Article details

Illamola S.M., Sherwin C.M. & Hasselt J.G.C. van (2018), Clinical Pharmacokinetics of Amikacin in Pediatric Patients: A Comprehensive Review of Population Pharmacokinetic Analyses, *Clinical Pharmacokinetics* 57(10): 1217-1228.
Doi: 10.1007/s40262-018-0641-x

Clin Pharmacokinet (2018) 57:1217–1228
https://doi.org/10.1007/s40262-018-0641-x

REVIEW ARTICLE

Clinical Pharmacokinetics of Amikacin in Pediatric Patients: A Comprehensive Review of Population Pharmacokinetic Analyses

Sílvia M. Illamola[1,2,3] · Catherine M. Sherwin[1] · J. G. Coen van Hasselt[4]

Published online: 23 March 2018

Abstract Amikacin plays a key role in the treatment of severe hospital-acquired infections with Gram-negative bacteria. Therapeutic use of amikacin is challenged by high inter-individual variability (IIV) combined with a narrow therapeutic spectrum. Pediatric patients represent a particularly fragile population where adequate dosing is crucial yet challenging to achieve due significant IIV associated with developmental processes and other factors. The current review provides an overview of parametric population pharmacokinetic analyses of amikacin in pediatric patients and associated patient-specific determinants of IIV. We searched PubMed for parametric population pharmacokinetic analyses of amikacin in pediatric patients. Information on patient population, study design, pharmacokinetic model characteristics, and identified patient-specific predictors of IIV was collected. Comparative analyses across studies were conducted to characterize quantitative differences reported for different studies and patient populations. Eight eligible publications were identified, of which six analyses involved neonates up to 3 months of age and two studies investigated older pediatric patients (age 2–17 years). Most commonly included covariates were current body weight for both clearance and volume of distribution, followed by age-related covariates on clearance in neonatal studies (four of six models). Quantitative comparisons of different models reported generally showed similar developmental effects in neonatal populations. The present review provides a comprehensive overview of parametric population pharmacokinetic studies for amikacin. Future studies could address the knowledge gap of patients between 3 months and 2 years of age. Furthermore, systematic studies of additional potential predictors for IIV (e.g., sepsis, inflammatory markers, renal function biomarkers) could be of relevance to address the significant IIV remaining after inclusion of the most commonly identified covariates.

Key Points

Optimal dosing of amikacin in pediatric patients is challenging due to significant inter-individual variability (IIV) associated with developmental processes.

All analyses reported current body weight as a predictor for IIV in clearance and volume of distribution, while some analyses identified other predictors including age-related covariates and predictors of glomerular filtration rate.

Between the age of 3 months and 2 years, there is a lack of studies that characterize the pharmacokinetics of amikacin.

✉ Sílvia M. Illamola
07silvia@gmail.com

1 Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, 295 Chipeta Way 1S100, Salt Lake City, UT 84108, USA

2 Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, Universitat de Barcelona, Barcelona, Spain

3 Biochemistry Service, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

4 Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands

1 Introduction

Amikacin is an aminoglycoside antibiotic primarily used for the treatment of infections caused by aerobic Gram-negative bacilli when first-line antibiotic treatment is ineffective [1]. Amikacin has an important place in the treatment of bacterial infections in pediatric patients. It is the second most commonly used antibiotic in neonatal intensive care units [2], primarily prescribed for the treatment of neonatal sepsis, necrotizing enterocolitis, meningitis, and empirical antibiotic therapy [3]. In addition, amikacin has an important role in the treatment of acute pulmonary exacerbations of cystic fibrosis patients [4, 5].

Therapeutic use of amikacin is challenged by high inter-individual variability (IIV) combined with a narrow therapeutic spectrum. Therapeutic drug monitoring (TDM) therefore plays an important role in optimizing amikacin dosing. A ratio of the maximum (peak) concentration (C_{max}) divided by the minimum inhibitory concentration (MIC) of a given pathogen (peak/MIC) of at least 8–10 is recommended for effective amikacin therapy, with target trough concentrations (C_{trough}) as low as possible [6]. However, TDM approaches can only be implemented some time after treatment is started. Therefore, identification of patient-specific predictors of IIV in clearance (CL) and volume of distribution (V_d) in individual patients is crucial to achieve effective and safe dose regimens as early as possible.

Dose optimization in the pediatric population is particularly challenging. Several studies have demonstrated that drug plasma CL and V_d are affected by developmental processes beyond change in body size alone [7]. Similarly, significant changes in body water and body fat occur during pediatric development [7]. In addition, pathophysiological states such as sepsis or burns may affect the pharmacokinetics of amikacin and can introduce further IIV [8].

Population pharmacokinetic modeling now has an established role in identifying patient-specific predictors that determine IIV and rationally deriving individualized dose regimens [9]. Indeed, various population pharmacokinetic analyses of amikacin in the pediatric population have been reported for different pediatric sub-populations. The aim of this review is to identify, summarize, and compare parametric population pharmacokinetic analyses of amikacin in the pediatric population in order to identify the most commonly identified predictors of IIV and knowledge gaps that remain.

