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REVIEW ARTICLE

A Review of Vancomycin, Gentamicin, and Amikacin Population Pharmacokinetic Models in Neonates and Infants

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Abstract

Population pharmacokinetic (popPK) models are an essential tool when implementing therapeutic drug monitoring (TDM) and to overcome dosing challenges in neonates in clinical practice. Since vancomycin, gentamicin, and amikacin are among the most prescribed antibiotics for the neonatal population, we aimed to characterize the popPK models of these antibiotics and the covariates that may influence the pharmacokinetic parameters in neonates and infants with no previous pathologies. We searched the PubMed, Embase, Web of Science, and Scopus databases and the bibliographies of relevant articles from inception to the beginning of February 2024. The search identified 2064 articles, of which 68 met the inclusion criteria (34 for vancomycin, 21 for gentamicin, 13 for amikacin). A one-compartment popPK model was more frequently used to describe the pharmacokinetics of the three antibiotics (91.2% vancomycin, 76.9% gentamicin, 57.1% amikacin). Pharmacokinetic parameter (mean ± standard deviation) values calculated for a "typical" neonate weighing 3 kg were as follows: clearance (CL) 0.34 ± 0.80 L/h for vancomycin, 0.27 ± 0.49 L/h for gentamicin, and 0.19 ± 0.07 L/h for amikacin; volume of distribution (V_d): 1.75 ± 0.65 L for vancomycin, 1.54 ± 0.53 L for gentamicin, and 1.67 ± 0.27 L for amikacin for one-compartment models. Total body weight, postmenstrual age, and serum creatinine were common predictors (covariates) for describing the variability in CL, whereas only total body weight predominated for V_d. A single universal popPK model for each of the antibiotics reviewed cannot be implemented in the neonatal population because of the significant variability between them. Body weight, renal function, and postmenstrual age are important predictors of CL in the three antibiotics, and total body weight for V_d. TDM represents an essential tool in this population, not only to avoid toxicity but to attain the desired pharmacokinetic/pharmacodynamic index. The characteristics of the neonatal population, coupled with the lack of prospective studies and external validation of most models, indicate a need to continue investigating the pharmacokinetics of these antibiotics in neonates.

1 Introduction

Infections remain a leading cause of death in neonates [1]. Systemic infections cause about 2.3 million neonatal deaths each year globally [1, 2]. The ethical, logistical, regulatory, and technical difficulties associated with conducting studies on newborns have prevented them from being considered

Key Points

The significant variability in pharmacokinetics between neonatal populations with vancomycin, gentamicin, and amikacin makes a universal population pharmacokinetic model for each antibiotic unfeasible.

Total body weight, postmenstrual age, and serum creatinine were the covariates most frequently included to explain variability in drug clearance. The primary explanatory factor for variability in the volume of distribution was total body weight.

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a high-priority population for inclusion in clinical trials, despite their high prevalence of infections [3, 4]. Of 40 antibiotics approved for use in adults since 2000, only four have included dosing information for neonates in their labeling [1].

Misuse of antibiotics or inadequate dosing can lead to treatment failure and the emergence of drug-resistant pathogens, resulting in longer hospital stays and increased mortality [5]. Neonates exhibit major and rapid physiological changes in the distribution, metabolism, and excretion of drugs administered intravenously [6]. The neonatal population is characterized by a higher body water percentage, reduced protein binding, and decreased renal clearance at birth, which gradually increases as the renal system matures [7, 8]. Fat and extracellular water proportions vary extensively across ages. Fat percentage increases with age (6% in premature infants, 13.4% in full-term infants, 18% in adults, and 30% in elderly people), whereas the water proportion decreases (80% in premature infants, 70% in full-term infants, 60% in adults, and 54% in elderly people) [9]. Compared with adults, newborns have higher inter- and intraindividual variability in pharmacokinetics, especially for antibiotics [6, 10].

The pharmacokinetic differences between newborns and adults justify specific pharmacokinetic studies in neonates. After the introduction of the nonlinear mixed-effects modeling methodology, the population pharmacokinetic (popPK) approach became a reference technique in the neonate population. The population-based modeling method assesses both intra- and inter-individual variability. This allows for the determination of optimal dosing regimens by identifying and quantifying sources of pharmacokinetic variability, thereby improving our understanding and optimization of pharmaceutical interventions [4, 11]. This method has an advantage over classical pharmacokinetic analysis in that the effects of covariates such as age, weight, disease state, and organ function on pharmacokinetic parameters can be obtained through sparse sampling from each subject. This reduces the need for blood sampling, which facilitates this type of study because it is unpractical and unethical to take multiple blood extractions from neonates [5, 12].

Choosing the appropriate popPK model for each antibiotic is essential in clinical practice, as it improves therapeutic drug monitoring (TDM) by providing better individualized predictions [5]. Model-informed precision dosing (MIPD) is a clinical strategy that employs mathematical and pharmacokinetic/pharmacodynamic models, along with patient-specific data, to optimize and personalize drug-dosing regimens. This approach leverages prior knowledge (such as population-based models) and real-time patient information (such as drug concentrations and clinical responses) to achieve the best therapeutic outcomes while minimizing adverse effects [13]. However, the performance of most of the published popPK models remains unknown in other groups of patients than those used for its development [14, 15]. Other previous reviews of popPK models have been conducted in pediatrics, including neonates, infants, and children [5, 16, 17]. However, we focused only on the neonatal and infant population because of its specific characteristics and the remaining knowledge gaps in this population, which may account for the high intra-individual variability and may predict dosing. In addition, it includes common antibiotics used in clinical practice and candidates for TDM, allowing us to compare the covariates influencing each of them.

The aim of the present study was to review the popPK models of the most widely prescribed antibiotics that are subject to TDM (vancomycin, gentamicin, and amikacin) in neonates and infants and to determine the applied structural models in this population. We analyzed the covariates that significantly influence the pharmacokinetics of each antibiotic and compared the standardized pharmacokinetic parameters (clearance [CL] and volume of distribution [V_d]) of the studies included. We also collected the pharmacodynamic targets of each study included.

2 Search Methodology

2.1 Literature Search Strategy

We searched the MEDLINE (via PubMed), Embase, Web of Science, and Scopus databases from inception to the beginning of February 2024 using the following combination of terms for each antibiotic: (vancomycin OR gentamicin OR amikacin) AND (pharmacokinetic model OR pharmacokinetic analysis OR population pharmacokinetics) AND (newborn OR neonate). The initial search was limited to studies performed in humans that described popPK models of the antibiotics chosen. We also inspected the bibliographies of relevant articles.

2.2 Inclusion and Exclusion Criteria

All articles had to meet the following criteria: (i) observational studies or clinical trials describing popPK models in neonates and infants with no previous pathologies, including those with patent ductus arteriosus, (ii) intravenous administration of the antibiotic, (iii) gestational age (GA) $\leq$ 44 weeks, and (iv) written in English, Spanish, French, or German.

We excluded the following: (i) articles lacking equations to explain the effect of covariates on pharmacokinetic parameters and mean values of the pharmacokinetic parameters, (ii) reviews of published popPK models, (iii) validation studies for published popPK models, (iv) popPK models in neonates undergoing extracorporeal membrane oxygenation or

controlled hypothermia and pathological conditions such as cystic fibrosis or hypoxic–ischemic encephalopathy, (v) studies including neonates and other populations (young infants, children, or adults) for model development, and (vi) studies for which the full text was not available upon request to the author.

2.3 Data Extraction

One investigator reviewed the literature by assessing the titles and abstracts according to the inclusion criteria. Any discrepancies were settled by consensus with a second investigator. One investigator extracted the following data from the studies: years of study duration, study design, country, statistical modeling software, total number of samples and patients, population characteristics, structural pharmacokinetic model, developed model for calculating the following pharmacokinetic parameters: clearance (CL), intercompartmental clearance (Q), volume of distribution (V_d), volume of distribution of central compartment (V_c), volume of distribution of peripheral compartment (V_p), and their variability, the included covariates in each equation, as well as the mean CL in L/h/kg and V_d in L/kg, as well as the pharmacodynamic target. CL and V_d standardized by the mean or median weight of the included population were calculated manually if such data were not provided in the article but could be calculated from the information provided in the text. In that case, the weight used is specified under the CL or V_d value.

To describe the characteristics of the population included in each study, the range for GA in weeks, postnatal age (PNA) in days, postmenstrual age (PMA) or post-conceptional age (PCA) in weeks, and total body weight (WT) expressed as mean ± SD or median (range) were recorded. Some studies included the PCA instead of the PMA, and we included this information, even though the American Academy of Pediatrics Committee on the Fetus and Newborn [18] recommend that PCA should no longer be used in clinical pediatrics.

3 Characteristics of Population Pharmacokinetic Models

A total of 2064 articles were identified. After removing duplicates, 887 relevant studies were screened according to the title and abstract. Finally, 178 full texts were assessed for eligibility, and 68 of these were included in this review (34 for vancomycin, 21 for gentamicin, and 13 for amikacin) (Fig. 1). The year of publication ranged from 1982 until the end of 2023.

3.1 Vancomycin

Vancomycin had the highest number of popPK models in the literature, totaling 36 across 34 studies. Although the study years ranged from 1983 to 2021, most models were developed after the year 2000. All studies except Cristea et al. [19] were conducted in only one country and mostly in a single hospital. The studies included neonates ranging in age from 0 to 562.8 days, GA from 22 to 42.1 weeks, and PMA from 22 to 110 weeks. The WT at the time of the study ranged from 0.32 to 14.9 kg. Nonlinear mixed-effects modeling was the most widely used approach for describing vancomycin popPK models in neonates, with most (25 of 36 models [69.4%]) using NONMEM® statistical modeling software to estimate the individual pharmacokinetic parameters. Other studies used a Bayesian forecasting approach (Abbott Base Pharmacokinetic System, ADAPT II, Pumas or Phoenix™ NLME) to calculate pharmacokinetic parameters. Jarugula et al. [20] used the largest number of vancomycin samples ($n = 2471$) to develop the model and the largest sample of patients ($n = 934$). Vancomycin popPK were best described by a one-compartment (1-CMT) approach in 31 models and by a two-compartment (2-CMT) approach in five models. Seay et al. [21] developed both a 1-CMT and a 2-CMT model using the same population. In most cases, studies with rich sampling found that a 2-CMT model [19, 21–23] better described the pharmacokinetic parameters than did a 1-CMT model.

