem) by ARC yielded additional gains. Exponential models of male gender, and SCR or CRCL standardized to median covariate values were also considered modifiers of typical CL values. Modification of CL by CRCL yielded superior fits compared to SCR in the parametric approach (ΔOFV −9.42 versus −14.56) and did not differ significantly in the nonparametric approach (AIC = 591.2 versus 589.5; $P > 0.05$). Male gender did not significantly affect CL; however, it showed an association with Vc in the model build but was not retained in the final model (Table S1). Ultimately, the best PK model scaled CL to TBW (allometric scaling) PNA (Hill model) ARC status and CRCL and scaled V to TBW (allometric scaling) and ARC status (nonparametric, final model versus base model, AIC 541.7 versus 840.7; $P < 0.001$; parametric, final model versus base model, ΔOFV −115.62; the condition number of the final model = 32). The parametric and nonparametric estimates from the final covariate-adjusted PK models are shown in Table 4. The nonparametric model indicated that the median patient with ARC would have 1.49-fold higher CL and 1.56-fold greater Vc compared to a patient without ARC, whereas the parametric model predicts that the average patient with ARC would have 1.66-fold (i.e., $e^{0.507}$) higher CL and 1.66-fold (i.e., $e^{0.505}$) greater Vc. Median (IQR) covariate-adjusted estimates for CL and V (i.e., Vc plus Vp) for the final nonparametric model were 1.49 (0.72 to 2.48) liter/h and 26.7 (16.0 to 48.5) liter, and 2.98 (1.68 to 4.24) liter/h and 49 (24.3 to 75.6) liter for the final parametric model, respectively.

Model diagnostics and simulations. A plot of the observed versus predicted concentrations is shown for the final nonparametric and parametric models in Fig. 3. The bias and imprecision of the final nonparametric population model were −0.713 $\mu\text{g/ml}$ and 8.54 mcg^2/ml^2 , respectively. The final parametric population model predictions had a root mean squared error (RMSE) of 1.77 $\mu\text{g/ml}$, whereas the individual predictions had a RMSE of 1.03 $\mu\text{g/ml}$ for observed concentrations. Figure S3 shows the plots of normalized prediction distribution errors (NPDE) versus time, and predicted concentrations for the final nonparametric and parametric models reflected the sparse nature of the sampling. Overall, 94.1% of the observations fell within the predictive interval of

TABLE 3 Classification matrix of ARC according to CRCL^a

Parameter	ARC	CRCL > 130 ml/min/1.73 m ²		Sensitivity for ARC (%)
		No ARC	ARC	
Drug CL > 130 ml/min/1.73 m ²	No ARC	48	41	54
	ARC	12	22	65
Predictive value for ARC (%)		80	35	

^aAbbreviations: ARC, augmented renal clearance; CL, clearance; CRCL, creatinine clearance.

the nonparametric model (Fig. S3). Diagnostic plots of the NPDE versus predicted concentration suggested that the parametric model underpredicted lower concentrations. Altering the residual error model did not resolve these slight mispredictions and resulted in worse model fits (data not shown). A sensitivity analysis that censored concentrations of <0.2 $\mu\text{g/ml}$ yielded parameter estimates that were within the bootstrap 95% confidence interval (CI) of the final parametric model. Figure S4 shows the prediction-corrected visual predictive checks (VPCs) for the final model (panel A) and for a model generated by censored data (panel B). Censoring low concentrations did not lead to significant improvements.

PTA and PTE across PNA groups. Exposures for simulated subjects based on the final models are summarized in Table 5. According to the parametric model, maximum concentration from 0 to 24 h ($C_{\text{max},0-24}$) and AUC_{0-24} were reduced on average by 38% and 34%, respectively, in patients with ARC across PNA groups. Simulations using the nonparametric model suggested that median $C_{\text{max},0-24}$ and AUC_{0-24} were reduced on average by 12% and 19%, respectively, in patients with ARC. Plots of probability of target attainment (PTA) versus MIC targets for 7 and 10 mg/kg of body weight dosing are shown in Fig. S5, and plots of PTA versus MIC targets for 12 mg/kg are shown in Fig. 4. According to simulations using the nonparametric model, in patients receiving 7 mg/kg, 90% PTA for AUC/MIC and $C_{\text{max}}/\text{MIC}$ targets were reliably achieved only at MICs up to 0.5 and 1 $\mu\text{g/ml}$ irrespective of ARC status (Fig. S5, part 1, panels A and B). In patients without ARC receiving 10 mg/kg, 90% PTA was achieved only at MICs up to 1 and 2 $\mu\text{g/ml}$ for the AUC/MIC and $C_{\text{max}}/\text{MIC}$ targets, respectively. ARC reduced the highest attainable MIC by one dilution (Fig. S5, part 1, panels C and D). In patients without ARC receiving 12 mg/kg, PTA fell below 90% at an MIC of 2 $\mu\text{g/ml}$ according to the AUC/MIC goal (Fig. 4A) and fell below 90% at an MIC of 4 $\mu\text{g/ml}$

FIG 2 Comparison of nonlinear and linear regression models of postnatal age on clearance. Fits of linear regression versus nonlinear least-squares regression of clearance (CL) versus postnatal age (PNA). AIC, Akaike information criterion.