2 Methods

2.1 Search Strategy

The following PubMed search query was used to identify relevant publications: (“amikacin”[title] OR “amikacine”[title] OR “Amikin”[title]) AND (“population pharmacokinetic*”[tiab] OR “NONMEM”[tiab] OR “WinNonMix”[tiab] OR “*bugs”[tiab] OR “SAAM”[tiab] OR “*ADAPT”[tiab] OR “monolix”[tiab] OR “mixed effect”[tiab] OR “population model*”[tiab] OR “popPK”[tiab] OR “pop PK”[tiab] OR “NLME”[tiab] OR “compartmental pharmacokinetic*”[tiab] OR “pharmacokinetic* model*” [tiab]) AND (“pediatric” [tiab] OR “paediatric” [tiab] OR “neonates”[tiab]) AND (“1900/01/01”[PDat] : “2016/12/31”[PDat]) NOT (review[pt]) AND (“english”[LA]) NOT (“foal*”[tiab] OR “mice”[tiab] OR “rat*”[tiab] OR “rabbit”[tiab]). Additional studies were identified from the reference lists of selected papers.

Publications were included if they described a parametric population pharmacokinetic analysis of amikacin in pediatric patients (neonates, infants, children, or adolescents). Studies that used non-compartmental or non-parametric approaches were not included.

2.2 Data Extraction

The following information was extracted for each of the included publications: aim of the study, patient population, key demographics and laboratory measurements, study design characteristics related to drug treatment and sampling design, data analysis software, structural and statistical model parameter estimates, patient-specific covariates predictive of IIV, and model evaluation strategy.

2.3 Comparison of Studies

Study and patient characteristics, pharmacokinetic parameters, identified covariates, and model analysis strategies were summarized in tables. We quantitatively compared differences in typical parameter estimates for CL and V_d across reported models. We scaled the typical parameter estimates and their associated distributions for IIV by current body weight. For additional continuous covariates present in some models we used the respective median values reported in the study. For binary covariates (ibuprofen/non-steroidal anti-inflammatory drug [NSAID] use, ventilation, inotropes, small for gestational age [GA]), we assumed these were not present. For a model that included sex as covariate, we assumed males.

3 Results

We identified a total of 16 studies, of which seven studies were eligible and nine studies were excluded. Reasons for exclusion were not using a parametric population analysis [10–12], reporting of simulations alone [13], unable to retrieve publication [14], lack of human subjects [15], and application of an existing population pharmacokinetic model [16–18]. One additional study was identified through the selected papers [19]. Identified studies were published between 1998 and 2016.

The population characteristics, study design, and model analysis details of the included eight publications are provided in Tables 1, 2, and 3, respectively. Six of the included publications studied neonates, and two publications studied children and adolescents, of which one studied pediatric burn patients [20] (Table 1).

As expected, all analyses aimed to characterize IIV in amikacin pharmacokinetics and to identify predictors for dosing. In addition, two analyses [21, 22] also proposed a new dose schedule based on the developed model. Only one publication [21] additionally explored the relation between pharmacokinetics and treatment failure, allowing the estimation of new amikacin target concentrations and the development of an alternative dosing regimen.

Amikacin was administered as an intravenous infusion in all cases except in one study [23] where an intravenous bolus dose was used. Dose regimens studied ranged

Table 1 Overview of study population characteristics

Patients	*n* (M/F)	Age (y)	GA	PNA	PMA	Weight (kg)	SCR (mg/dL)	eGFR (mL/min/1.73 m^2)[a]	References
Neonates									
	874 (nr/nr)		30.5 [24–43]	2 [1–30]	nr	1.52 [0.39–4.78]	nr	nr	[22][b]
	80 (46/34)		28 [24–41]	9 [3–64]	29.43 [24.7–44]	1.03 [0.45–4.43]	0.66 [0.23–1.26]	nr	[21]
	205 (nr/nr)		28 [24–30]	< 3	nr	1.07 ± 0.34	nr	nr	[19]
	715 (nr/nr)		nr	< 29	nr [24–43]	nr [0.39–4.78]	nr	nr	[24]
	53 (30/23)		35.1 ± 3.6	3.1 ± 3.1	nr	2.1 ± 0.8[c]	nr	nr	[23]
	149 (86/63)		31.8 [24.3–41]	28 [1–86]	248 [175–360]	1.92 [0.50–4.65]	0.58 [0.19–2.50]	32.28 [5.87–121.5]	[25]
Infants/children/adolescents									
Children (burns)	70 (45/25)	4.5 [2–10][d]				20 [13–49][d]	nr	nr	[28]
Children/ adolescents	32 (20/12)	7 [2–14][d]				22.9 [14.8–46.3][d]	nr	nr	[28]
Infants/ children/ adolescents (burns)	70 (45/25)	4.5 [0.6–17]				20 [8–90]	nr	nr	[20]

Values are expressed as median [range] or mean ± standard deviation

eGFR estimated glomerular filtration rate, *F* female, *GA* gestational age, *M* male, *nr* not reported, *PMA* postmenstrual age, *PNA* postnatal age, *SCR* serum creatinine

[a] eGFR from the Schwartz formula

[b] The study of De Cock et al. [22], although modeled independently, was based on data from two previously published studies [19, 24]

[c] Refers to birth weight (kg)

[d] Values expressed as median (interquartile range)