3.2 Gentamicin

A total of 26 models for gentamicin were described in 21 articles. The years of study ranged from before 1988 to 2013. Most models were developed in the Netherlands ($n = 4$) and the USA ($n = 3$). The studies included neonates ranging from 0 to 120 days, GA from 22 to 43 weeks, and PMA from 23.3 to 43.8 weeks. The WT at the time of the study ranged from 0.44 to 5.51 kg. The most-often used statistical modeling software was NONMEM®, which was used in 14 of the 26 models described (53.8%). Fuchs et al. [24] had the largest gentamicin ($n = 3039$) and patient ($n = 1449$) samples. Four authors [25–28] reported more than one model using different covariates in each one. Most commonly, a 1-CMT model was applied ($n = 21$) to describe gentamicin popPK in newborns. Three studies applied a 2-CMT model, and two studies used a 3-CMT model. Like the vancomycin studies, those with more samples better fit a 2-CMT or 3-CMT than a 1-CMT model to describe the pharmacokinetics of gentamicin.

3.3 Amikacin

The fewest popPK models were found for amikacin ($n = 14$ in 13 studies). The years of study ranged from 1987 to 2021.

Most models were developed in Belgium ($n = 5$). The studies included neonates ranging from 0 to 86 days, GA from 24 to 43 weeks, and PMA from 24 to 51.4 weeks. The WT at the time of the study ranged from 0.39 to 5.04 kg. NONMEM® was again the most used statistical modeling software, in 11 of the 14 models developed (78.6%). The largest amikacin samples ($n = 2186$) and neonatal population ($n = 874$) came from the study by De Cock et al. [29]. Illamola et al. [30] reported two popPK models using a different set of covariates. An external validation of published amikacin models in Indian term neonates found that the model from Illamola et al. provided the lowest relative median absolute prediction error and relative root mean square error [31]. Smits et al. [32] prospectively evaluated the model by De Cock et al. [29] and re-estimated it to develop a new one to optimize dosing in neonates with suboptimal trough levels. Eight studies used a 1-CMT approach to describe the data, and the remaining six studies used a 2-CMT approach. The largest population studies preferred 2-CMT over 1-CMT models to describe pharmacokinetic parameters.

General information about the articles and the characteristics of the populations included is presented in Table 1.

4 Population Pharmacokinetic Analysis

4.1 Vancomycin

The median values of the pharmacokinetic parameters of vancomycin popPK models are summarized in Table 2.

The frequency of covariates included in the popPK model ranged from one to six for CL. WT (83.3%), serum creatinine (Cr) (50.0%), PMA (44.4%), estimated creatinine clearance (ClCr; 13.8%), PNA (13.8%), and GA (11.1%) were the most frequently reported significant predictors of vancomycin CL. In general, vancomycin CL was positively affected by WT, PMA, GA, and PNA and negatively affected by Cr levels. Some models also included PCA, dopamine, concomitant therapy with a nonselective cyclooxygenase inhibitor, artificial ventilation, concomitant therapy with amoxicillin–clavulanic acid, vancomycin volume of infusion, and urine output as covariates.

The covariates included in vancomycin popPK models for estimating V_d included up to two covariates, although most models only included one ($n = 30$). WT was the most frequently reported significant predictor of V_d among almost all popPK models (91.7%). The model by Kato et al. [47] assumed a fixed V_d (1.19 L), like the 2-CMT model of Song et al. [48], with fixed V_c (1.27 L) and V_p (2.422 L). The V_d was influenced only by PMA in the model by Silva et al. [36]. Two models included concomitant treatment with inotropes or spironolactone as covariates [41, 42].

4.2 Gentamicin

The median values of the pharmacokinetic parameters of gentamycin popPK models are summarized in Table 3.

The number of covariates included in the popPK models ranged from one to four for CL. Four studies did not report the equations for CL and V_d. The covariates most frequently included to estimate gentamicin CL were WT (72.7%), PNA (40.9%), GA (31.8%), Cr (18.2%), PCA (14.2%), and PMA (9.5%). Other covariates also included in some models were Apgar score, sex, birth weight (BW), and ClCr.

The covariates included in gentamicin popPK models for estimating V_d included up to two covariates. WT was reported to be a significant predictor of V_d among 18 popPK models (81.8%). GA ($n = 5$) and sepsis ($n = 2$) were the other covariates also included in the equations for estimating gentamicin V_d.

4.3 Amikacin

The median values of the pharmacokinetic parameters of amikacin popPK models are summarized in Table 4.

The number of covariates included in the popPK model ranged from one to six for CL. Three studies did not report the equations for CL and V_d. The covariates most frequently included to estimate gentamicin CL were WT (66.7%), PMA (41.7%), PNA (25.0%), and Cr (16.7%), which aligns with the study by Match et al. [31]. Other covariates also included in some models were sex, concomitant therapy with nonselective cyclooxygenase inhibitors, nonsteroidal anti-inflammatory drug or ibuprofen, intrauterine growth retardation, GA, BW, inotropes, artificial ventilation, shock, sepsis, and ClCr.

Amikacin popPK models for estimating V_d included up to four covariates. WT was reported to be a significant predictor of V_d among nine popPK models (64.3%). The most complex equation for CL and V_d was in the study by Allegaert et al. [80], which included five and four covariates for estimating CL and V_d, respectively.

Allegaert et al. developed three popPK models for amikacin [40, 79, 80]. One [40] used the same equation for vancomycin and amikacin CL and a correction factor ($FCl_{amikacin}$) for scaling vancomycin to amikacin CL.

The equations for CL and V_d derived from popPK models of the included studies are summarized in Table 5, and the model variability is shown in Table S1 in the supplementary material. The CL and V_d calculated for a "typical" neonate of WT 3kg, PNA 30 days, PMA 40 weeks, GA 30 weeks, BW 2 kg, Cr 0.6 mg/dL (53 µmol/L), ClCr 30 ml/min/1.73m^2, and no other covariates are summarized in Table S2 in the supplementary material.

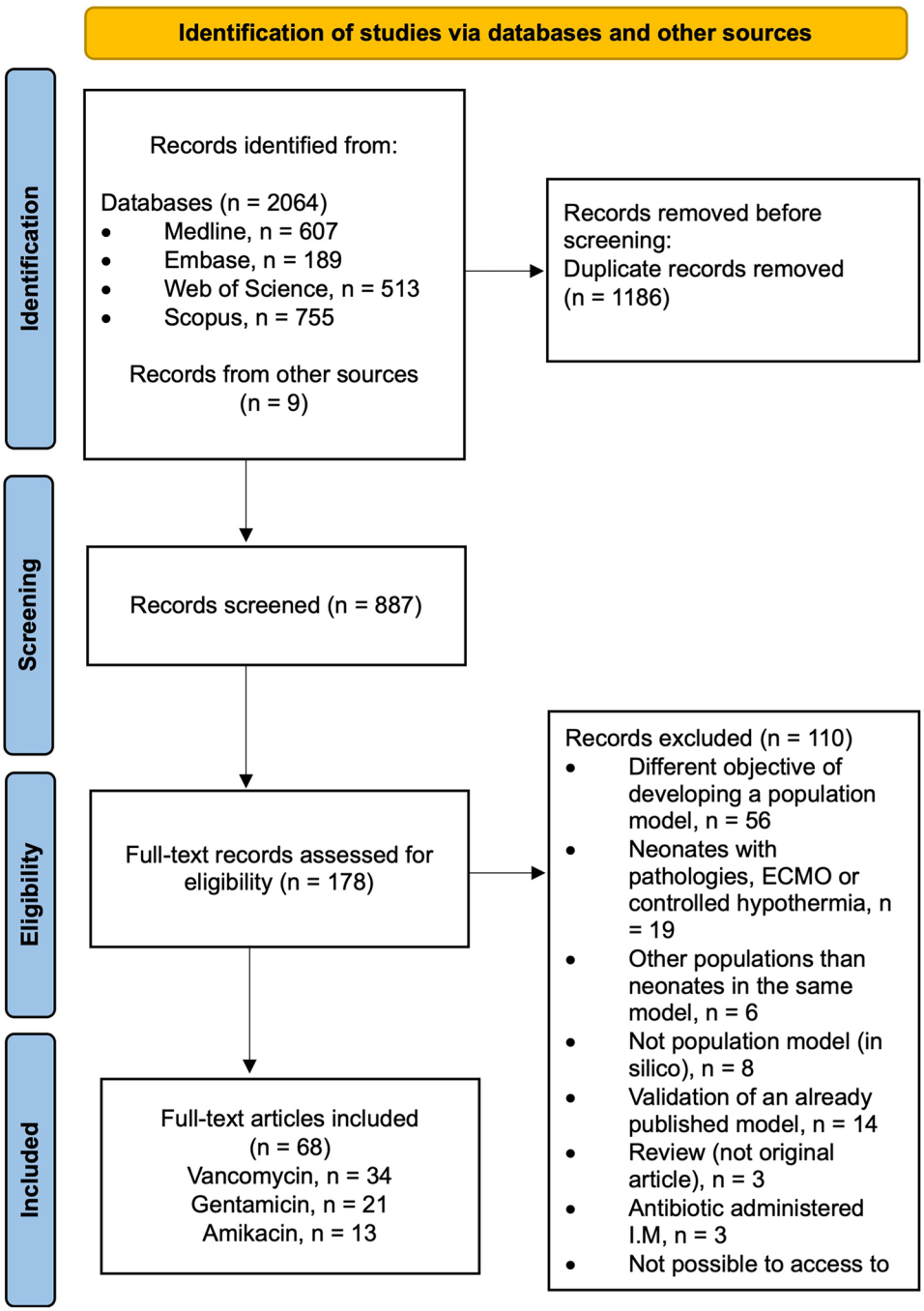

Fig. 1 Flow chart of the article selection process. Abbreviations: ECMO: extracorporeal membrane oxygenation; I.M: intramuscular

5 Discussion

This literature review identified 68 popPK models for vancomycin, gentamicin, and amikacin in neonates and infants. The most models have been developed for vancomycin (n = 34) because of its wide use in clinical practice and experience with TDM, followed by gentamicin (n = 21) and, to a lesser extent, amikacin (n = 13). In all three antibiotics, the most common covariate included to explain the variability in CL was WT, especially in vancomycin (83.3%). Some studies [6, 24, 40, 41, 43, 49, 51, 54, 56–58, 72, 74, 75, 79, 80, 84–86] included this covariate in the equation using the accepted and commonly used allometric scaling of weight, with a fixed exponent of 0.75. Others [29, 30, 32, 44, 46, 48, 61, 69, 73, 78, 81, 82] reported estimated values ranging from 0.155 to 1.45. This wide range could be because the estimation of the allometric coefficient may be quite imprecise and depends mainly on the weight distribution in the subjects used to develop the popPK model [87].

