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Systematic Review of Linezolid Population Pharmacokinetics in Pediatric: Models, Covariates, and Dosing Implication

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ABSTRACT

Background: The increasing prevalence of bacterial resistance has positioned linezolid as a promising antibiotic for treating infections, including in pediatric patients. Knowledge of pharmacokinetic parameters is very useful in optimizing the dose to be used in patient therapy. However, pharmacokinetic data to guide optimized dosing in children remain limited.

Objectives: This review aims to summarize population pharmacokinetic (PopPK) models of linezolid in pediatric populations and identify significant covariates influencing its pharmacokinetics.

Methods: A systematic search was conducted in PubMed and ScienceDirect databases for studies published between 2014 and May 2025 using the keywords "linezolid", "population pharmacokinetics", and "pharmacokinetic model".

Results: Six studies met the inclusion criteria and were analysed. The pharmacokinetic models were mainly based on blood concentration measurements and constructed using NONMEM in four studies. Most studies employed one-compartment models. Clearance values ranged from 0.068 to 5.82 L/h, and volume of distribution from 0.783 to 10.5 L. Body weight consistently emerged as a significant predictor of clearance, while body surface area was associated with volume of distribution.

Conclusion: PopPK modeling highlights considerable variability in linezolid pharmacokinetics among pediatric patients, influenced primarily by weight and other covariates. Further studies are needed to compare oral versus IV formulations and to incorporate unbound (free) drug concentrations for improved dose optimization in pediatric populations.

Keywords: linezolid; pediatric; population pharmacokinetic

INTRODUCTION

The emergence of multidrug-resistant (MDR) bacteria has led to the increasing use of linezolid as a last-line antibiotic. Linezolid is the first member of oxazolidinone class and exert its antibacterial activity by inhibiting bacterial protein synthesis and preventing bacterial reproduction. It can be done by binding to the bacterial 23S ribosomal RNA of the 50S subunit blocking the formation of a functional 70S initiation complex.[1,2]

Linezolid is approved for the treatment of Gram-positive infections such as nosocomial pneumonia, complicated skin and soft tissue infections, and vancomycin-resistant *Enterococcus faecium* (VRE).[3] It has also been recommended as part of the treatment regimen for multidrug-resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB), and has demonstrated promising results in the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[4,5] Due to its excellent oral bioavailability (~100%), linezolid allows for seamless switching from intravenous to oral therapy in clinically stable patients.[2]

Study about pharmacokinetic profile of linezolid has been largely conducted in healthy volunteer. The volume of distribution of linezolid at the steady stated averaged 40-50 L with the plasma binding protein approximately 31%. About 30% of linezolid is eliminated unchanged through the kidneys, while roughly 50% undergoes metabolism via oxidation of its morpholine ring, producing two inactive carboxylic acid metabolites.

The elimination of this antibiotic varies from 3 to 7 hours, requiring twice daily dosing regimens.[3,6] However, body size (weight, lean body weight and body surface area), creatinine clearance (CLcr) and age significantly influenced the pharmacokinetic of linezolid.[7] In addition, linezolid exhibits time-dependent antibacterial activity, with its effectiveness most accurately reflected by pharmacokinetic/pharmacodynamic (PK/PD) measures such as an AUC/MIC ratio at steady state of roughly 80–85, and a T > MIC value indicating plasma concentrations remain above the MIC for approximately 85–100% of the dosing interval. Clinical effectiveness is generally achieved when steady-state concentrations (C_{ss}) range between 2–10 µg/mL. In contrast, C_{ss} levels above 10 µg/mL are linked to about a 50% higher incidence of thrombocytopenia.[8,9]

In pediatric population, linezolid has been widely used in intensive care settings to treat infections caused by multidrug-resistant Gram-positive pathogens.[10] The regimen of 10 mg/kg q8h IV for children under 12 years and 600 mg q12h IV for children aged 12 years and above has been suggested for clinical treatment.[11] Pediatric patients undergo dynamic physiological changes that can significantly influence drug disposition, making it inappropriate to extrapolate adult dosing regimens. Therefore, study about pharmacokinetic profile is essential for optimizing dosage regimens in this vulnerable group. Despite its growing use in children, pharmacokinetic (PK) data remain limited. A review study stated that the median clearance values in infants and children are higher than adults.[7] While multiple reviews have examined the population pharmacokinetics (popPK) of linezolid in pediatric patients, none have comprehensively addressed the broader aspects of this group.[7,12,13] Most discussions have concentrated on adult populations, particularly those with specific conditions like renal or hepatic impairment, or those in critical care settings. This article aims to comprehensively summarize published popPK studies of linezolid in pediatric populations and to identify covariates that significantly influence its pharmacokinetics. These insights are expected to support evidence-based dose optimization and improve clinical outcomes in pediactric patients receiving linezolid therapy.