Table 2 Study design characteristics

Patients	Drug treatment		Samples			References
	Dose (mg/kg)	Interval (h)	Times	*n*/patients	Total	
Neonates						
	nr [15.5–20]	24–42	P, T	nr [2–nr]	2186	[22]
	nr [15–18]	24–48	P, T	nr [1–nr]	358	[21]
	nr [15.5–20]	24–42	P, T	nr [2–nr]	410	[19]
	nr [15.5–20]	24–42	P, T	nr [2–nr]	1862	[24]
	nr [7.5–15][a]	12–24	P, T	2 [2]	106	[23]
	11.62 [2.8–58.4]	8–48	P, T	2–11	446	[25]
Infants/children/adolescents						
Children (burns)	16 [13–20][b]	8	P, T	nr [1–nr]	282	[28]
Children/adolescents	15 [8–16][b]	24	P, T	nr [1–nr]	99	[28]
Infants/children/adolescents (burns)	16.4 ± 3.9	6–12	P, T	nr [1–nr]	282	[20]

Values are expressed as median [range] or mean ± standard deviation

nr not reported, *P* peak samples, *T* trough samples

[a]With a previous loading dose of either 17.5 mg/kg or 10 mg

[b]Expressed as median [interquartile range]

Table 3 Modeling analyses characteristics

Patients	Aims[a]	Number of compartments	Model evaluation	Software	External validation[b]	References
Neonates						
	1, 2	Two	DP, IS, BO, EE	NONMEM®	Yes (239)	[22]
	1, 2, 3	One	DP, IS, BO	NONMEM®	No	[21]
	1	One	No	NONMEM®	No	[19]
	1	One	No	NONMEM®	No	[24]
	1	One	No	NONMEM®	No	[23]
	1, 2	Two	DP, IS, BO, EE	NONMEM®	Yes (53)	[25]
Infants/children/adolescents						
Children (burns)	1, 2	One	DP, IS, BO	NONMEM®	No	[28]
Children/adolescents	1, 2	One	DP, IS, BO	NONMEM®	No	[28]
Infants/children/adolescents (burns)	1	Two	DP, BO	NONMEM®	No	[20]

BO bootstrap, *DP* diagnostic plots, *EE* external evaluation, *IS* internal simulation

[a]Aims: (1) to characterize pharmacokinetics and identify predictors for dosing/pharmacokinetic parameters; (2) to propose a new dose schedule; (3) to investigate pharmacodynamics

[b]Number of individuals used for the external validation given in parentheses

between 2.8–58.4 and 8–20 mg/kg per dose and dosing intervals ranged between 8–48 and 6–24 h for neonates and older pediatric patients, respectively (Table 2). All analyses were retrospective and based on amikacin concentrations generated during routine TDM. Of note, the study by De Cock et al. [22], although modeled independently, was based on clinical study data described in two previously published analyses also included in this review [19, 24]. Study datasets generally consisted of sparsely sampled data, i.e., after end of infusion (C_{max}) and just before the next drug administration (C_{trough}). The majority of analyses reported one-compartment models, with the exception of two analyses in neonates [22, 25] and one analysis in pediatric burn patients [20] (Table 3), where additional opportunistic samples were available.

The identified mean population pharmacokinetic parameter estimates and associated covariate models for patient-specific predictors of IIV are summarized in Table 4. Typical parameter estimates and associated IIV for CL and central volume of distribution (V_c) scaled by weight are shown in Fig. 1. The median values and range of CL and V_c of amikacin in neonates were 0.037 L/h/kg (0.026–0.056 L/h/kg) and 0.477 L/kg (0.334–0.574 L/kg), and 0.120 L/h/kg (0.101–0.141 L/h/kg) and 0.277 L/kg (0.239–0.324 L/kg) in non-neonatal populations. In general, CL in neonates was lower than in the other pediatric populations (Fig. 1).

For neonatal populations, covariates selected among the different analyses were demographic factors including weight (birth weight [BWT] and current weight [cWT]), age (postnatal, postmenstrual, and postconceptional ages) and sex, renal function parameters (serum creatinine and estimated glomerular filtration rate [eGFR]), administration of drugs (ibuprofen and use of inotropes), intrauterine growth retardation (dichotomous variable), and positive pressure artificial ventilation. All identified models incorporated cWT on V_c and CL, except the analysis by De Cock et al. [22], which incorporated BWT instead of cWT on CL (Table 5). For non-neonatal populations, the only covariate included on both V_c and CL was cWT (Table 5). Figure 2 shows the change in predicted CL in relation to body weight.

The majority of analyses estimated IIV on CL and V_c. De Cock et al. [22] only estimated IIV on CL. Two analyses which identified two-compartmental pharmacokinetics also estimated IIV on inter-compartmental CL (Q) in neonates [25] and older pediatric patients [20]. In neonatal studies, IIV on CL was significant and ranged substantially from 4.6 to 34.93%. IIV in V_c ranged from 0.446 to 45.1%. Similar variability was also seen in non-neonatal studies for CL (24.5–54.9%) and V_c (10–24.9%). Only Illamola et al. [25] reported eta shrinkage values of 17.9 and 42.4% for CL and V_d, respectively.

Inter-occasion variability (IOV) in pharmacokinetic parameters is of clinical importance as significant IOV impacts the effectiveness of TDM strategies [26]. IOV was not included in the models of the non-neonatal analyses. For the neonatal analyses it was reportedly assessed in three analyses [21, 24, 25] and was incorporated in only one publication [24], with an IOV estimated for CL of 11.6%. Other analyses may potentially not have had sufficient multiple occasions data to allow its estimation. Residual variability, which can constitute intra-subject variability but also errors due to bioanalytical methodology, sample time recording, or model misspecifications, ranged from a proportional error of 18–50% across analyses, with an additive error ranging from 0.283 to 1.59 mg/L in neonates, and from 0.499 to 1.80 mg/L in a non-neonatal population.