Table 1 Characteristics of the neonate population pharmacokinetic studies included in the review

Study, publication year	Years of study	Study design	Country	Statistical modeling software	Samples (N)	Patients (N)	Range GA (wk)	Range PNA (days)	Range PMA/PCA (wk)	Current weight (kg)	Structural pharmacokinetic model
Vancomycin pharmacokinetic models											
Schaible et al., 1986 [33]	1983	PD	USA	ND	ND	11	27–40	7–70	PCA 29–48	2.00 ± 1.22	1-CMT
Asbury et al., 1993 [34]	1990–1991	RD	USA	ND	28	19[a]	23–41	6–102	PCA 26.3–45.6	1.78 ± 1.08	1-CMT
Seay et al., 1994 [21]	1987–1989	RD	USA	NONMEM®	520	192	22–42	1–73	ND	1.48 ± 1.05 (0.39–4.35)	1- or 2-CMT
Rodvold et al., 1995 [35]	1989–1992	RD	USA	Abbott Base Pharmacokinetic System	31	29	23–41	4–88	PCA 23.5–47.5	1.86[b] (0.58–4.82)	1-CMT
Burstein et al., 1997 [22]	ND	PD	USA	ADAPT II	12	11	29.4–34	4–117	PCA 30.8–48.7	1.19 ± 1.25	2-CMT
Silva et al., 1998 [36]	1993–1996	RD	Portugal	NONMEM®	60	44	25–40	1–52	PCA 28–45	1.94 ± 0.95	1-CMT
Grimsley and Thomson, 1999 [37]	ND	PD	UK	NONMEM®	347	59	25–41	2–76	PCA 26–45	1.52 (0.57–4.23)	1-CMT
De Hoog et al., 2000 [38]	1992–1997	RD	Netherlands	NONMEM®	ND	108	24–41	3–27	PCA 26–42	1.0 (0.49–4.63)	1-CMT
Capparelli et al., 2001 [23]	1994–1997	PD	USA	NONMEM®	1103	374	33.5 ± 6.0	70 ± 100	ND	2.82 ± 2.33	2-CMT
Kimura et al., 2004 [39]	ND	PD	Japan	NONMEM®	88	19	24.1–41.3	3–71	PCA 25.1–48.4	0.710–5.2	1-CMT
Allegaert et al., 2007 [40]	2002–2006	PD	Belgium	NONMEM®	648	249	23–34	1–27	PMA 24–37	1.25 ± 0.47	1-CMT
Anderson et al., 2007 [41]	2002–2005	RD	Belgium	NONMEM®	604	214	ND	1–27	PMA 24–34	1.30 (0.42–2.6)	1-CMT
Marqués-Miñana et al., 2010 [42]	ND	PD	Spain	NONMEM®	ND	70	24–42	4–63	PMA 25.1–48.1	1.7 (0.7–3.7)	1-CMT
Lo et al., 2010 [43]	1999–2005	RD	Malaysia	NONMEM®	835	116	23–31	1–32	PMA 23–34	0.82 ± 0.11[c]	1-CMT
Mehrotra et al., 2014 [85]	1990–2007	RD	USA	NONMEM®	267	134	23–41	1–121	PMA 24.6–44	2.5 ± 1.1	1-CMT

Table 1 (continued)

Study, publication year	Years of study	Study design	Country	Statistical modeling software	Samples (N)	Patients (N)	Range GA (wk)	Range PNA (days)	Range PMA/PCA (wk)	Current weight (kg)	Structural pharmacokinetic model
Zhao et al., 2013 [44]	2010–2011	PD	France	NONMEM®	207	116	ND	1–120	PMA 24.4–49.4	1.70 ± 0.96; 1.4 (0.46–5.68)	1-CMT
Frymoyer et al., 2014 [45]	2007–2012	RD	USA	NONMEM®	1702	249	22–42	0–173	PMA 24–54	2.9 (0.5–6.3)	1-CMT
Bhongsatiern et al., 2015 [46]	2006–2011	RD	USA	NONMEM®	528	152	24–33	15–41	PMA 28.5–39.4	1.5 (0.45–4.3)	1-CMT
Kato et al., 2017 [47]	2010–2015	RD	Japan	Phoenix™ NLME	ND	10	23.4–31.6	11–28	PCA 26.1–34.4	0.97 ± 0.23; 0.93 (0.69–1.43)	1-CMT
Song et al., 2017 [48]	2011–2016	RD	China	Phoenix™ NLME	421	316	28–41	2–77	ND	3.95 (1.25–7.62)	2-CMT
Tseng et al., 2018 [49]	2011–2016	RD	Singapore	NONMEM®	429	76	23.9–40.3	4–223.7	PMA 25.1–57.5	1.04 (0.32–6.59)	1-CMT
Li et al., 2018 [50]	ND	PD	China	NONMEM®	165	80	25.7–41.1	4–126	PMA 29–47.1	2.87 ± 0.89; 2.74 (1.4–5.6)	1-CMT
Chen et al., 2018 [51]	2014–2017	RD	China	NONMEM®	330	213	25–42	6–59	PMA 28–47.9	2.73 (0.88–5.1)	1-CMT
Reilly et al., 2019 [52]	2009–2015	RD	USA	NONMEM®	212	182	ND	22.3 ± 19.2[c]	PMA 30.9 ± 4.4[c]	1.31 ± 0.73[c]	1-CMT
Germovsek et al., 2019 [53]	2014–2015	PD	UK	NONMEM®	102	54	23.7–41.9	1–156	ND	ND	1-CMT
Cristea et al., 2019 [19]	ND	PD	Netherlands, Portugal	ND	ND	319	23–34	1–30	PMA 24–38	1.26[b] (0.49–2.63)	2-CMT
Back et al., 2019 [54]	ND	RD	Korea	NONMEM®	ND	93	22.9–40.3	0.7–562.8	PCA 25.6–110	3.2 ± 2.6; 0.4–14.9	1-CMT
Dao et al., 2019 [55]	2006–2016	RD	Switzerland	NONMEM®	1831	405	24–42.1	0–146	PMA 28.3–36.5	1.1 (0.46–5.66)	1-CMT
Mulubwa et al., 2020 [56]	ND	PD	South Africa	Monolix®	45	19	23–34	3–58	PMA 30–34.7	1.48 (0.93–2.62)	1-CMT
Lee et al., 2021 [6]	2008–2017	RD	Korea	NONMEM®	900	207	23.3–41.5	0–115	PMA 24–48.4	1.8 (0.5–5.9)	1-CMT
Sasano et al., 2021 [57]	2009–2018	PD	Japan	NONMEM®	62	19	22.6–30.3	0–75	PMA 23.9–39.0	0.89 (0.45–1.46)	1-CMT

Table 1 (continued)

Study, publication year	Years of study	Study design	Country	Statistical modeling software	Samples (N)	Patients (N)	Range GA (wk)	Range PNA (days)	Range PMA/PCA (wk)	Current weight (kg)	Structural pharmacokinetic model
Jarugula et al., 2022 [20]	2011–2018	RD	USA	Pumas (v1.0.5)	2471	934	ND	0–184	PMA 20.89–66.68	3.58 (0.37–11.88)	1-CMT
Alsultan et al., 2023 [58]	ND	RD	Arabia Saudi	Monolix®	214	162	22–35	1–30	PMA 22–39	1.0 ± 0.29; (0.46–1.7)	1-CMT
Chung and Seto, 2023 [59]	2017–2021	RD	Canada	NONMEM®	442	ND	IQR 25.3–34.9	IQR 9–41.5	PMA (IQR) 30.2–38.5	1.71 (IQR 1.02–2.5)	1-CMT
Gentamicin pharmacokinetic models											
Kelman, 1984 [25]	ND	PD	UK	NONMEM®	82[d]	43[d]	26–39	0–120	ND	0.8–3.7	1-CMT
Thomson et al., 1988 [26]	ND	PD	UK	NONMEM®	270	113	26–41	1–46	ND	ND	1-CMT
Dodge et al., 1991 [60]	1988–1989	RD	USA	NPEM and STS	295	129	28.6 ± 2.2	ND	ND	ND	1-CMT
Izquierdo et al., 1992 [27]	ND	PD	Spain	MULTI2 program	ND	97	28–43	2–30	ND	ND	1-CMT
Jensen et al., 1992 [61]	ND	ND	USA	NONMEM®	ND	150	25–43	<7	ND	2.4[b] (0.62–4.9)	1-CMT
Rodvold et al., 1993 [62]	ND	PD	USA	Abbott base Pharmacokinetic System	19	19	27–41	1–84	PCA 27–44	1.95[b] (0.85–4.12)	1-CMT
Weber et al., 1993 [63]	ND	PD	Germany	NONMEM®	1057	469	ND	ND	ND	2.34	1-CMT
Vervelde et al., 1999 [64]	1996–1997	PD	Netherlands	NPEM	182	34	25–38	1–24	ND	1.82 ± 0.78; 0.69–3.9	1-CMT
Stickland et al., 2001 [65]	ND	PD	New Zealand	PKBUGS	ND	53	ND	ND	PMA 27–42	2.4 ± 1.16; 0.54–5.15	1-CMT
Touw et al., 2001[28]	1996–2001	RD	Netherlands	MW/PHARM (STS and IT2B)	ND	24	24.7–37	ND	ND	ND	1-CMT
Stolk et al., 2002 [66]	1998–2000	RD	Netherlands	MW/PHARM (IT2B) and NPEM2	725	177	24–42.4	0–8	ND	1.85 ± 1.04; 0.57–4.35	1-CMT
Botha et al., 2003 [67]	ND	PD	South Africa	NONMEM®	139	79	27–40	3–7	ND	2.06 ± 0.75; 1.95 (0.88–3.60)	1-CMT

Table 1 (continued)