TABLE 4 Population pharmacokinetic parameter estimates from the final nonparametric and parametric models of aminoglycosides in pediatric patients with various levels of renal function^a

Nonparametric model						Parametric model				
Parameter	Weighted parameter estimates			Variability and shrinkage		Parameter	Stochastic approximation		Bootstrap (n = 1,000)	
	Median	2.5th	97.5th	CV%	Shrink%		Estimate	RSE (%)	2.5th	97.5th
CL ₀	1.00	0.84	1.14	37	47	CL ₀	4.35	5.42	2.699	5.061
CL _{ARC}	1.49	1.18	2.04	56	47	CL _{ARC}	0.507	15.8	0.231	0.746
CL _{CRCL}	0.15	0.07	0.32	127	53	CL _{CRCL}	0.306	23.3	0.181	0.889
CL _{TBW}	0.75					CL _{TBW}	0.75			
V _c	6.89	6.28	8.04	50	56	V _c	7.56	9.81	4.635	9.129
V _{ARC}	1.56	0.99	1.71	88	58	V _{ARC}	0.505	29.4	0.146	1.222
V _{TBW}	1					V _{TBW}	1			
Q	0.51	0.27	0.78	102	61	Q	0.834	28.8	0.517	1.666
V _p	16.75	9.04	99.99	103	59	V _p	32	41.1	9.132	53.640
V _{pTBW}	1					V _{pTBW}	1			
h	0.16	0.07	0.18	105	54	h	0.13	43.6	0.006	0.571
PNA ₅₀	7.48	1.87	13.66	82	63	PNA ₅₀	7.27	56.5	0.262	47.436
						ω _{CL}	0.108	42.8	0.068	0.441
						ω _{Vc}	0.218	48.8	0.088	0.630
						ω _Q	1.22	28	0.368	1.466
						ω _{Vp}	1.25	27.5	0.598	2.033
						ω _h	1.32	22.6	0.793	3.450
						ω _{PNA50}	2.59	28.3	0.560	3.516
Error model gamma	0.6758					Error model b	0.342	6.94	0.284	0.392

^aAbbreviations: CV%, coefficient of variation; RSE, relative standard error. The final nonparametric model for clearance was parameterized as: $CL = CL_0 \cdot (TBW/30)^{CL_{TBW}} \cdot PNA^h / (PNA_{50}^h + PNA^h) \cdot (CRCL/120)^{CL_{CRCL}} \cdot (CL_{ARC})^{ARC}$ and V was parameterized as $V = V_c \cdot (TBW/30)^{V_{cTBW}} \cdot (V_{cARC})^{ARC} + V_p \cdot (TBW/30)^{V_{pTBW}}$, whereas the final parametric model for clearance was parameterized as $CL = CL_0 \cdot (TBW/30.8)^{CL_{TBW}} \cdot PNA^h / (PNA_{50}^h + PNA^h) \cdot (CRCL/118.3)^{CL_{CRCL}} \cdot e^{CL_{ARC} \cdot ARC}$ and V was parameterized as $V = V_c \cdot (TBW/30.8)^{V_{cTBW}} \cdot e^{V_{cARC} \cdot ARC} + V_p \cdot (TBW/30.8)^{V_{pTBW}}$.

ml according to the C_{max}/MIC goal (Fig. 4B). However, for patients with ARC, PTA fell below 90% at one MIC dilution lower versus those without ARC. Simulation results from the parametric model were generally similar to those obtained from the nonparametric model but revealed distinct patterns. The PTA analysis in patients with ARC receiving 7 mg/kg showed that target attainment was >90% for all PNA groups only up to MICs of 0.25 and 1 $\mu g/ml$ for AUC/MIC and C_{max}/MIC goals, respectively (Fig. S5, part 2, panels A and B). Results in patients with ARC receiving 10 mg/kg were similar, except that target attainment was >90% only up to MICs of 0.5 and 1 $\mu g/ml$ for AUC/MIC and C_{max}/MIC goals, respectively (Fig. S5, part 2, panels C and D). In patients with ARC receiving 12 mg/kg, target attainment was >90% in all PNA groups only up to MICs of 0.5 and 2 $\mu g/ml$ for AUC/MIC and C_{max}/MIC goals, respectively (Fig. 4C and D).

With respect to the probability of toxic exposure (PTE), the nonparametric PTE analysis suggested that the risk of trough of >2 $\mu g/ml$ was greatest among children aged 2 years or younger, irrespective of ARC status (Fig. 5); however, ARC modestly attenuated the risk in all groups. For patients 4 years or older without ARC, the PTE was <5%. PTE decreased in stepwise fashion as PNA increased, and PTE increased in stepwise fashion as dose increased (Fig. 5A), and ARC attenuated the risk of toxicity. Similar to the nonparametric analysis, the parametric analysis suggested that PTE generally decreased in stepwise fashion as PNA increased, and PTE increased in stepwise fashion as dose increased (Fig. 5B) and ARC attenuated the risk of toxicity. In contrast to the nonparametric simulations, among patients without ARC, the parametric analysis suggested that PTE was greater than 10% only in patients receiving 10 mg/kg or more and only if they were 2 years old or younger. In the nonparametric model, potentially toxic exposures were seen in all simulated patients without ARC who were aged 2 years or younger, which supports the hypothesis that the nonparametric approach gives greater weighting to this subpopulation than does the parametric approach.