Most analyses used standard pharmacokinetic model evaluation diagnostic methods such as goodness-of-fit plots and visual predictive checks [27]. Only two neonatal studies [22, 25] performed an external evaluation using pharmacokinetic data from a cohort of patients not used for model development. Of note, the population pharmacokinetic analysis by De Cock et al. [22] finally incorporated part of the data [21] used for the external evaluation to re-estimate the parameters of the final model. Three studies [19, 23, 24] did not report any details of model evaluation.

4 Discussion

This review summarizes eight population pharmacokinetic analyses of amikacin in the pediatric population, the majority of which were based on considerable study sizes of >50 patients, thus allowing good identification of the covariates with a significant effect on the final estimated pharmacokinetic parameters. Only the analysis of non-burned children and adolescents studied by Yu et al. [28] had a lower sample size ($n = 32$). There was a large overlap in the underlying study data used for the population pharmacokinetic analysis by De Cock et al. [22] and the analyses from Allegaert et al. [19, 24].

The use of sparse pharmacokinetic data derived from TDM practice is very common in pharmacokinetic analyses of neonatal populations due to the limitations of implementing rich sampling strategies in this group of patients (e.g., ethical challenges, blood volume). For this reason, TDM data sometimes become a useful alternative for pharmacokinetic studies. For instance, the limitations of using such sparse pharmacokinetic data are made clear by the general inability to identify two-compartmental pharmacokinetic models. Potentially, more frequently identified one-compartment models may lead to sub-optimal characterization of early distribution kinetics and a less accurate prediction of target peak coverage than with two-compartment models.

Overall, there was a reasonable agreement in estimates of amikacin pharmacokinetic parameters and identified predictors for IIV. Clear developmental effects for CL were identified across all analyses. The analysis by De Cock et al. [22], which included the largest dataset of immature preterm neonates, reported the lowest CL estimates. After inclusion of covariates, IIV in CL still remained between 4.6 and 55%. Sherwin et al. [21] reported notably small estimates for IIV in both CL and V_c compared with most other analyses. These lower estimates could be associated with the fact that most of the neonates included in the pharmacokinetic analysis were extremely low-birth-weight

Table 4 Summary of the population pharmacokinetic models: equations and parameter estimates

Population	Study	CL (L/h)		V_c (L)		V_p (L)		Q (L/h)	
		Equation	Estimate	Equation	Estimate	Equation	Estimate	Equation	Estimate
Neonates									
	De Cock et al. [22]	$\theta1 \times ((BWT/1750)^{\theta2}) \times (1 + \theta3 \times (PNA/2)) \times (\theta4 \times IB)$	$\theta1 = 0.0493$; $\theta2 = 1.34$; $\theta3 = 0.213$; $\theta4 = 0.838$	$\theta5 \times (cWT/1750)^{\theta6}$	$\theta5 = 0.833$; $\theta6 = 0.919$	$(V_c = V_p)$ $\theta7$	$\theta7 = 0.833$	$\theta8$	$\theta8 = 0.415$
	Sherwin et al. [21]	$\theta1 \times (cWT/70)^{\theta2} \times ((PMA/40)^{\theta3})$	$\theta1 = 0.23$; $\theta2 = 0.691$; $\theta3 = 3.23$	$\theta4 \times (cWT/2)^{\theta5}$	$\theta4 = 0.957$; $\theta5 = 0.89$	na	na	na	na
	Allegaert et al. [19]	$(\theta1 \times (cWT/70)^{\theta2}) \times \exp(\theta3 \times (PCA - 24) \times (\theta4^{FNSAID}))$	$\theta1 = 0.486$; $\theta2 = 0.75$ (f); $\theta3 = 0.11$; $\theta4 = 0.788$	$\theta5 \times (cWT/70)^{\theta6}$	$\theta5 = 40.2$; $\theta6 = 1$ (f)	na	na	na	na
	Allegaert et al. [24]	$(\theta1 \times (cWT/70)^{\theta2}) \times (1 + \theta3 \times (PMA - 40)) \times (((516 \times \exp(\theta4 \times ((PMA - 30)/52 - 40)))/SCR)/6) \times (\theta5^{FVENT}) \times (\theta6^{FINO}) \times (\theta7^{SGA})$	$\theta1 = 1.49$; $\theta2 = 0.75$ (f); $\theta3 = 0.032$; $\theta4 = 0.0034$; $\theta5 = 0.977$; $\theta6 = 0.945$; $\theta7 = 0.872$	$\theta8 \times (cWT/70)^{\theta9} \times (1 + \theta10 \times (PNA)) \times (\theta11^{FINO}) \times (\theta12^{FVENT})$	$\theta8 = 31.7$; $\theta9 = 1$ (f); $\theta10 = 0.005$; $\theta11 = 1.09$; $\theta12 = 1.08$	na	na	na	na
	Botha et al. [23]	$(\theta1 \times cWT^{\theta2}) \times \theta3^{SEX}$	$\theta1 = 0.031$; $\theta2 = 1.45$; $\theta3 = 1.28$	$\theta4 \times cWT^{\theta5}$	$\theta4 = 0.316$; $\theta5 = 1.44$	na	na	na	na
	Illamola et al. [25]	$\theta1 \times ((cWT/1920)^{\theta2}) \times ((eGFR/32.28)^{\theta3})$	$\theta1 = 0.094$; $\theta2 = 0.799$; $\theta3 = 0.659$	$\theta4 \times ((cWT/1920)^{\theta5})$	$\theta4 = 0.641$; $\theta5 = 1.04$	$\theta6$	$\theta6 = 0.478$	$\theta7 \times (cWT/1920)^{\theta8}$	$\theta7 = 0.042$ $\theta8 = 0.909$
Infants/children/adolescents									
Children (burns)	Yu et al. [28]	$\theta1 \times (cWT/70)^{\theta2}$	$\theta1 = 7.22$; $\theta2 = 0.75$ (f)	$\theta3 \times (cWT/70)^{\theta4}$	$\theta3 = 22.7$; $\theta4 = 1$ (f)	na	na	na	na
Children/adolescents	Yu et al. [28]	$\theta1 \times (cWT/70)^{\theta2}$	$\theta1 = 5.36$; $\theta2 = 0.75$ (f)	$\theta3 \times (cWT/70)^{\theta4}$	$\theta3 = 18.7$; $\theta4 = 1$ (f)	na	na	na	na
Infants/children/adolescents (burns)	Sherwin et al. [20]	$\theta1 \times (cWT/70)^{\theta2}$	$\theta1 = 5.98$; $\theta2 = 0.75$ (f)	$\theta3 \times (cWT/70)^{\theta4}$	$\theta3 = 16.7$; $\theta4 = 1$ (f)	$\theta5 \times (cWT/70)^{\theta6}$	$\theta5 = 40.1$; $\theta6 = 1$ (f)	$\theta7 \times (cWT/70)^{\theta8}$	$\theta7 = 3.38$; $\theta8 = 0.75$ (f)