Study, publication year	Years of study	Study design	Country	Statistical modeling software	Samples (N)	Patients (N)	Range GA (wk)	Range PNA (days)	Range PMA/PCA (wk)	Current weight (kg)	Structural pharmacokinetic model
DiCenzo et al., 2003 [68]	2000–2001	PD	USA	ADAPT II	ND	139	23–42	ND	ND	1.92 (0.47–5.00)	1-CMT
Lanao et al., 2004 [69]	1999–2003	RD	Spain	WINNONMIX	ND	97	24–39	1–26	ND	1.93 ± 0.84 (0.6–4.2)	1-CMT
Lingvall et al., 2005 [70]	2000–2003	RD	Sweden	NONMEM®	576	277	22–42	0–27	ND	2.52 (0.47–5.08)	1-CMT
García et al., 2006 [71]	ND	RD	Spain	NONMEM®	417	200	32.2 ± 3.0	5.5 ± 5.4	ND	1.68 ± 0.63	2-CMT
Nielsen et al., 2009 [72]	2005–2006	PD	Sweden	NONMEM®	894	61	23.3–42.1	0–45	ND	1.40 (0.50–5.05)	3-CMT
Sherwin et al., 2009 [73]	1999–2007	RD	New Zealand	NONMEM®	363	116	33.8 ± 5.4	2.7 ± 6.8	34.2 ± 5.6	2.3 ± 1.2	1-CMT
Fuchs et al., 2014 [24]	2006–2011	RD	Switzerland	NONMEM®	3039	1449	24–42	0–94	PMA 24.2–42.4	2.17 (0.44–5.51)	2-CMT
Germovsek et al., 2016 [74]	2012–2013	RD	UK	NONMEM®	1325	205	23.3–42.1	1–66	PMA 23.3–43.8	2.12 ± 0.63	3-CMT
Bijleveld et al., 2017 [75]	2012–2013	PD	Netherlands	NONMEM®	136	65	25–42	0–31	ND	ND	2-CMT
Amikacin pharmacokinetic models											
Assael et al., 1982 [76]	ND	PD	Italy	ND	ND	29	28.5–42	ND	ND	ND	2-CMT
Kenyon et al., 1990 [77]	1987	PD	Canada	ND	ND	28	ND	ND	PCA 26–36	1.38 ± 0.47; 0.61–2.31	1-CMT
Botha et al., 1998 [78]	ND	PD	South Africa	NONMEM®	53	106	35.1 ± 3.6	6.3 ± 3.3	ND	ND	1-CMT
Allegaert et al., 2006 [79]	1999–2004	PD	Belgium	NONMEM®	410	205	24–30	1–3	PCA 24–30	1.05 (0.48–1.91)	1-CMT
Allegaert et al., 2007 [40]	2002–2006	PD	Belgium	NONMEM®	564	282	24–30	1–3	PMA 24–30	0.97 (0.45–1.98)	1-CMT
Allegaert et al., 2008 [80]	2005–2007	PD	Belgium	NONMEM®	1862	715	24–43	1–30	PMA 24–43	1.99 (0.385–4.780)	1-CMT
Sherwin et al., 2009 [81]	2003–2007	RD	New Zealand	NONMEM®	358	80	24–41	3–64	PMA 24.7–44.0	1.03 (0.45–4.43)	1-CMT

Table 1 (continued)

Study, publication year	Years of study	Study design	Country	Statistical modeling software	Samples (N)	Patients (N)	Range GA (wk)	Range PNA (days)	Range PMA/PCA (wk)	Current weight (kg)	Structural pharmacokinetic model
De Cock et al., 2012 [29]	ND	RD	Belgium	NONMEM®	2186	874	24–43	1–30	ND	1.82[c] (0.39–4.78)	2-CMT
Smits et al., 2015 [32]	2011–2012	PD	Belgium	NONMEM®	1195	579	24–41	1–30	PMA 24–45	2.1 (0.42–5.04)	2-CMT
Illamola et al., 2016 [30]	2000–2006	RD	France	NONMEM®	446	149	24.3–41	1–86	PMA 25–51.4	1.92 (0.50–4.65)	2-CMT
Amponsah et al., 2017 [82]	2013–2014	PD	Ghana	NONMEM®	419	247	25–44	0–1	ND	2.3 (0.9–5.2)	1-CMT
Caceres-Guido et al., 2017 [83]	2003–2007	PD	Argentina	Monolix®	50	27	28–40	6–58	PMA 29–43	2.65 (1.4–4.0)	1-CMT
Severino et al., 2023 [84]	2019–2021	PD	Chile	NONMEM®	329	116	29–38	10–41.8	PMA 32–42.4	2.8 (1.6–3.8)	2-CMT

Data are presented as mean ± standard deviation or median (range) unless otherwise indicated

Abbreviations: GA, gestational age; ND, no data; PCA, post-conceptional age; PD, prospective data; PMA, postmenstrual age; PNA, postnatal age; RD, retrospective data; wk, week(s); 1-CMT, one-compartment model; 2-CMT, two-compartment model; 3-CMT, three-compartment model

[a]Only included patients from group 1: patients with vancomycin and without indomethacin

[b]Mean value

[c]Weighted averages of the subgroups of the included patients

[d]Only included neonates from Glasgow Hospital (group I)

Table 2 Median values of the pharmacokinetic parameters of the vancomycin population pharmacokinetic models calculated for the "typical" neonate

1-CMT ($n = 29$)		2-CMT ($n = 4$)			
Cl	V_d	Cl	Q	V_c	V_d
0.18 [0.05–4.33] L/h/kg	1.73 [0.138–2.81] L/kg	0.198 [0.08–0.45] L/h/kg	0.387 [0.09–1.14] L/h/kg	1.32 [0.42–1.59] L/kg	0.87 [0.08–2.29] L/kg

Data are presented as median (range)

Abbreviations: Cl, clearance; Q, intercompartmental clearance; Vc volume of distribution of peripheral compartment model; V_d volume of distribution; Vp, volume of distribution of peripheral compartment; 1-CMT, one-compartment model; 2-CMT, two-compartment model

Similarly, WT was the most frequent covariate used to describe the variability in V_d, especially in vancomycin (91.7%). The exponent for the allometric scale was fixed to one in most models, which is supported by fractal geometric concepts and observations from diverse areas in biology [87]. However, 12 models estimated a value other than one [19, 27, 29, 30, 32, 44, 50, 69, 73, 78, 81, 82]. The application of allometric scaling methods for size scaling has been employed to overcome the limitations associated with simplistic weight-scaled approaches when characterizing V_d and CL parameters in neonates. In general, changes in body size can affect the distribution of drugs in the body, and this can be represented by V_d. Although CL is more closely related to maturation of organ functions than size, the latter could also affect CL because of physiological development [54]. Fat-free mass might be expected to estimate better than WT when there are wide variations in fat affecting body composition, although the percentage of fat is low in newborns [87]. However, it is a more challenging parameter to determine in routine clinical practice than WT, although it has already been incorporated in vancomycin pediatric popPK models [88, 89].

PMA seems to have a substantial influence on vancomycin (44.4%) and amikacin (36.4%) and less so on gentamicin (9.5%). Clearance pathways develop in the fetus before birth. Although PMA is the covariate most frequently used to describe age-dependent maturation in pediatric PopPK models, it is important to characterize development before birth and maturation after birth separately, so it is interesting to consider other covariates such as PNA and GA to explain the changes after birth [87, 90, 91]. In the updated version of the Rhodin et al. [90] function, PNA was included as a descriptor of renal maturation, as it describes changes after birth. The transition from the intrauterine to the extrauterine environment is linked with major changes in blood flow and oxygenation. This can cause changes in glomerular filtration rate (GFR), kidney function, and drug metabolism. Therefore, PNA maturation has been used to account for those changes in addition to that predicted using PMA [92]. PMA was commonly included in popPK models using a sigmoidal function, especially in vancomycin [51, 53, 55, 58, 59, 74]. A nonlinear relationship between organ maturation and PMA has been described, which can be explained using a sigmoidal maximum response (E_{max}) model of gradual maturation of CL in early life leading to a mature adult CL achieved at a later age according to the Hill equation [54, 90].

Another covariate frequently reported to be a determinant predictor of CL in all three antibiotics was Cr, which was included in over half of the popPK models for vancomycin. Cr concentration decreases with age in the newborn; in the first few days of life, it reflects the mother's concentrations rather than neonatal renal function, and subsequent concentrations are influenced by tubular reabsorption [87, 93]. Three studies used an equation to predict the creatinine production rate [40, 41, 80]. Preterm infants have a slower increase in the GFR during their first weeks of life than do full-term infants [87].

Extracellular water is relatively higher in neonates than in children [94]. For this reason, the V_d for hydrophilic drugs such as aminoglycosides and vancomycin is higher in neonates than in infants and older children. Extracellular water decreases during development, from 80 to 70% WT in newborns to 61.2% in 1-year-old infants [5, 95]. According to previous literature, the average V_d for aminoglycosides was 0.45 ± 0.1 L/kg in neonates and decreased to 0.3 ± 0.1 L/kg in adults. Premature neonates tend to have a larger V_d (nearer 0.5–0.55 L/kg), whereas full-term neonates tend to have smaller values (nearer 0.4–0.45 L/kg) [95]. When assessing the pharmacokinetic parameters standardized for a "typical" neonate of 3 kg, the results obtained in our review for gentamicin were mean± SD V_d 1.54 ± 0.53 L for the 1-CMT models and V_c 1.32 ± 0.08 L for the 2-CMT and 3-CMT models. For amikacin, the mean V_d was slightly higher (1.67 ± 0.27 L) for the 1-CMT models, and the V_c was 1.17 ± 0.19 L for the 2-CMT models. In the case of vancomycin, the mean V_d has been reported to be 0.56 ± 0.02 L/kg in premature neonates and ranged from 0.69 to 0.79 in infants and full-term neonates [95]. In our review for the "typical" neonate, mean ± SD

Table 3 Median values of the pharmacokinetic parameters of the gentamycin population pharmacokinetic models calculated for the "typical" neonate.

1-CMT ($n = 21$)		2-CMT ($n = 3$)				3-CMT ($n = 2$)					
Cl	V_d	Cl	Q	V_c	V_p	Cl	Q_2	Q_3	V_c	V_{p2}	V_{p3}
0.16 (0.05–2.15) L/h/kg	1.435 (0.41–1.79) L/kg	0.19 (0.142–0.2) L/h/kg	0.05 (0.005 –0.2) L/h/kg	1.45 (1.39–1.60) L/kg	0.73 (0.42–0.77) L/kg	0.317 (0.184–0.45) L/h/kg	0.205 (0.2–0.21) L/h/kg	0.03 (0.025–0.04) L/h/kg	1.17 (1.14–1.20) L/kg	0.92 (0.91–0.93) L/kg	10.78 (6.34–15.21) L/kg

Data are presented as median (range)

Abbreviations: Cl, clearance; Q, intercompartmental clearance; Q_2 and Q_3: Intercompartmental clearances between the central and each of the two peripheral compartments; V_c volume of distribution of peripheral compartment model; V_d volume of distribution; V_p, volume of distribution of peripheral compartment; V_{p2} and V_{p3}: volume of distribution of peripheral compartments; 1-CMT, one-compartment model; 2-CMT, two-compartment model; 3-CMT, three-compartment model

V_d was 1.75 ± 0.65 L for the 1-CMT models, and mean V_c was 1.08 ± 0.55 L for the 2-CMT models.