FIG 3 Regression plots of the observed versus predicted concentrations for the population and individual based on the final nonparametric (A and B) and parametric (C) population PK models. (A and B) Observed (OBS) versus predicted regressions from the nonparametric model. (C and D) Observed versus predicted regressions from the parametric model.

DISCUSSION

We developed parametric and nonparametric population PK models of systemically administered aminoglycosides in critically ill pediatric patients using a parallel approach. This methodology leveraged a systematic approach and used the resulting PK models to simulate target attainment and toxicity risks according to ARC status. We found that ARC independently impacted CL and V_c, resulted in lower PTA at similar MICs and reduced the risk of minimum concentration ($C_{\min}$) of $>2 \mu\text{g/ml}$. Our models support the need for increased dosing in pediatric patients with ARC but concurrently suggest caution if the MIC is at or above the upper limit of the susceptible range for *Enterobacteriales* and *Pseudomonas* (i.e., MIC = $4 \mu\text{g/ml}$) (21). Results of both parametric and nonparametric PTA

TABLE 5 Mean or median PK exposures among simulated patients according to PNA and ARC^a

Parameter and PNA	Patients not showing ARC			Patients showing ARC			% decrease with ARC ^b		
	C _{max,0-24}	C _{min,0-24}	AUC ₀₋₂₄	C _{max,0-24}	C _{min,0-24}	AUC ₀₋₂₄	C _{max,0-24}	C _{min,0-24}	AUC ₀₋₂₄
Parametric mean PK									
1.2	28.64	1.22	102.17	18.58	0.86	71.83	35	30	30
2	30.36	1.18	108.88	19.37	0.69	72.59	36	42	33
4	32.78	1.09	112.23	20.50	0.69	75.55	37	37	33
8	33.58	0.94	117.33	21.10	0.54	78.09	37	42	33
12	35.56	0.90	131.97	21.79	0.54	84.02	39	40	36
16	35.96	0.78	137.63	21.97	0.45	88.66	39	43	36
20	36.76	0.72	142.10	22.29	0.50	93.51	39	31	34
Avg	33.38	0.98	121.76	20.80	0.61	80.61	38	38	34
Nonparametric median PK									
1.2	32.50	0.38	98.47	27.79	0.32	77.27	15	16	22
2	33.95	0.34	103.30	29.36	0.40	80.72	14	−17	22
4	34.41	0.25	100.29	29.78	0.22	79.25	13	12	21
8	35.61	0.32	102.71	31.24	0.28	84.21	12	12	18
12	36.61	0.42	109.98	32.28	0.38	90.91	12	9	17
16	37.09	0.22	114.85	32.96	0.28	96.15	11	−26	16
20	37.35	0.28	117.68	33.28	0.25	99.46	11	10	15
Avg	35.36	0.32	106.75	30.96	0.31	86.85	12	4	19

^aPK exposures for first 24 h were simulated ($n = 1,000$ per PNA group) for patients with and without ARC. Simulated patients received 10 mg/kg dosing, and the mean (parametric) and median (nonparametric) simulated exposures were calculated from all simulated profiles. Abbreviations: PNA, postnatal age; PTA, probability of target attainment; PTE, probability of toxic exposure; ARC, augmented renal clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; AUC, area under the curve.

^bA negative percent decrease represented an increase with ARC.

analyses suggested that ARC reduces attainment rates at similar MICs and above an MIC of 1 $\mu\text{g/ml}$, standard dosing regimens will likely be suboptimal.

A convergence between parametric and nonparametric population PK approaches has been previously observed with imipenem in critically ill adult patients (22). However, this is the first PK study to compare parametric and nonparametric approaches in critically ill pediatric patients. Similar to previous population PK studies in pediatric patients with ARC (6, 10, 23), we found that allometric scaling of clearance (CL) and volume (V) to total body weight (TBW) yielded improved data fits. Likewise, we as others, found that including a maturation function of PNA on CL yielded improved data fits (6, 10). Unlike previous studies, we evaluated a range of dosing strategies and simultaneously assessed the probability of efficacy and toxicity and compared simulated profiles between patients with and without ARC. Our simulations suggested that, compared to patients without ARC, those with ARC were more likely to experience lower rates of PK/PD target attainment at similar MIC values. Additionally, we found similar trends in the parametric and nonparametric model simulations suggesting the risk of toxicity increased as doses increased and declined with increasing PNA > 2 years. ARC independently reduced the risk of toxicity at every PNA evaluated. Thus, for selected patients with ARC and MICs within the susceptible range, increasing the dose may be an acceptable option. However, our findings suggest caution with aminoglycoside monotherapy and may suggest the need to increase the dose of other renally cleared drugs in this population.