Table 4 continued

Population	Study	IIV (%) [CV%]				RUV [CV%]	
		CL	V_c	V_p	Q	Add (mg/L)	Prop (%)
Neonates							
	De Cock et al. [22]	29.98 [14.9]	na	na	na	0.517 [27.2]	24.78 [8.19]
	Sherwin et al. [21]	4.6. [nr]	0.446 [nr]	na	na	nr [2.42]	nr [3.8]
	Allegaert et al. [19]	33.6 [7.2]	45.1 [3.3]	na	na	1.59 [31.7]	na
	Allegaert et al. [24]	11.4 [1.6]	8 [1.1]	na	na	0.644 [24.3]	0.18 [14.3]
	Botha et al. [23]	18 [nr]	13 [nr]	na	na	na	29.15 [nr]
	Illamola et al. [25]	34.93 [16.5]	21.33 [26.2]	na	50.6 [63.7]	0.507 [15.9][a]	28.3 [6.9][a]
Infants/children/adolescents							
Children (burns)	Yu et al. [28]	24.5 [25.2]	10 (fix)	na	na	1.80 [37.5]	19.1 [25.1]
Children/adolescents	Yu et al. [28]	55 [22.7]	10 (fix)	na	na	0.499 [25.5]	19.5 [33.2]
Infants/children/adolescents (burns)	Sherwin et al. [20]	29.6 [26.4]	24.2 [9.6]	na	10 (fix)	1.35 [45.14]	19.6 [33.24]

Add additive, *BWT* birth weight, *CL* total clearance, *CV* coefficient of variation, *cWT* current body weight (kg), *eGFR* estimated glomerular filtration rate, *f* fixed parameter, *FINO* (dichotomic) scaling factor for the use of inotropes, *FNSAID* scaling factor for premature neonates given a non-steroidal anti-inflammatory drug, *FVENT* (dichotomic) scaling factor for the use of inotropes, *IB* (dichotomic) ibuprofen administration, *IIV* inter-individual variability, *na* not applicable, *nr* not reported, *PCA* postconceptional age (days), *PMA* postmenstrual age (days), *PNA* postnatal age (days), *Prop* proportional; *Q* inter-compartmental clearance, *RUV* residual variability, *SCR* serum creatinine, *SEX* (dichotomic) gender, *SGA* (dichotomic) intrauterine growth retardation, V_c central distribution volume, V_p peripheral distribution volume

[a]RUV values provided in the original reference were inverted by error

infants (<1000 g) and extremely premature (GA <28 weeks), therefore providing a possible bias in the pharmacokinetic model. V_d values were typically larger in neonates than in older pediatric individuals. This may be explained by the fact that for highly water-soluble compounds, such as amikacin, V_d values in neonates are usually greater than in adults [29]. In general, reported values of IIV in V_d and CL were quite similar, but with some exceptions such as the study of Sherwin et al. [21], which reported an IIV in V_d of 4.6 and 0.446% in CL. In this case, and as stated in the limitations of the paper, the opportunity to capture IIV was limited due to the great similarity of the neonates included in the study (most of them extremely low BWT and premature). Another example is the study of Yu et al. [28], specifically the group of non-burned children and adolescents, where IIV in V_d was not estimated but fixed at 10%. Therefore, the reported IIV in V_d could be falsely low, and thus the difference between IIV in V_d and CL erroneous. Nonetheless, the magnitude of IIV in V_d and CL is of great importance, especially in the context of TDM, as it highlights the need to monitor C_{max} and C_{trough}, respectively.