Pathological states such as sepsis also influenced the V_d of all three antibiotics. Sepsis involves increased permeability, which is responsible for a fluid shift and may be consistent with higher V_d [82]. Moreover, the volume expanders given by intravenous infusion in the sepsis state contribute to an increase in extracellular fluid volume [73]. For these reasons, the V_d in neonates with sepsis [46, 59, 70, 73, 82, 84] is higher than in neonates without sepsis. For gentamicin, Lingvall et al. showed that V_d increased by 14% in septic neonates, which implies that larger doses may be required to achieve peak therapeutic concentrations [70]. Similarly, for amikacin, the septic population studied by Amponsah et al. had a higher V_d than the median (1.15 L/kg) [82]. Because of the higher V_d for water-soluble drugs in neonates and the nonlinear scale of clearance, neonates must receive higher doses of gentamicin per kilogram of bodyweight than older pediatric patients and adults to achieve comparable plasma and tissue concentrations [96, 97].

The aminoglycosides are mainly eliminated by glomerular filtration, and their elimination rates are reduced at birth. In preterm newborns, the GFR corresponds to 25–30% of the adult value [16]. CL of aminoglycosides is lower in neonates than in more mature infants [98]. The mean ± SD CL in neonates has been reported to be 0.05 ± 0.01 L/kg/h, increasing to 0.13 ± 0.03 L/h/kg in children and 0.08 ± 0.03 L/kg/h in adults [95]. The mean ± SD values obtained for gentamicin in our review for the "typical" neonate were CL 0.27 ± 0.49 L/h for 1-CMT models and 1.32 ± 0.08 L/h for the 2-CMT and 3-CMT models. For amikacin, the mean ± SD CL was 0.19 ± 0.07 L/h for 1-CMT models and 0.24 ± 0.13 L/h for 2-CMT models. In newborns, renal function increases rapidly; GFR tends to double during the first 14 days of life because of the rapid changes in glomerular hemodynamics, which are characterized by an increase in arterial blood pressure and renal blood flow and a decrease in renal vascular resistance [90, 99]. CL of aminoglycosides is lower in low-birth-weight neonates than in non-premature and normal weight newborns [26, 60, 79, 80].

Similarly, vancomycin CL increases with PMA and PNA, leading to a greater elimination rate constant and shorter half-life in premature neonates [100]. In the review by Chung et al. [5], the typical CL for neonates ranged from 0.014 to 0.273 L/kg/h (median 0.06 L/kg/h). In our review, the median for a "typical" neonate was 0.18 L/h (0.05–4.33 L/h) in the 1-CMT models and 0.20 L/h (0.081–0.45 L/h) in the 2-CMT models.

The data of the pharmacodynamic targets included in our review show how these targets have evolved over time, especially for vancomycin. Historically, vancomycin dosing has been titrated to obtain serum trough concentrations of

Table 4 Median values of the pharmacokinetic parameters of the amikacin population pharmacokinetic models calculated for the "typical" neonate

1-CMT (n = 8)		2-CMT (n = 6)			
Cl	V_d	Cl	Q	V_c	V_p
0.15 (0.11–0.304) L/h/kg	1.62 [1.37 – 2.26] L/kg	0.17 (0.13–0.43) L/h/kg	0.15 (0.06–0.18) L/h/kg	1.08 (1.01–1.40) L/kg	1.36 (0.16–1.44) L/kg

Data are presented as median (range).

Abbreviations: Cl, clearance; Q, intercompartmental clearance; V_c volume of distribution of peripheral compartment model; V_d volume of distribution; V_p, volume of distribution of peripheral compartment; 1-CMT, one-compartment model; 2-CMT, two-compartment model.

10–15 mg/L for mild infections and 15–20 mg/L for severe infections [6]. However, several vancomycin pharmacodynamic targets are currently available for neonates. In the initial studies, peak and trough were the most used parameters for monitoring. However, there has been a transition from trough concentrations to area under the concentration–time curve over minimum inhibitory concentrations (AUC_{0-24}/MIC) with a target of 400–600 [5, 57–59]. Peaks and troughs are still used for gentamicin. In most studies, the target was trough ~1–2 mg/L and peak ~ 5–10 mg/L, although some studies used higher peaks [68, 71]. The variation in trough values was greater for amikacin, with target values ~1–3 mg/L. However, for the peak, there appears to be consensus of ~25–35 mg/L. Data for the pharmacodynamic targets of each study are summarized in Table S1 in the supplementary material.

The limited antibiotic blood samples in most studies meant that a 1-CMT approach was more frequently described than a 2-CMT approach. Nevertheless, in all three antibiotics, the studies with more samples used 2-CMT or 3-CMT models to describe the pharmacokinetic parameters (CL and V_d). Aminoglycosides exhibit a three-compartment distribution when given intravenously, but the V_c is quite small, at approximately one-third to one-half of the volumes used for general dosing with 1-CMT approaches [101]. The first distribution phase, during the first hour, is generally not detected because it is masked by the infusion time (0.5–1 h) [95]. For vancomycin, 1-CMT, 2-CMT, and 3-CMT approaches have all been described in adults, although 1-CMT models seem to be a valid tool for predicting serum concentrations in the post-distribution phase in newborns [102].

Optimal dosing of these three antibiotics is challenging in newborns and infants because of their physiological characteristics and the pharmacokinetic characteristics of the drugs. The higher level of extracellular fluids per kilogram in neonates affect the V_d of water-soluble medications. Moreover, as nephrogenesis is completed late in gestation, the renal function of premature neonates is compromised regarding renally excreted drugs [97]. Vancomycin and aminoglycosides have narrow therapeutic margins and can easily lead to nephrotoxicity. Therefore, TDM has a fundamental role in this population, not only to avoid toxicity but also to attain the desired pharmacokinetic/pharmacodynamic target [7]. PopPK models combined with TDM help to achieve the goal of MIPD, improving drug treatment outcomes by achieving an optimal balance between beneficial effects and toxicity [13].

TDM using Bayesian forecasting can be a valuable tool for optimizing drug therapy in clinical practice [5]. A Bayesian approach allows the estimation of individual pharmacokinetic parameters (i.e. CL and V_d) based on the data but also considers prior information from the literature. Nevertheless, before implementing a popPK model into clinical practice, an external validation should be conducted to evaluate its predictive performance. In addition, other aspects that need to be considered when selecting one pharmacokinetic model over another are the characteristics of the population in which it has been developed and the covariates, as well as the complexity and feasibility of adapting the model to a certain software.

This research highlights the numerous attempts that have been made to characterize the pharmacokinetics of antibiotics in newborns and infants to respond to the special characteristics of this population. The multiple model properties (constants and functions) and covariates included in the popPK models account for the differences among this population regarding age, physiological development, and comorbidities. From our review, for each of the antibiotics, different models could be considered to assess their performance in clinical practice before implementing them. For vancomycin and gentamycin, a meta-analysis was carried out for each to determine a "meta-model" for neonates [74, 103]. For vancomycin, a 2-CMT "meta-model" was built using NONMEM® incorporating the current weight (CW), PMA, and Cr as significant covariates for CL [103]. For gentamycin, a 3-CMT "meta-model" was built using NONMEM® with the covariates WT, PMA, PNA, and Cr for the CL and WT for the V_d [74].

Our review provides a comprehensive summary of all the evidence published to date related to popPK models for vancomycin, gentamicin, and amikacin in neonates. Previous

Table 5 Population pharmacokinetic model equations and mean values of pharmacokinetic parameters

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Vancomycin pharmacokinetic models						
Schaible et al., 1986 [33]	M1: PCA M2: WT, Cr	M1: CL (L/h) = 0.0224 × PCA − 0.639 M2: CL (L/h) = 0.06 × WT + 0.095 × 1/Cr − 0.141	M1: 0.129 M2: 0.069 (for mean weight 2 kg, PCA 40 wks, Cr 0.62 mg/dL)	M1 and 2: WT	V (L) = 0.563 × WT + 0.052	1.18 (for mean weight 2 kg, PCA 40 wks, Cr)
Asbury et al., 1993 [34]	PCA	CL (L/h) = 0.0281 × PCA − 0.818	0.072[a]	WT	V (L) = 0.557 × WT − 0.051	0.52[a]
Seay et al., 1994 [21]	M1 and 2: WT, DA, GA	M1: 1-CMT: CL (L/kg/h) = 0.0626 × WT × 0.455^{Z1} × 0.656^{Z2} M2: 2-CMT: CL (L/kg/h) = 0.0590 × WT × 0.643^{Z1} × 0.46^{Z2} Z1 = 1 if exposed to DA, else Z1= 0, and Z2 = 1 if GA ≤32 wks, else Z2 = 0 Q (L/h) = 0.0313 ×WT	M1: 1-CMT: 0.063 M2: 2-CMT: 0.059 (if no DA and GA >32 wks), Q = 0.0313	M1 and 2: WT	M1: 1-CMT: V (L) = 0.496 × WT M2: 2-CMT: V_c (L) = 0.44 × WT V_{ss} (L) = 0.764 × WT $V_{ss} = V_c + V_p$	M1: 1-CMT: V = 0.496 M2: 2-CMT: V_c = 0.44 V_{ss} = 0.764
Rodvold et al., 1995 [35]	CLCr	CL (L/h) = 0.411 × CLCr + 0.541	0.061	WT	V (L) = 0.551 × WT	0.551
Burstein et al., 1997 [22]	WT	CL (L/h) = 0.038 × WT Q (L/h) = 0.38 × WT	CL = 0.038, Q = 0.38	WT	V_c (L) = 0.19 × WT V_{ss} (L) = 0.48 × WT $V_{ss} = V_c + V_p$	V_c = 0.19 V_{ss} = 0.48
Silva et al., 1998 [36]	IND, VENT	CL (L/h) = 0.07 if concomitant treatment with IND or VENT CL (L/h) = 0.086 if absence of treatment with IND or VENT	0.07 presence or 0.086 absence of concomitant treatment with IND or VENT	PMA	V (L) = 0.562 if PMA ≤32 wks V (L) = 0.498 if PMA >32 wks	0.562 (PMA ≤32 wks) 0.498 (PMA >32 wks)
Grimsley et al., 1999 [37]	WT, Cr	CL (L/h) = 3.56 × WT / Cr[b]	0.11 (for median Cr 49 µmol/L and weight 1.52 kg)	WT	V (L) = 0.669 × WT	0.669
De Hoog et al., 2000 [38]	WT	CL (L/h) = 0.057 × WT	0.057	WT	V (L) = 0.43 × WT	0.43
Capparelli et al., 2001 [23]	WT, Cr, PNA, GA	CL (L/h) = WT × (0.028/Cr + 0.000127 × PNA + 0.0123 × GA28) + 0.006 GA28 = 1 if GA >28 wks; 0 if GA <28 wks Q (L/h) = 0.0334 × WT	CL = 0.066, Q = 0.0334	WT	V_c (L) = 0.666 × V_{ss} V_{ss} (L) = 0.793 × WT + 0.01 $V_{ss} = V_c + V_p$	V_{ss} = 0.793 V_c = 0.528 V_p = 0.265
Kimura et al., 2004 [39]	WT, Cr	CL (L/h) = 0.025 × WT/Cr for PCA <34 wks CL (L/h) = 0.0323 × WT/Cr for PCA ≥34 wks	0.075 (for median weight 1.38 kg, Cr 0.6 mg/dL and PCA 37 wks)	WT	V (L) = 0.66 × WT	0.66