Our population models estimated that both V and CL were independently impacted by ARC. On average, ARC increased CL by 49 to 66% and increased Vc by 56 to 66%. These increases are consistent with prior work (6, 20). Our previous study showed significant increases in both CL and Vc in patients with ARC compared to those without (Vc, 0.26 liter/kg versus 0.22 liter/kg; overall CL [CL_{overall}], 102.13 ml/min/1.73 versus 72.98 ml/min/1.73; P values, <0.001) (6). These findings were also consistent with a previous study of patients with ARC receiving vancomycin. The analysis showed that patients with ARC had a significantly higher Vc and CL compared to those without ARC (Vc, 0.66 liter/kg versus 0.62 liter/kg; P value, 0.001; CL_{overall}, 141.3 ml/min/1.73 versus 91.7 ml/min/1.73, P value: <0.001) (20). This consistency provides some evidence to

FIG 4 Probability of target attainment (PTA) for AUC/MIC and $C_{\max}$ /MIC goals from the nonparametric (A and B) and parametric (C and D) population PK models. (A and B) Nonparametric PK model: semiparametric Monte Carlo simulation sampling of the final nonparametric model using a multimodal distribution. (C and D) Parametric PK model: MCS sampling using population mean and variance estimates.

indicate that ARC may concurrently affect CL and the volume of distribution (V_d). Evidence regarding the specific mechanism for ARC is scarce. It is hypothesized that patients with ARC exhibit altered PK parameters due to the potential short-term changes in physiology (i.e., glomerular filtration rate, protein binding, capillary leak, etc.) (17, 24). To our knowledge, only one clinical mechanistic study examined the potential changes in glomerular filtration rate (GFR) and renal tubular function in patients with ARC. A study by Udy and colleagues looked at various exogenous markers and found that compared to 12 healthy adult patients, 20 adult patients with ARC exhibited altered exogenous markers suggestive of changes at the level of the nephron (25).

FIG 5 Probability potentially toxic exposures according to nonparametric (A) and parametric (B) models. (A) Nonparametric model. Semiparametric MCS sampling of nonparametric model estimates are shown. (B) Parametric model. MCS sampling of population mean and variance estimates are shown.

Briefly, they found that patients with ARC had increased sinistrin CL, increased tubular anion secretion of *p*-aminohippuric acid, increased net tubular reabsorption of fluconazole, and decreased tubular secretion of *rac*-pindolol compared to healthy individuals (25). The authors concluded that ARC seems to cause alterations in GFR, renal tubular secretion, and tubular reabsorption. Given the limited studies available, more work is needed to describe the multifactorial processes that may drive the observed phenomenon of ARC.

Our study has limitations. First, the study was a retrospective observational study of a heterogeneous group of critically ill patients. Thus, differences in pathogen and disease severity may have influenced the degree of interindividual variability and the precision of our model estimates. Further, we were unable to model gentamicin and tobramycin separately. Importantly, we relied on sparsely sampled PK data obtained from two distinct clinical sites that used standard of care automated PK sample analysis. Only seven samples were below the limit of quantification (BLQ) and imputed using M5 (26), and a sensitivity analysis censoring these samples did not alter our conclusions. As the M5 method can be associated with increased bias compared to M3 or M4 methods, it is notable that only seven samples were BLQ. While the PK sampling was based on clinical care and subject to various causes of process noise, our residual error estimates were low, and our final models had low bias and imprecision (22). The population estimates from the nonparametric model were generally similar to those of the parametric model; however, we found that the parametric model tended to underestimate concentrations relative to the nonparametric model, which may have influenced the final CL and V parameter estimates. Notably, our data set included 28% peak concentrations and 24% random concentrations, making the exact estimation of covariate effects on volume challenging. However, our observation that ARC modified Vc was interesting. These preliminary findings should be confirmed in subsequent studies. The final nonparametric model exhibited moderate shrinkage; however, moderate shrinkage is expected with sparsely sampled data (27), and this is especially true with the nonparametric method. In spite of the limited sampling per subject, Monolix identified low η shrinkage based on the conditional distribution (data not shown). Nonparametric model parameter ranges tend to be wider than those from parametric estimation methods (22). Additionally, interindividual variability estimates for the nonparametric (i.e., coefficient of variation percentage [CV%]) and parametric models (i.e., between-subject variation [BSV]) were somewhat elevated. This observation is not surprising given the dynamic nature of critical illness. Previous studies have also documented large interindividual variability in critically ill pediatric patients (10, 23). Renal dysfunction can have a major effect on aminoglycoside PK; however, sensitivity analyses excluding patients with renal dysfunction from the model did not alter our conclusions. Future prospective studies in this population are needed to confirm our model estimates. Finally, our PTA and PTE analyses are based on accepted targets for aminoglycosides but do not account for infection site and end-organ exposures (e.g., changes in drug penetration at various sites) that might occur in critical illness. Therefore, caution should be used in interpreting our PTA and PTE analyses because they reflect serum PK only. Likewise, our models cannot account for pharmacodynamic or toxicodynamic variability.