Some inherent limitations in the comparisons of CL and V_d across studies exist based on scaling by current body weight as there are significant differences in the additional covariates present and associated parametrizations. The parameters were scaled linearly, and additional covariates that were present were not considered. In case of the study by De Cock et al. [22] BWT was reported, which makes the comparison with the other studies potentially less clear. Nonetheless we believe this comparison is of relevance as it suggests general agreement between studies in specific pediatric patient populations.

The most commonly included predictors of IIV on CL were cWT, age-related covariates (postnatal age [PNA], postmenstrual age [PMA], postconceptional age [PCA]), and predictors of glomerular filtration rate [GFR]. For V_c, cWT was the most common covariate included as predictor. All pediatric analyses included cWT for CL and V_c, except the analysis by De Cock et al. [22], which incorporated BWT instead of cWT on CL. The introduction of BWT instead of cWT was chosen by the authors to potentially more accurately reflect the antenatal maturation, while PNA, also introduced on CL, represents the postnatal maturation. The relationship between body weight and either CL or V_c was described by allometric equations [30] in all analyses. In all non-neonatal and in only two of the six neonatal analyses, a fixed allometric power parameter value of 0.75 for CL and 1 for V_c were assigned. These values were estimated in the remaining four neonatal analyses.

Age descriptors included in the models were PCA [19], PMA [21, 24], and PNA [22]. PCA and PMA, which are a

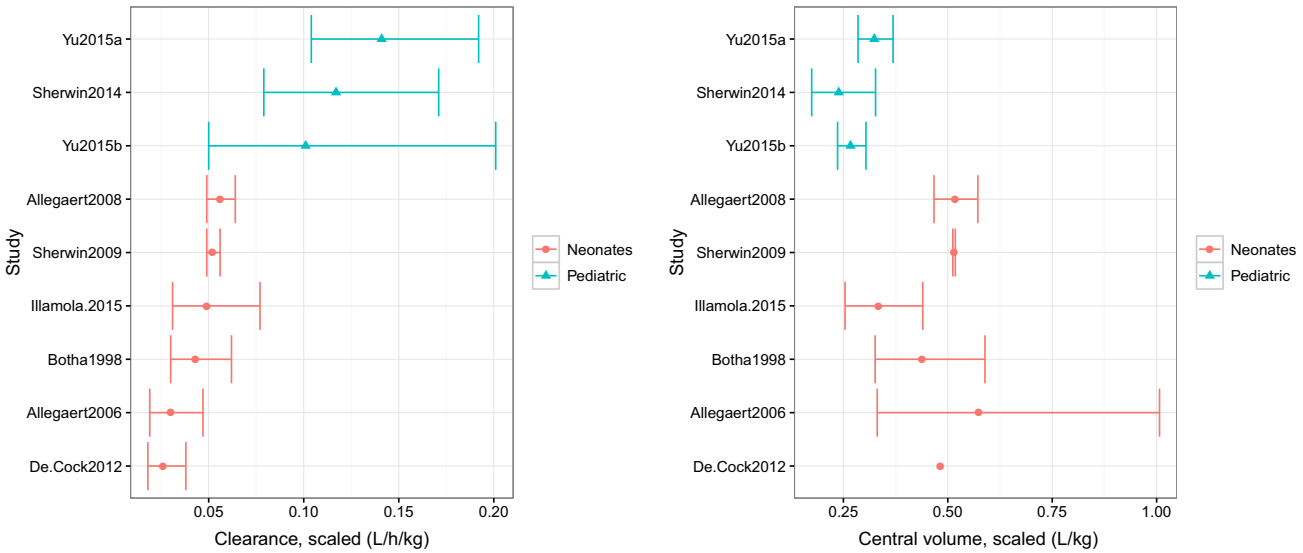

Fig. 1 Typical parameter estimates for clearance and central volume, scaled by body weight. The error bars represent the 10th and 90th percentile for inter-individual variability, if estimated. It should be noted that De Cock et al. [22] use birth weight and not current body weight

Table 5 Covariates tested and retained for total clearance and central volume of distribution for different models

Population	Study	Covariates tested	Retained covariates in final model	
			Covariates ~ CL	Covariates ~ V_c
Neonates				
	De Cock et al. [22]	cWT, BWT, GA, PMA, PNA, SCR, IB, PEB	BWT, PNA, IB	cWT
	Sherwin et al. [21]	SEX, cWT, GA, PMA, PNA, SCR, AP1, AP5, SEP	cWT, PMA	cWT
	Allegaert et al. [19]	cWT, PCA, FNSAID, PEB, PEI, AP1, AP10, PNC	cWT, PCA, FNSAID	cWT
	Allegaert et al. [24]	cWT, PMA, PNA, SGA, SCR, DP, IB, PBC, RS	cWT, PMA, SGA, SCR, FINO, FVENT	cWT, PNA, FINO, FVENT
	Botha et al. [23]	SEX, GA, PCA, PNA, SFGA, DR, AP1, AP5	SEX, cWT	cWT
	Illamola et al. [25]	SEX, GA, BWT, HT, eGFR, SCR, PMA, PNA	cWT, CLCR	cWT
Infants/children/adolescents				
Children (burns)	Yu et al. [28]	AGE, SEX, cWT, HT, SCR, PBS, TEB	cWT	cWT
Children/adolescents	Yu et al. [28]	AGE, SEX, cWT, HT, SCR	cWT	cWT
Infants/children/adolescents (burns)	Sherwin et al. [20]	AGE, SEX, cWT, HT, SCR, PBS	cWT	cWT