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Allegaert et al., 2007 [40]	WT, PMA, FNCOX, CLCr, Cr, GA	CL (L/h) = $1.58 \times (WT/70)^{0.75} \times e^{[0.0456 \times (PMA-30)]} \times RF \times FNCOX \times FSGA$ RF = RF standardized to CLCr 6 L/h/70 kg in a 40-year-old male assuming a CPR of 516 µmol/h calculated as CPR (µmol/h) = $516 \times e^{(Kage \times ((PMA-30)/52-40))}$ (Kage = 0.00766) and CLCr (L/h) = CPR/Cr FNCOX = 0.795 if given nonselective COX inhibitor (scaling factor) FSGA = 0.838 for scaling SGA	0.079 (for mean weight 1.3 kg, 30 wks PMA and appropriate for GA)	WT	V (L) = $39.3 \times$ (WT/70)	0.730 (for mean weight 1.3 kg, 30 wks PMA and appropriate for GA)
Anderson et al., 2007 [41]	WT, PMA, CLCr, Cr, VENT	CL (L/h) = $2.19 \times (WT/70)^{0.75} \times [1 + 0.0216 \times (PMA - 40)] \times RF \times$ Fventilation $\times$ Vent) Fventilation = 0.942 if positive pressure for VENT Vent = 1 if VENT and 0 if absent RF = RF standardized to CLCr 6 L/h/70kg in a 40-year-old person with a serum Cr 85.947 µmol/L, calculated as CPR (µmol/h) = $516 \times e^{(Kage \times ((PMA-40)/52-40))}$ (Kage = 0.00789) and CLCr (L/h)	0.049 (for mean weight 1.3 kg, 34 wks PMA and no VENT)	WT, INO	V (L) = $39.0 \times$ (WT/70) $\times$ Finotrope $\times$ Inot Finotrope = 1.18 if use of INO Inot = 1 if INO present, 0 if absent	0.724 (for mean weight 1.3 kg, 34 wks PMA and no artificial ventilation)
Marqués-Miñana et al., 2010 [42]	WT, PMA, AMX	CL (L/h) = $0.00192 \times PMA \times WT \times (1 + 0.65 \times AMX)$ AMX = 1 if co-therapy with AMX; 0 if absent	0.066	WT, SPI	V (L) = $(0.572 \times (1 - 0.344 \times SPI)) \times WT$	0.572
Lo et al., 2010 [43]	WT, GA, PMA	CL (L/h) = $1.0 \times (WT/70)^{0.75} \times (PMA/30)^{3.16} \times [0.83 \times GA + 1.03 \times (1 - GA)]$ GA = 1 for SGA infants and 0 for appropriate-for-GA infants	0.052	WT	V (L) = $36.6 \times$ (WT/70)	0.523
Mehrotra et al., 2012 [85]	WT, Cr, PMA	CL (L/h) = $0.18 \times (WT/2.5)^{0.75} \times (0.42/Cr)^{0.7} \times (PMA/37)^{1.4}$	0.14 (for mean weight 2.5 kg, Cr 0.6 mg/dL and PMA 37 wks)	WT	V (L) = $1.7 \times$ (WT/2.5)	1.7 (for mean weight 2.5 kg, Cr 0.6 mg/dL and PMA 37 wks)
Zhao et al., 2013 [44]	WT, BW, PNA, Cr	CL (L/h) = $0.0571 \times (WT/1.416)^{0.513} \times (BW/1.010)^{0.599} \times (1 + 0.282 \times PNA/17) \times [1/(Cr^b/42)^{0.525}]$	0.073 (for median weight 1.41 kg, BW 1.01 kg, PNA 17 days, Cr 42 µmol/L)	WT	V (L) = $0.791 \times (WT/1.416)^{0.898}$	0.791 (for median weight 1.41 kg, BW 1.01 kg, PNA 17 days, Cr 42 µmol/L)

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Frymoyer et al., 2014 [86]	WT, PMA, Cr	CL (L/h) = $0.345 \times (WT/2.9)^{0.75} \times [1/(1 + (PMA/34.8)^{-4.53}] \times (1/Cr)^{0.267}$	0.095	WT	V (L) = $1.75 \times (WT/2.9)$	0.603
Bhongsatiern et al., 2015 [46]	WT, CLCr, PMA	CL (L/h) = $0.095 \times (WT/1.5)^{0.585} \times (CLCr/36)^{0.720} \times (PMA/33)$	0.068	WT	V (L) = $0.905 \times (WT/1.5)$	0.62
Kato et al., 2017 [47]	Cr, volume of infusion	CL (L/h) = $0.054 \times (Cr/0.59)^{-0.80} \times (V_{infusion}/159.3)^{0.98}$	0.054 (for median weight 0.93kg, Cr 0.59 mg/dL and $V_{infusion}$ 159.3mL)	None	V (L) = 1.19	1.28 (for median weight 0.93 kg, Cr 0.59 mg/dL and $V_{infusion}$ 159.3 mL
Song et al., 2017 [48]	BW, PNA	CL (L/h) = $0.42 \times (BW/3.22)^{0.888} \times (PNA/29)^{0.449}$ Q (L/h) = 1.161	CL = 0.106, Q = 0.294	None	V_c (L) = 1.27 V_p (L) = 2.422	V_c = 0.32 V_p = 0.613
Tseng et al., 2018 [49]	WT, PMA, Cr	CL (L/h) = $0.0519 \times WT^{0.75} \times (PMA/30.1)^{2.4} \times (43/Cr^b)^{0.246}$	0.052	WT	V (L) = $0.498 \times WT$	0.498
Li et al., 2018 [50]	WT, Cr	CL (L/h) = $0.309 \times (WT/2.9)^{1.55} \times (23.3/Cr^b)^{0.337}$	0.309 (for mean weight 2.9 kg, Cr 23.3 µmol/L)	WT	V (L) = $2.63 \times (WT/2.9)^{1.05}$	2.63 (for mean weight 2.9 kg, Cr 23.3 µmol/L)
Chen et al., 2018 [51]	WT, PMA, Cr	CL (L/h) = $4.87 \times (WT/70)^{0.75} \times [PMA^{4.61}/(PMA^{4.61} + 34.5^{4.61})] \times (Cr/0.28)^{-0.221}$	0.103	WT	V (L) = $40.7 \times (WT/70)$	0.581
Reilly et al., 2019 [52]	WT, PNA, Urine output	CL (L/h) = $0.0558 \times WT \times (PMA/30)^{1.26} \times (PNA/18)^{0.104} \times (urine\ output/3.8)^{0.505}$	0.056	WT	V (L) = $0.491 \times WT$	0.491
Germovsek et al., 2019 [53]	WT, PMA	CL (L/h) = $5.7 \times (WT/70)^{0.632} \times [PMA^{3.4}/(PMA^{3.4} + 47.7^{3.4})]$	0.081	WT	V (L) = $39.3 \times (WT/70)$	0.561
Cristea et al., 2019 [19]	WT, PNA	CL (L/h) = $0.053 \times (WT/1.76)^{1.34} \times (1 + (0.213 \times (PNA/2)) \times Fibu \times Findo$ Fibu = 0.838 if concurrent use of IBU Findo = 0.447 if concurrent use of IND Q (L/h) = $0.904 \times CL$	CL = 0.138, Q = 0.124 (for mean weight 1.76 kg, PNA 15 days, no IND and no IBU)	WT	V_c (L) = $0.913 \times (WT/1.75)^{0.919}$ $V_c = V_p$	V_c = 0.913 V_p = 0.913 (for mean weight 1.76 kg)
Back et al., 2019 [54]	WT, PMA	CL (L/h) = $69.4 \times (WT/70)^{0.75} \times [PMA^{3.68}/(PMA^{3.68} + 33.3^{3.68})]$	1.46 (for mean weight 3.2 kg and PMA 41 weeks)	WT	V (L) = $3.23 \times (WT/70)$	0.148 (for mean weight 3.2 kg)
Dao et al., 2020 [55]	WT, PMA, Cr	CL (L/h) = $0.273 \times WT^{0.438} \times [(54/Cr^b)^{0.473}] \times [PMA^{3.54}/(PMA^{3.54} + 46.4^{3.54})]$	0.060 (for median weight 1.1 kg, PMA 32 wks and Cr 54 µmol/L)	WT	V (L) = $0.628 \times WT$	0.571 (for median weight 1.1 kg, PMA 32 wks and Cr 54 µmol/L)
Mulubwa et al., 2020 [56]	WT	CL (L/h) = $0.102 \times (WT/1.48)^{0.75}$	0.102 (for mean weight 1.48 kg)	WT	V (L) = $0.884 \times (WT/1.48)$	0.884 (for mean weight 1.48 kg)
Lee et al., 2021 [6]	WT, PMA, CLCr	CL (L/h) = $2.09 \times (WT/70)^{0.75} \times (PMA/31.7)^{0.795} \times (CLCr/50.3)^{0.741}$	0.086	WT	V (L) = $45.6 \times (WT/70)$	0.651