Conclusions. In summary, we developed nonparametric and parametric population PK models in parallel and converged on similar model structures. The PK models yielded similar but distinct simulation results, demonstrating that patients with ARC can be expected to experience lower rates of target attainment within the susceptible MIC range. Patients with ARC may benefit from increased aminoglycoside dosing empirically; however, the risk of toxicity must be carefully considered in patients less than 2 years old. In patients with ARC and MICs greater than 1 $\mu\text{g/ml}$, combination therapy or nonaminoglycoside alternative agents should be considered because optimal PK/PD exposures are unlikely to be achieved with standard dosing.

MATERIALS AND METHODS

Patient data, definitions, and PK samples. We conducted a retrospective observational PK study. Patients were included if they received systemic intravenous (IV) aminoglycosides (gentamicin or

tobramycin) between 1999 and 2016 at two pediatric hospitals (Miller Children's Hospital or Rady Children's Hospital of San Diego) and were admitted to the pediatric intensive care unit (PICU). The study was approved by the institutional review boards at each institution, and only completely deidentified data were made available to Midwestern University (MWU) researchers (human subjects' research determination on file).

Patients were included if they were 1 year through 21 years of age (per NIH definition of pediatrics at the time of study) (28) and received an aminoglycoside for ≥ 24 h while in the PICU irrespective of baseline renal function. Patients were excluded if they were receiving hemodialysis or were pregnant.

Serum aminoglycoside concentrations and serum creatinine were determined by each hospital's validated laboratory assay/standards, as previously described (6, 29). For patients with aminoglycoside concentrations below the limit of quantitation (LOQ), half the LOQ (i.e., the M5 method) was imputed as the observed value in the PK modeling (26).

Covariates screened *a priori* in this study included total body weight (TBW), postnatal age (PNA), serum creatinine (SCR), and creatinine clearance (CRCL) normalized to 1.73 m^2 body surface area (BSA) defined by the modified Schwartz or Cockcroft-Gault equations (depending on PNA) (30, 31). The modified Schwartz method was used to estimate CRCL in those < 17 years old (31), and the Cockcroft-Gault equation (normalized to BSA) was used to estimate CRCL for patients aged ≥ 17 years (30).

Augmented renal clearance (ARC) was defined as a 24-h aminoglycoside clearance (i.e., CL_{0-24}) $\geq 130 \text{ ml/min/1.73 m}^2$ based upon prior studies (6, 20, 32). Urinary creatinine was not collected in these children, therefore Bayesian drug CL_{0-24} was used as a surrogate (33) for true renal clearance, as aminoglycosides are not secreted nor significantly reabsorbed (34) and nonrenal clearance is minimal.

Twenty-four-hour aminoglycoside clearance estimation. Aminoglycoside concentrations were calculated using nonparametric model estimates using a base two-compartment structure. Individual median Bayesian posterior parameter estimates at 12-min intervals were calculated for each patient for the first 24 h of therapy initiation and used to determine serum PK exposures (i.e., AUC_{0-24} , $C_{\text{max},0-24}$, and $C_{\text{min},0-24}$). CL_{0-24} was calculated by dividing the first 24-h dose (dose_{0-24}) by the AUC_{0-24} for each patient (i.e., $\text{CL}_{0-24} = \text{dose}_{0-24} / \text{AUC}_{0-24}$).

Receiver operating characteristic curves. Receiver operating characteristic (ROC) comparative analysis was performed using the "roctab" command in Stata IC 16.1 (StataCorp, College Station, TX). The predictor of CRCL was used for the classification of ARC (binary outcome: yes/no). Sensitivity, specificity, and the percentage of patients correctly classified were calculated using predictive matrices for each value of CRCL. A predictive matrix was also created using the CRCL and drug CL cutoff $> 130 \text{ ml/min/1.73 m}^2$ BSA.

Pharmacokinetic models. We utilized the Nonparametric Adaptive Grid (NPAG) algorithm (35–37) within the *Pmetrics* (version 1.5.2) package (Los Angeles, CA) (37) for R (Vienna, Austria) (38) to conduct the nonparametric analysis. Multiple physiologically relevant PK model structures were tested. Covariate effects were evaluated using regressions of covariates versus parameter estimates, bias, and imprecision, and visual inspection of weighted residuals. Both linear and nonlinear covariate relationships were explored, including power transformations and Hill-type models (39). Assay error (standard deviation [SD]) and process noise was accounted for using an error polynomial as a function of the measured concentration, Y , (i.e., $\text{SD} = C_0 + C_1 Y$) with C_0 and C_1 inputs of 0.25 and 0.15, respectively. The inverse of the observed variance (SD^2) was used as the first estimate for observation weighting (37). Residual error was modeled using the multiplicative gamma (i.e., $\text{error} = \text{gamma} \times \text{SD}$) with gamma initially set at 5 with a final value estimated by NPAG. Model selection was guided by the rule of parsimony and Akaike's information criterion (AIC) score. Predictive performance of the final model was evaluated as previously described (40) via simulation (e.g., normalized prediction distribution errors [NPDE]).