AP1 Apgar score at minute 1, *AP5* Apgar score at minute 5, *AP10* Apgar score at minute 10, *BWT* birth weight, *CL* total clearance, *cWT* current body weight, *DP* co-administration of dopamine, *DR* dosing regimen (once or twice per day), *eGFR* estimated glomerular filtration rate, *FINO* scaling factor for the use of inotropes, *FNSAIDs* scaling factor for premature neonates given a non-steroidal anti-inflammatory drug, *FVENT* scaling factor for the use of positive pressure artificial ventilation, *GA* gestational age, *HT* height, *IB* co-administration of ibuprofen, *PBC* positive blood culture, *PBS* percentage of body surface burned, *PCA* postconceptional age, *PEB* prenatal exposure to betamethasone, *PEI* prenatal exposure to indomethacin, *PMA* postmenstrual age, *PNA* postnatal age, *PNC* perinatal chorioamnionitis, *RS* respiratory support, *SCR* serum creatinine, *SEP* sepsis, *SEX* gender, *SFGA* size for gestational age, *SGA* intrauterine growth retardation, *TEB* amount of time elapsed since the burn injury, V_c central volume of distribution

combination of GA and PNA, quantify both maturation before and after birth, whilst PNA only quantifies maturation after birth. The inclusion of one or other age descriptor in the model could be influenced by which of

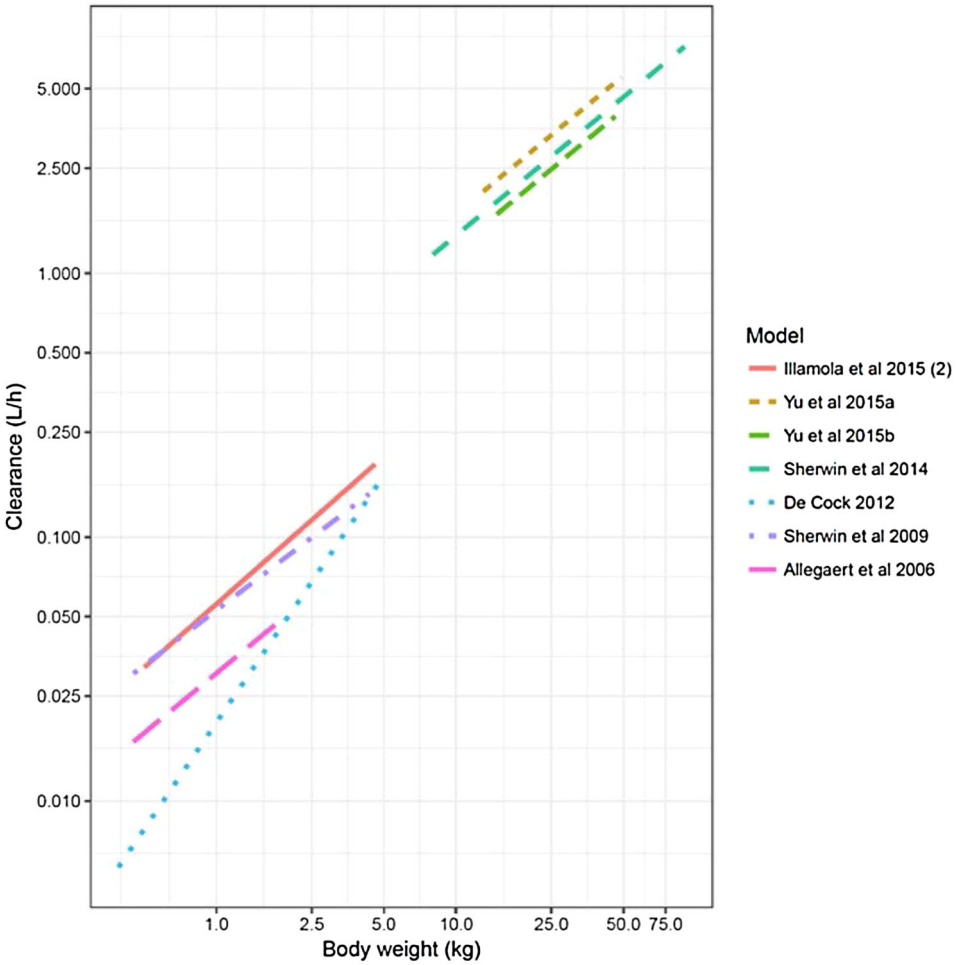

Fig. 2 Change in mean population pharmacokinetic model-predicted clearance in relation to body weight, in neonates and pediatric patients. It should be noted that De Cock et al. [22] use birth weight and not current body weight

these covariates were tested. While three [21, 22, 25] of the six neonatal analyses tested three different age descriptors (GA, PMA, and PNA), the three remaining analyses only tested one. Age descriptors are composite metrics that include description of both changes in size and renal function. As the majority of models included both cWT and age descriptors, the function of age in such models can thus be interpreted as a surrogate marker for renal function. A limitation of such an approach may be cases where patients have an atypical renal function for their respective age.