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Sasano et al., 2021 [57]	WT, Cr	CL (L/h) = 0.056 × (WT/0.887)$^{0.75}$ × (0.35/Cr)$^{0.539}$	0.056	WT	V (L) = 0.827 × (WT/0.887)	0.827
Jarugula et al., 2022 [20]	WT, Cr, PMA	CL (L/h) = 0.237 × (WT/3.5)$^{0.75}$ × (0.45/Cr)$^{0.87}$ × (PMA/42)$^{0.81}$	0.237	WT	V (L) = 2.98 × (WT/3.5)	2.98
Alsultan et al., 2023 [58]	WT, PMA, Cr	CL (L/h) = 0.09 × (WT/0.93)$^{0.75}$ × (0.6/Cr)$^{0.48}$ × [PMA$^{4.42}$/(PMA$^{4.42}$ + 26.3$^{4.42}$)]	0.09 (for mean weight 0.93 kg, Cr 0.6 mg/dL and PMA 29 wks)	WT	V (L) = 0.81 × (WT/0.93)	0.81 (for mean weight 0.93 kg, Cr 0.6 mg/dL and PMA 29 wks)
Chung et al., 2023 [59]	WT, PMA, Cr	CL (L/h) = 13.9 × (WT/70) × [PMA$^{0.739}$/(PMA$^{0.739}$ + 47.7$^{0.739}$)] × (Cr^{b}/34)$^{-0.653}$	0.088	WT	V (L) = 65.5 × (WT/70)	0.93
Gentamycin pharmacokinetic models						
Kelman et al., 1984 [26]	M1: WT, PNA, Cr M2: WT, Cr	M1: CL (L/h) = 0.057 × WT + 0.00074 × PNA − 0.00019 × Cr^{b} M2: CL (L/h) = 0.063 × WT − 0.00019 × Cr^{b}	M1: 0.057 M2: 0.063	M1 and 2: WT	M1 and 2: V (L) = 0.46 × WT	0.46
Thomson et al., 1988 [26]	M1: WT, Cr, AP M2: PCA, AP	M1: CL (L/h) = 0.055 × WT − 0.00013 × Cr^{b} × (0.86 if AP < 7) M2: CL (L/h/kg) = 0.053 × (0.83 if PCA <34 wks) × (0.82 if AP < 7)	0.053 if PCA >34 wks and AP ≥7; 0.044 if PCA ≤34 wks and AP <7; 0.036 if PCA ≤34 wks and AP <7	M1 and 2: WT	M1 and 2: V (L) = 0.47 × WT	0.47
Dodge et al., 1991[60]	ND	ND	0.046 if GA ≤31 wks, 0.094 if GA 31–34 wks	ND	ND	0.703 – 0.767 if GA ≤31 wks 0.643–0.653 if GA 31−34 wks
Izquierdo et al., 1992 [27]	M1: WT, GA, PNA M2: WT, PNA, PCA Premature pts: PCA, WT	Overall population (>38 wks): M1: CL (L/h) = −0.0958 + 0.0025 × GA + 0.0024 × PNA + 0.0630 × WT M2: CL (L/h) = −0.0896 + 0.0022 × PCA + 0.0022 × PNA + 0.0647 × WT Premature pts (28–38 GA): CL (L/h) = −0.2310 + 0.0070 × PCA + 0.0612 × WT	0.069[c]	All models: WT	Overall population (>38 wks): V (L) = 0.1821 + 0.4799 × WT V (L) = 0.6422 × WT$^{0.8466\times (8.42\times10\text{-}7)}$ Premature pts (28 − 38 GA): V (L) = 0.4086 + 0.3763 × WT V (L) = 0.7517 × WT$^{0.6483\times (3.03\times10\text{-}4)}$	0.547[c]
Jensen et al., 1992 [61]	WT	CL (L/h) = 0.120 × (WT/2.4)$^{1.36}$	0.05	WT	V (L) = 0.429 × WT	0.429
Rodvold et al., 1993 [62]	CLCr	CL (L/h) = (0.0604 × CLCr) + 0.333	0.022	None	V (L) = 0.56 × WT	0.56
Weber et al., 1993 [63]	ND	ND	0.0534	ND	ND	0.66
Vervelde et al., 1999 [64]	ND	ND	0.059	ND	ND	0.70
Stickland et al., 2001 [65]	ND	ND	0.046 (for mean weight 2.4 kg)	ND	ND	0.46 (for mean weight 2.4 kg)

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Touw et al., 2001 [28]	M1: WT M2: GA	M1: CL (L/h) = −0.0342 + 0.0655 × WT M2: CL (L/h) = −0.259 + 0.0106 × GA	0.0387 (It2B modeling) − 0.0404 (STS modeling)	WT, GA	M1: V (L) = −0.034 + 0.647 × WT M2: V (L) = −2.39 + 0.109 × GA	0.586 (It2B modeling) − 0.623 (STS modeling)
Stolk et al., 2002 [66]	ND	ND	ND	WT, GA	V (L) = 1.076 + 0.666 × WT − 0.0372 × GA	0.631[c]
Botha et al., 2003 [67]	WT, GA, sex (P)	CL (L/h) = 0.001 × WT × GA × P P = 1.2 for girls and 1 for boys	0.042	WT	V (L) = 0.472 × WT	0.472
DiCenzo et al., 2003 [68]	GA, BW	CL (L/h) = (0.00504 + [0.00108 × GA]) × BW	0.076 (for median BW 1.92 kg and GA 32 wks)	ND	ND	0.136 (for median BW 1.92 kg)
Lanao et al., 2004 [69]	WT, PNA	CL (L/h) = $0.032 \times WT^{1.482}$ + 0.0024 × PNA	0.032	WT	V (L) = $0.636 \times WT^{0.852}$	0.636
Lingvall et al., 2005 [70]	GA, AP	CL (L/h/kg) = 0.0177 + 0.00147 × (GA −20) + 0.000635 × AP	0.046	Sepsis	V (L/kg) = 0.483 + 0.0656 × sepsis	0.483
García et al., 2006 [71]	WT, PNA, CLCr	CL (L/h/kg) = (0.00582 × WT + 0.00106 × CLCr) × WT + 0.00131 × PNA Q (L/h) = 0.0157	CL = 0.078, Q = 0.009 (for mean weight 1.69 kg and PNA 5.49 days)	WT	V_c (L) = 0.484 × WT V_p (L) = 1.25	V_c = 0.813 V_p = 0.74 (for mean weight 1.69 kg and PNA 5.49 days)
Nielsen et al., 2009 [72]	WT, GA, PNA	CL (L/h) = $0.00999 \times WT^{0.75}$ × [1 + 0.0862 × (GA − 29)] × (1+ $PNA^{0.548}$) Q_2 (L/h) = $0.0939 \times WT^{0.75}$ Q_3 (L/h) = $0.0173 \times WT^{0.75}$	CL = 0.026, Q_2 = 0.121, Q_3 = 0.022 (for mean weight 1.4 kg, GA 29 days and PNA 1 day)	WT, GA	V_c (L) = 0.405 × WT × [(1 − 0.0116) × (GA − 29)] V_{p2} = 0.310 × WT V_{p3} = 5.07 × WT	V_c = 0.567 V_{p2} = 0.434 V_{p3} = 7.1 (for mean weight 1.4 kg, GA 29 days and PNA 1 day)
Sherwin et al., 2009 [73]	WT, PNA	CL (L/h) = $0.097 \times (WT/2)^{1.3}$ × $(PNA/7)^{0.29}$	0.037 (for mean weight 2.3 kg, PNA 3 days)	WT, sepsis	V (L) = $1.07 \times (WT/2)^{0.8}$ + (sepsis × 0.13) Sepsis = 1 if confirmed sepsis, 0 if absent	0.687 (for mean weight 2.3kg and no sepsis)
Fuchs et al., 2014 [24]	WT, GA, PNA, DA	CL (L/h) = 0.089 × $(WT/2.17)^{0.75}$ × [1 + 1.870 × ((GA − 34)/34)] × [1 + 0.054 × (PNA − 1)] × (1 − 0.120) Q (L/h) = 0.157 × $(WT/2.17)^{0.75}$	CL = 0.089, Q = 0.157 (for mean weight 2.17 kg, GA 34 wks and PNA 1 day)	WT, GA	V_c (L) = 0.908 × (WT/2.17) × [1− 0.922 × ((GA − 34)/34)] V_p (L) = 0.560 × (WT/2.17)	V_c = 0.908 V_p = 0.560 (for mean weight 2.17 kg, GA 34 wks and PNA 1 day)
Germovsek et al., 2016 [74]	WT, PMA, Cr, PNA	CL (L/h/70kg) = 6.21 × $(WT/70)^{0.632}$ × [$PMA^{3.33}$/($PMA^{3.33}$ + $55.4^{3.33}$) × $(Cr/TSCr)^{-0.13}$ × [PNA/(1.70 + PNA)] TSCr = 2.849 × PMA + 166.48 Q_2 (L/h /70kg) = 2.15 × $(WT/70)^{0.75}$ Q_3 (L/h /70kg) = 0.27 × $(WT/70)^{0.75}$	CL = 0.036, Q_2 = 0.074, Q_3 = 0.009	WT	V_c (L) = 26.5 × (WT/70) V_{p2} (L) = 21.1 × (WT/70) V_{p3} (L) = 148 × (WT/70)	V_c = 0.379 V_{p2} = 0.303 V_{p3} = 2.114

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Bijleveld et al., 2017 [75]	WT, PMA	CL (L/h) = $0.0413 \times WT^{0.75} \times (PMA/32.14)^{1.89}$ Q (L/h) = $0.0236 \times WT^{0.75}$	CL = 0.066, Q = 0.037 (for mean weight 1.85 kg, PMA 32 wks)	WT	V_c (L) = 0.534 × WT V_p (L) = 0.244 × WT	V_c = 0.99 V_p = 0.45 (for mean weight 1.85 kg, PMA 32 wks)
Amikacin pharmacokinetic models						
Assael et al., 1982 [76]	ND	ND	0.0516	ND	ND	V_c = 0.49 V_{ss} = 0.80
Kenyon et al., 1990 [77]	ND	ND	0.0504	ND	ND	0.57
Botha et al., 1998 [78]	WT, sex (P)	CL (L/h) = $0.031 \times WT^{1.45} \times P$ P = 1.28 for girls; 1.0 for boys	0.048	WT	V (L) = $0.316 \times WT^{1.44}$	0.434
Allegaert et al., 2006 [79]	WT, PCA, NSAID	CL (L/h/70kg) = $[0.486 \times (WT/70)^{0.75}] \times e^{[0.11 \times (PCA-24) \times FNSAID]}$ FNSAID = 0.788 if a premature neonate is given NSAID	0.028 (for mean weight 1 kg, PCA 27 wks, and no NSAID)	WT	V (L) = 40.2 × (WT/70)	0.574
Allegaert et al., 2007 [40]	WT, PMA, FNCOX, CLCr, Cr, GA	CL (L/h) = $1.58 \times (WT/70)^{0.75} \times e^{[0.0456 \times (PMA-30)]} \times RF \times FNCOX \times FCl_{amikacin} \times FSGA$ RF = CLCr/(6 L/h/70kg) FNCOX = 0.795 if given nonselective COX inhibitor (scaling factor) $FCl_{amikacin}$ = 0.567 for scaling amikacin CL relative to that of vancomycin FSGA = 0.838 for scaling SGA	0.040 (for mean weight 1 kg, 28 wks PMA and appropriate for GA)	WT	V (L) = 39.3 × (WT/70)	0.561 (for mean weight 1 kg, 28 wks PMA and appropriate for GA)