Parametric models were developed using Monolix v2019R2 and compared using the Sycomore v2019R2 workflow management software (41). Model construction proceeded similar to that of the nonparametric build (e.g., one- and two-compartment structural models were evaluated). Population parameters were assumed to be normally distributed, and individual random effects were assumed to be log normally distributed. Continuous covariates were log transformed. Covariates were included in the model if they yielded a decrease in the objective function value (ΔOFV) of > 3.84 between nested models, which is analogous to $P < 0.05$ according to the χ^2 distribution with 1 degree of freedom. Covariates were retained if their removal yielded an increase in the ΔOFV of > 6.63 between nested models, which is analogous to $P < 0.01$. Between-subject variation (BSV) was handled using an exponential model (i.e., omega). Various residual error model structures (i.e., additive, proportional, or combined) were evaluated. Model selection was guided by inspection of NPDE versus concentration and time, prediction-corrected visual predictive checks (VPCs), and the corrected Bayesian Information Criterion (BICc).

Simulations and probabilities of target attainment and toxic exposure. Predicted concentrations were evaluated against PK/PD targets of $C_{\text{max}}/\text{MIC} > 8$ and $\text{AUC}/\text{MIC} > 70$, as each of these indices has been associated with efficacy for aminoglycosides (15, 16). The probability of target attainment (PTA) was assessed for doubling MICs from 0.25 to $4 \mu\text{g/ml}$ for each of the PK/PD goals above, which represents MICs within the susceptible range for *Enterobacteriales* and *Pseudomonas aeruginosa* (21). Additionally, the likelihood of experiencing elevated trough concentrations ($C_{\text{min}} > 2 \mu\text{g/ml}$) was assessed as a surrogate (42) for the risk of nephrotoxicity and ototoxicity in pediatric patients (43), and this defined the probability of toxic exposure (PTE).

The final nonparametric PK model was used to generate simulations. NPDE was generated using 1,000 simulations for each patient in the model with grid bounds set between 0- and 3-fold the upper bounds of the original model. For PTA and PTE, Monte Carlo simulations were generated from the weighted, multivariate, multimodal, distribution generated a population with 1,000 parameter sets for

each covariate condition and dose regimen (44). From the simulated population, concentration-time profiles were generated every 0.2 h for 7-, 10-, and 12-mg/kg once-daily dosing regimens infused over 0.5 h.

A similar simulation approach was taken for the parametric model. Nonparametric bootstrap resampling of parameter estimates was completed using the *Rsmix* package (45) for R. The *simulx* function available in the *mixR* package (46) for R and the final model parameter estimates were used to conduct Monte Carlo simulations for PTA and PTE analysis. For each covariate condition and dosing regimen, 1,000 concentration-time profiles were generated every 0.2 h for the first 24 h of therapy. The same PTA and PTE exposure indices and the same MIC targets were evaluated as in the nonparametric approach.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

ACKNOWLEDGMENTS

This study was conducted as part of our routine work. Jennifer Le and John Bradley receive support from the NICHD (1R01HD095547-01, principal investigator [PI], J. Bradley) for participation in this project in pediatric clinical pharmacology.

We declare that we have no conflicts of interest.

S.N.A. and R.R. completed the modeling and drafted the manuscript. J.B. provided comments and edits to the draft. J.L. and N.J.R. conceived of the work, edited the draft, and supervised the modeling. All authors approved of the final version of the manuscript.