Three [21, 22, 25] of the six neonatal studies evaluated the potential use of predictors of GFR (e.g., serum creatinine, eGFR) as predictors of IIV on CL instead of age, with one analysis finally selecting eGFR as a final predictor [25]. This has the advantage of being a more direct renal function marker that is directly relevant for the renal CL of amikacin, and which thereby may allow it to better handle atypical patients. However, the use of serum creatinine levels in neonates is still controversial due to the influence of maternal creatinine levels and variations during the first year of PNA [31], as well as the bioanalytical method used for its quantification. In addition to predictors of GFR, some analyses included indirect predictors that may affect renal function, including the use of NSAIDs [19, 22] and inotrope support [24]. Finally, burn injuries are known to have significant effects on the pharmacokinetics of several drugs [32–34]. Indeed, also for amikacin, Yu et al. [28] reported increased CL and V_c values of 34.5 and 21.4%, respectively, in a group of children with burn injuries compared with a group of children without. Across all analyses, the inclusion of potential predictors for IIV was generally guided by data-driven decision making, i.e., by goodness-of-fit metrics, except for decisions to include fixed allometric scaling.

Residual variability is of great importance when the developed models are used for TDM applications because high additive and proportional errors may significantly impact the uncertainty of predicted C_{trough} and C_{max} values, respectively. For that reason, these values will dictate the utility of the developed model to identify the optimal schedule dosing regimen in clinical practice.

Only two population analyses also proposed optimized model-based dosing regimens for neonates [21, 22, 25]

Table 6 Amikacin dosing recommendations for neonates suggested by different population pharmacokinetic analyses

Study	Population	PMA (weeks)	PNA (days)	cWT (g)	Dose (mg/kg)	Interval (h)	Target
Sherwin et al. [21]	Neonates	< 29	na	na	15	36	C_{max}: 24–35 mg/L
		29–36			14	24	AUC_{24}: 130–590 mg h/L
		> 36			15	24	
De Cock et al. [22]	Neonates	na	< 14	0–800	16	48	C_{max}: 24–35 mg/L
				800–1200	16	42	C_{trough}: 1.5–3 mg/L
				1200–2000	15	36	
				2000–2800	13	30	
				≥ 2800	12	24	
			≥ 14	0–800	20	42	
				800–1200	20	36	
				1200–2000	19	30	
				2000–2800	18	24	
				≥ 2800	17	20	

AUC_{24} area under the concentration–time curve from time zero to 24 h, C_{max} maximum (peak) concentration, C_{trough} trough concentration, *cWT* current body weight, *na* not applicable, *PMA* postmenstrual age, *PNA* postnatal age

(Table 6). The dosing guidelines proposed by Sherwin et al. [21] are based on PMA, and those of De Cock et al. [22] are based on combinations of PNA and cWT. In both cases, the recommended dose intervals increase with the immaturity of the neonates. However, based on the considerable IIV of CL reported, amikacin dosing intervals can differ significantly within the same group. For the development of the proposed dosing regimens, both Sherwin et al. [21] and De Cock et al. [22] adopted C_{max} values between 24 and 35 mg/L as the target value. However, Sherwin et al. [21] additionally used the area under the concentration–time curve from time zero to 24 h (AUC_{24}) (130–590 mg h/L), while De Cock et al. [22] used C_{trough} (1.5–3 mg/L). The dose regimen by De Cock et al. [22] appeared to be derived without full consideration of IIV since the authors note simulations were conducted "with exclusion of the interindividual and residual variability". However, it was the only recent proposed optimized dosing regimen that was also successfully prospectively validated [17] to improve target C_{trough} and C_{max} values in almost all individuals.

In order to define rational dosing regimens, population pharmacokinetic/pharmacodynamic studies in children are needed. In this review, only one study explored pharmacokinetic/pharmacodynamic relationships on the basis of individual pharmacokinetic parameter estimates, which brings to light a lack of pharmacokinetic/pharmacodynamic studies in pediatrics that needs to be urgently rectified [9, 35]. The current overview of different published population pharmacokinetic models for amikacin will allow further pharmacokinetic/pharmacodynamic simulation studies to calculate the target attainment for different dose regimen across models, and particularly within different pediatric patient populations studied.

5 Conclusions

This review summarizes key analysis of the population pharmacokinetics of amikacin. We summarized key predictors that can be considered for amikacin dose regimen optimization, which include a combination of body weight and age or renal function-based predictors. Population pharmacokinetic studies of amikacin in non-neonatal patients are, however, limited, and are non-existent for most of the infant population (3 months to 2 years of age), which represents an important knowledge gap as there is a clear change in typical CL between these two age groups. Furthermore, studies in specific patient groups where the use of amikacin is of relevance (i.e., cystic fibrosis) were not identified. These pathologies could contribute to changes on amikacin pharmacokinetics. The clinical implementation of improved amikacin dosing regimens derived from population pharmacokinetic analyses could have an important contribution to further treatment optimization. However, the IIV that remains even after inclusion of patient-specific predictors is significant and the use of TDM is likely to remain necessary.

Compliance with Ethical Standards

Funding No sources of funding were used to assist with the preparation of this review.

Conflict of interest Sílvia M. Illamola, Catherine M. Sherwin, and J. G. Coen van Hasselt have no conflicts of interest that are relevant to the content of this review.

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