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Allegaert et al., 2008 [80]	WT, PMA, VENT, INO, SGA	CL (L/h/70kg) = 1.49 × $(WT/70)^{0.75}$ × [1+ 0.032 × (PMA − 40)] × RF × Fventilation × VENT × Finotrope × INO × Fiugr × SGA) Finotrope = 0.945 applied if use of INO Fventilation = 0.977 applied if use of positive pressure VENT Fiugr = 0.872 applied if intrauterine growth retardation INO, VENT, and SGA have a value of 1 if present, 0 if absent. RF = RF standardized to CLCr 6 L/h/70 kg in a 40-year-old person with a serum Cr of 85.947 µmol/L, calculated as CPR (µmol/h) = 516 × $e^{(Kage\times((PMA-30)/52-40))}$ (Kage = 0.00344) and CLCr (L/h) = CPR/Cr	0.0497 (for mean weight 1 kg, PMA 34 wks, PNA 1 day, no INO, no VENT)	WT, PNA, VENT, INO,	V (L) = 31.7 × (WT/70) × (1 + 0.005 × PNA) × Finotrope × INO × Fventilation × VENT Finotrope = 1.09 applied if use of INO Fventilation = 1.08 applied if use of positive pressure VENT INO and VENT have a value of 1 if present, 0 if absent.	0.455 (for mean weight 1 kg, PMA 34 wks, PNA 1 day, no INO, no VENT)
Sherwin et al., 2009 [81]	WT, PMA	CL (L/h) = 0.23 × $(WT/2)^{0.691}$ × $(PMA/40)^{3.23}$	0.091 (for mean weight 2 kg, PMA 30 wks)	WT	V (L) = 0.957 × $(WT/2)^{0.89}$	0.957 (for mean weight 2 kg PMA 30 wks)
De Cock et al., 2012 [29]	BW, PNA, IBU	CL (L/h) = 0.0493 × $(BW/1.75)^{1.34}$ × (1+ 0.213 × (PNA/2) × IBU IBU = 0.838 if co-administration of IBU Q (L/h) = 0.415 × Cl	CL = 0.0493, Q = 0.020 (for mean BW 1.75 kg, PNA 2 days, no IBU)	WT	V_c (L) = 0.833 × $(WT/1.76)^{0.919}$ $V_c = V_p$	V_c = 0.833 V_p = 0.833 (for mean BW 1.75 kg and PNA 2 days no IBU)
Smits et al., 2015 [32]	BW, PNA, IBU	CL (L/h) = 0.066 × $(BW/2.285)^{1.30}$ × (1+ 0.302 × (PNA/2) × IBU IBU = 0.846 if co-administration of IBU Q (L/h) = 0.480 × Cl	CL = 0.066, Q = 0.032 (for median weigh 2.1 kg BW 2.28 kg, PNA 2 days, no IBU)		V_c (L) = 1.03 × $(WT/2.1)^{0.863}$ $V_c = V_p$	V_c = 1.03 V_p = 1.03 (for median weight 2.1 kg, BW 2.28 kg and PNA 2 days, no IBU)
Illamola et al., 2016 [30]	M1: WT, PNA M2: WT, CLCr	M1: CL (L/h) = 0.093 × $(WT/1.92)^{1.1}$ × $(PNA/28)^{0.299}$ Q (L/h) = 0.051 × $(WT/1.92)^{0.995}$ M2: CL (L/h) = 0.093 × $(WT/1.92)^{0.799}$ × $(CLCr/32.28)^{0.659}$ Q (L/h) = 0.042 × $(WT/1.92)^{0.909}$	M1: CL = 0.093, Q = 0.051 M2: CL = 0.093, Q = 0.042 (for mean weight 1.92 kg, PNA 28 days, CLCr 32.28 ml/min)	M1 and 2: WT	M1: V_c (L) = 0.637 × $(WT/1.92)^{1.030}$ V_p (L) = 0.480 M2: V_c (L) = 0.641 × $(WT/1.92)^{1.040}$ V_p (L) = 0.478	M1: V_c = 0.637 V_p = 0.48 M2: V_c = 0.641 V_p = 0.48 (for mean weight 1.92 kg, PNA 28 days, CLCr 32.28 ml/min)
Amponsah et al., 2017 [82]	BW	CL (L/h) = 0.153 × $(BW/2.5)^{1.31}$	0.058	BW	V (L) = 2.94 × $(BW/2.5)^{1.18}$	1.15
Cáceres Guido et al., 2017 [83]	ND	ND	ND	ND	ND	0.497

Table 5 (continued)

Study, year of publication	Variables used for CL estimation	CL equation	Mean CL in L/h/kg	Variables used for V_d estimation	V_d equation	Mean V_d in L/kg
Severino et al., 2023 [84]	WT, PMA, Cr, shock, sepsis	CL (L/h/70kg) = 1.79 × $(WT/70)^{0.75}$ × $(PMA/38)^{1.61}$ × [1 − 0.78 × (Cr − 0.44)] × [1 + (shock − 0) × (− 0.24)] × [1 + (sepsis − 0) × 0.33] Shock = 0.76 if shock present, 0 if absent Sepsis = 1.33 if sepsis present, 0 if absent Q (L/h) = 0.076 × $WT^{0.75}$	CL = 0.057 Q = 0.054	WT	V_c (L) = 25.1 × (WT/70) V_p (L) = 33.5 × (WT/70)	V_c = 0.359 V_p = 0.439

Abbreviations: AMX, amoxicillin-clavulanic acid; AP, Apgar score at 5 minutes; BW, birth weight; CL, clearance; CLCr, creatinine clearance; CPR, creatinine production rate; Cr, creatinine (mg/dL); DA, dopamine; GA, gestational age; IBU, ibuprofen; IND, indomethacin; INO, inotropes; M, model; ND, no data; NSAID, nonsteroidal anti-inflammatory drugs; PCA, post-conceptional age; PMA, postmenstrual age; PNA, postnatal age; Q, intercompartmental clearance; Q_2 and Q_3, intercompartmental clearances between the central and each of the two peripheral compartments; pts, patients; RF, renal function; SGA, intrauterine growth retardation; SPI, spironolactone; TSCr, typical value of serum creatinine concentration for a specific PMA; V_c, volume of distribution of the central compartment; V_d, volume of distribution; VENT, artificial ventilation; V_p, volume of distribution of peripheral compartment; V_{p2} and V_{p3}, volume of distribution of peripheral compartments; V_{ss}, volume of distribution at steady state; wks, weeks; WT, total body weight; 1-CMT, one-compartment model; 2-CMT, two-compartment model

[a] Values of patients from group 1: patients with vancomycin and without indomethacin

[b] Serum creatinine (µmol/L)

[c] Weighted averages of the subgroups of included patients

reviews focused on pediatrics (children, infants, and neonates) and included patients with and without pathologies as well as those undergoing extracorporeal membrane oxygenation and/or controlled hypothermia [5, 16]. However, our review focuses only on neonates and infants because of the physiological particularities of this population and includes only individuals with no previous pathologies, as we believe that a different approach is required for pathologic conditions. We included observational studies and clinical trials conducted in different countries to integrate a large number of popPK models developed from newborns with different racial backgrounds. Nevertheless, several limitations must be acknowledged when interpreting the results. First, our review cannot be classified as a systematic review since the literature search, data extraction, and interpretation of the results was conducted by a single investigator. However, any discrepancies were resolved with input from a second investigator. No formal evaluation of the quality of the included studies was performed. Second, the biggest limitation of the included studies was that most of the popPK models lacked external validation, which is essential to evaluate whether the models extend to neonates outside the original population used to develop the model and to assess bias and precision [5, 15]. The US Food and Drug Administration considers external validation to be the most stringent method for testing a developed model [15, 104]. Third, the number of blood samples used to develop some models was limited. This explains why the 1-CMT approach was more commonly described than the 2-CMT or 3-CMT approach. Fourth, our review focuses only on the neonatal and infant population because of its unique characteristics, especially in terms of body water content and lower fat content per kilogram, which influences the V_d of hydrophilic and lipophilic drugs and therefore drug distribution. Drug metabolism and clearance in neonates is influenced by size-related changes, ontogeny of isoenzymes, and maturation of renal function. Therefore, it is especially important to include a maturation function (on top of allometric scaling) in the equations for describing those changes. Although the pediatric population shares some physiological characteristics with the neonatal population, only models that included neonates in their development may be suitable to use in this population. Fifth, it is possible that some published popPK models may have been missed in the search and are not included in the review.

Considering these limitations, further research should prioritize the external validation of the popPK models developed, as advocated by the US Food and Drug Administration. External validation was performed in <10% of published pharmacokinetic models, and questions concerning the clinical applicability of models frequently remain unaddressed [15]. Moreover, endeavors should be directed toward expanding the scope of prospective studies with optimal sampling designs. By addressing these issues, future

research can substantially contribute to advancing the reliability, applicability, and clinical relevance of popPK models for neonates.

6 Conclusions

Overall, this study includes the best available evidence of neonatal popPK models used for some of the most commonly prescribed antibiotics (vancomycin, gentamicin, and amikacin) and enhances our understanding of them. WT, PMA, and Cr, followed by PNA, were the most frequent covariates included in CL equations, and WT was most commonly included in V_d equations. 1-CMT approaches were more commonly described than 2-CMT approaches, probably because of the difficulties of obtaining blood samples in neonates. The substantial variability between the popPK models for all three antibiotics and the characteristics of study populations, coupled with the limited prospective studies and the absence of external validation of most models, makes it impossible to implement a single, globally applicable, and uniform popPK model for all neonates.

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