REFERENCES

1. Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, Boots RJ, Lipman J. 2014. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. *Crit Care Med* 42:520–527. <https://doi.org/10.1097/CCM.0000000000000029>.
2. 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/nrneph.2011.92>.
3. Udy AA, Roberts JA, Lipman J. 2013. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med* 39:2070–2082. <https://doi.org/10.1007/s00134-013-3088-4>.
4. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. 2013. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. *Crit Care* 17:R35. <https://doi.org/10.1186/cc12544>.
5. Van Der Heggen T, Dhont E, Peperstraete H, Delanghe JR, Vande Walle J, De Paep P, De Cock PA. 2019. Augmented renal clearance: a common condition in critically ill children. *Pediatr Nephrol* 34:1099–1106. <https://doi.org/10.1007/s00467-019-04205-x>.
6. Avedissian SN, Rhodes NJ, Kim Y, Bradley J, Valdez JL, Le J. 2020. Augmented renal clearance of aminoglycosides using population-based pharmacokinetic modelling with Bayesian estimation in the paediatric ICU. *J Antimicrob Chemother* 75:162–169. <https://doi.org/10.1093/jac/dkz408>.
7. Avedissian SN, Skochko SM, Le J, Hingtgen S, Harvey H, Capparelli EV, Richardson A, Momper J, Mak RH, Neely M, Bradley JS. 2020. Use of simulation strategies to predict subtherapeutic meropenem exposure caused by augmented renal clearance in critically ill pediatric patients with sepsis. *J Pediatr Pharmacol Ther* 25:413–422. <https://doi.org/10.5863/1551-6776-25.5.413>.
8. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network. 2007. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11:R31. <https://doi.org/10.1186/cc5713>.
9. Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ. 2013. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. *J Crit Care* 28:695–700. <https://doi.org/10.1016/j.jcrc.2013.03.003>.
10. De Cock PAJG, Standing JF, Barker CIS, de Jaeger A, Dhont E, Carlier M, Verstraete AG, Delanghe JR, Robays H, De Paep P. 2015. Augmented renal clearance implies a need for increased amoxicillin-clavulanic acid dosing in critically ill children. *Antimicrob Agents Chemother* 59:7027–7035. <https://doi.org/10.1128/AAC.01368-15>.
11. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, Grundmeier R, Nadkarni VM, Thomas NJ. 2014. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med* 42:2409–2417. <https://doi.org/10.1097/CCM.0000000000000509>.
12. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, Nadel S, Schlapbach LJ, Tasker RC, Argente AC, Brierley J, Carcillo J, Carroll ED, Carroll CL, Cheifetz IM, Choong K, Cies JJ, Cruz AT, De Luca D, Deep A, Faust SN, De Oliveira CF, Hall MW, Ishimine P, Javouhey E, Joosten KFM, Joshi P, Karam O, Kneyber MCJ, Lemson J, MacLaren G, Mehta NM, Moller MH, Newth CJL, Nguyen TC, Nishisaki A, Nunnally ME, Parker MM, Paul RM, Randolph AG, Ranjit S, Romer LH, Scott HF, Tume LN, Verger JT, Williams EA, Wolf J, Wong HR, Zimmerman JJ, Kissoon N, Tissieres P. 2020. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 21:e52–e106. <https://doi.org/10.1097/PCC.0000000000002198>.
13. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. 2004. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 114:e111–e118. <https://doi.org/10.1542/peds.114.1.e111>.
14. Craig WA. 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 26:1–10, quiz 11–12. <https://doi.org/10.1086/516284>.
15. 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>.
16. Smith PF, Ballou CH, Booker BM, Forrest A, Schentag JJ. 2001. Pharmacokinetics and pharmacodynamics of aztreonam and tobramycin in hospitalized patients. *Clin Ther* 23:1231–1244. [https://doi.org/10.1016/S0149-2918\(01\)80103-X](https://doi.org/10.1016/S0149-2918(01)80103-X).
17. Roberts JA, Lipman J. 2009. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 37:840–851, quiz 859. <https://doi.org/10.1097/CCM.0b013e3181961bff>.
18. Sawchuk RJ, Zaske DE. 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm* 4:183–195. <https://doi.org/10.1007/BF01086153>.
19. Yu T, Stockmann C, Healy DP, Olson J, Wead S, Neely AN, Kagan RJ, Spigarelli MG, Sherwin CM. 2015. Determination of optimal amikacin dosing regimens for pediatric patients with burn wound sepsis. *J Burn Care Res* 36:e244–e252. <https://doi.org/10.1097/BCR.0000000000000159>.
20. Avedissian SN, Bradley E, Zhang D, Bradley JS, Nazer LH, Tran TM, Nguyen A, Le J. 2017. Augmented renal clearance using population-based pharmacokinetic modeling in critically ill pediatric patients.

- Pediatr Crit Care Med 18:e388–e394. <https://doi.org/10.1097/PCC.0000000000001228>.
21. Clinical and Laboratory Standards Institute. 2020. Performance standards for antimicrobial susceptibility testing. M100-ED30. Clinical and Laboratory Standards Institute, Wayne, PA.
 22. de Velde F, de Winter BCM, Neely MN, Yamada WM, Koch BCP, Harbarth S, von Dach E, van Gelder T, Huttner A, Mouton JW, COMBACTE-NET consortium. 2020. Population pharmacokinetics of imipenem in critically ill patients: a parametric and nonparametric model converge on CKD-EPI estimated glomerular filtration rate as an impactful covariate. *Clin Pharmacokinet* 59:885–898. <https://doi.org/10.1007/s40262-020-00859-1>.
 23. Beranger A, Benaboud S, Urien S, Moulin F, Bille E, Lesage F, Zheng Y, Genuini M, Gana I, Renolleau S, Hirt D, Treluyer JM, Oualha M. 2019. Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children with normal and augmented renal clearance. *Clin Pharmacokinet* 58:223–233. <https://doi.org/10.1007/s40262-018-0682-1>.
 24. Cook AM, Hatton-Kolpek J. 2019. Augmented renal clearance. *Pharmacotherapy* 39:346–354. <https://doi.org/10.1002/phar.2231>.
 25. Udy AA, Jarrett P, Stuart J, Lassig-Smith M, Starr T, Dunlop R, Wallis SC, Roberts JA, Lipman J. 2014. Determining the mechanisms underlying augmented renal drug clearance in the critically ill: use of exogenous marker compounds. *Crit Care* 18:657. <https://doi.org/10.1186/s13054-014-0657-z>.
 26. 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>.
 27. Xu XS, Yuan M, Karlsson MO, Dunne A, Nandy P, Vermeulen A. 2012. Shrinkage in nonlinear mixed-effects population models: quantification, influencing factors, and impact. *AAPS J* 14:927–936. <https://doi.org/10.1208/s12248-012-9407-9>.
 28. National Institutes of Health. 2015. Inclusion of children in clinical research: change in NIH definition. Notice number NOT-OD-16-010. National Institutes of Health, Bethesda, MD.
 29. Le J, Bradley JS, Murray W, Romanowski GL, Tran TT, Nguyen N, Cho S, Natale S, Bui I, Tran TM, Capparelli EV. 2013. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J* 32:e155–e163. <https://doi.org/10.1097/INF.0b013e318286378e>.
 30. Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41. <https://doi.org/10.1159/000180580>.
 31. Schwartz GJ, Work DF. 2009. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 4:1832–1843. <https://doi.org/10.2215/CJN.01640309>.
 32. Bilbao-Meseguer I, Rodriguez-Gascon A, Barrasa H, Isla A, Solinis MA. 2018. Augmented renal clearance in critically ill patients: a systematic review. *Clin Pharmacokinet* 57:1107–1121. <https://doi.org/10.1007/s40262-018-0636-7>.
 33. Hirai K, Ihara S, Kinae A, Ikegaya K, Suzuki M, Hirano K, Itoh K. 2016. Augmented renal clearance in pediatric patients with febrile neutropenia associated with vancomycin clearance. *Ther Drug Monit* 38:393–397. <https://doi.org/10.1097/FTD.0000000000000270>.
 34. Sunder S, Jayaraman R, Mahapatra HS, Sathi S, Ramanan V, Kanchi P, Gupta A, Daksh SK, Ram P. 2014. Estimation of renal function in the intensive care unit: the covert concepts brought to light. *J Intensive Care* 2:31. <https://doi.org/10.1186/2052-0492-2-31>.
 35. Leary R, Jelliffe R, Schumitzky A, Van Guilder M. 2001. An adaptive grid nonparametric approach to pharmacokinetic and dynamic (PK/PD) population models, p 389–394. *Proceedings of the 14th IEEE Symposium on Computer-Based Medical Systems*. IEEE, New York, NY.
 36. Tatarinova T, Neely M, Bartroff J, van Guilder M, Yamada W, Bayard D, Jelliffe R, Leary R, Chubatiuk A, Schumitzky A. 2013. Two general methods for population pharmacokinetic modeling: non-parametric adaptive grid and non-parametric Bayesian. *J Pharmacokinet Pharmacodyn* 40:189–199. <https://doi.org/10.1007/s10928-013-9302-8>.
 37. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. 2012. Accurate detection of outliers and subpopulations with Pmetrics, a non-parametric and parametric pharmacometric modeling and simulation package for R. *Ther Drug Monit* 34:467–476. <https://doi.org/10.1097/FTD.0b013e31825c4ba6>.
 38. R Core Team. 2018. R: a language and environment for statistical computing, 3rd ed. R Foundation for Statistical Computing, Vienna, Austria.
 39. Goutelle S, Maurin M, Rougier F, Barbaut X, Bourguignon L, Ducher M, Maire P. 2008. The Hill equation: a review of its capabilities in pharmacological modelling. *Fundam Clin Pharmacol* 22:633–648. <https://doi.org/10.1111/j.1472-8206.2008.00633.x>.
 40. Rhodes NJ, Gardiner BJ, Neely MN, Grayson ML, Ellis AG, Lawrentschuk N, Frauman AG, Maxwell KM, Zembower TR, Scheetz MH. 2015. Optimal timing of oral fosfomycin administration for pre-prostate biopsy prophylaxis. *J Antimicrob Chemother* 70:2068–2073. <https://doi.org/10.1093/jac/dkv067>.
 41. Traynard P, Ayrat G, Twarogowska M, Chauvin J. 2020. Efficient pharmacokinetic modeling workflow with the MonolixSuite: a case study of remifentanyl. *CPT Pharmacometrics Syst Pharmacol* 9:198–210. <https://doi.org/10.1002/psp4.12500>.
 42. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. 1999. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother* 43:1549–1555. <https://doi.org/10.1128/AAC.43.7.1549>.
 43. Rao SC, Srinivasjois R, Moon K. 2016. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. *Cochrane Database Syst Rev* 12:CD005091. <https://doi.org/10.1002/14651858.CD005091.pub4>.
 44. Goutelle S, Bourguignon L, Maire PH, Van Guilder M, Conte JE, Jr, Jelliffe RW. 2009. Population modeling and Monte Carlo simulation study of the pharmacokinetics and antituberculosis pharmacodynamics of rifampin in lungs. *Antimicrob Agents Chemother* 53:2974–2981. <https://doi.org/10.1128/AAC.01520-08>.
 45. Lavielle M, Chauvin J. 2019. Rsmix: R speaks 'Monolix'. R package version 2.0.2.
 46. Lavielle M. 2020. mixR: simulation of longitudinal data. R package version 4.1.3.