METHODS

Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to depict the flow of information throughout the different stages of the review process.[14] The articles gathered in this systematic review include 6 articles.

Search strategy

This review was conducted in June-July 2025. Literature collected for the review was systematically searched from PubMed and Science Direct databases with a time range of January 2014-May 2025. The following search term were employed: "Linezolid" AND ("population pharmacokinetic" OR "pharmacokinetics model"). The selection of articles was based on pediatric population. After obtaining articles from the two databases used for the article search, the next step is to select all the articles obtained. The selection was carried out by initially screening the titles and abstracts, followed by a review of the full text to determine eligibility based on the inclusion criteria.

Eligibility criteria

This study focusing on population pharmacokinetic of linezolid in pediatric patients, and the articles included in this study should matched to the following criteria: (1) patients ≤18 years of age; (2) original data was used; (3) the analysis method used in the article should be population pharmacokinetic analysis; (4) the language of the study should be in English. Meanwhile, excluded criteria used in this review were as follows: (1) the articles were not in human study; (2) the articles were meta-analysis, methodology, and review articles; and (3) the article did not use population PK modeling approach. The selection of articles based on the inclusion and exclusion criteria was done by two authors independently.

Data Extraction and Data Analysis

All literatures that met the inclusion criteria were collected and the relevant data of the study was extracted. Two authors performed data extraction manually using a data collection form. Each of the included articles provided the following information: (1) study characteristics (the first author, the publication year, the country of study), the characteristic of population (the number of patient (male/female), age, weight, clearance creatinine, and albumin level), study clinical protocol (the type of study, the dosage of linezolid, the frequency of sampling, and concentration measurement assay; (2) information regarding the population pharmacokinetic

modeling methods and techniques, which included software used in the studies, the methods of evaluation, and covariate selection strategies, as well as as well as the PopPK models and covariates analysis (including the final formula of PopPK structural and the values of related parameters, the covariates were tested and preserved). All data obtained were then analyzed by descriptive comparison of patient demographics involved in each study, clinical protocols, population pharmacokinetic modeling methods and their covariates, as well as the final model and population pharmacokinetic estimates.

RESULTS AND DISCUSSION

Study Identification

A total of 61 and 127 publications were obtained from PubMed and Science direct, respectively. After removing 7 duplicate articles, 181 articles were screened based on their relevance to the titles and abstracts. Finally, 146 articles were removed and only 35 remaining full-text articles were assessed for eligibility. All process of study identification is presented in the PRISMA flowchart in Figure 1.[14] After the full-text assessment, six of them met the inclusion criteria and were assessed using the JBI Checklist for Analytical Cross-Sectional Studies to evaluate research quality which consists of eight questions.[15] Questions 1 and 2 addressed the research subjects and background, 3 and 4 focused on exposure and measurement criteria, 5 and 6 covered confounding variables and their management, lastly 7 and 8 pertained to outcome measurements and statistical analysis. This process ensures methodological rigor, identifies potential biases, and confirms adherence to research standards. All studies were able to clearly address these aspects. Thus, we concluded that the six articles are applicable to be used in this review.

Study Characteristics

All six studies were published between 2014-May 2025 and information about the various characteristics of studies summarized on table I. Generally, all studies included in this review aim to establish population pharmacokinetic of linezolid in pediatric. However, some studies added other concerns to be explored based on the population pharmacokinetic information such as evaluating the drug safety in the Tian et al., Garcia-Prats et al., and Ogami et al.[11,16,17] In addition, estimation of dosing regimen of linezolid in pediatric was done in study by Yang et al., Li et al., and Garcia-Prats et al.[10,16,18] Patients included in this review were from three countries, specifically, four studies recruited patients from China, while the patients in one study were from South Africa and Japan, respectively. The number of patients included was also varied, which range from 15 patients in the research by Ogami et al. to 112 patients in study by Li et al.[17,18]

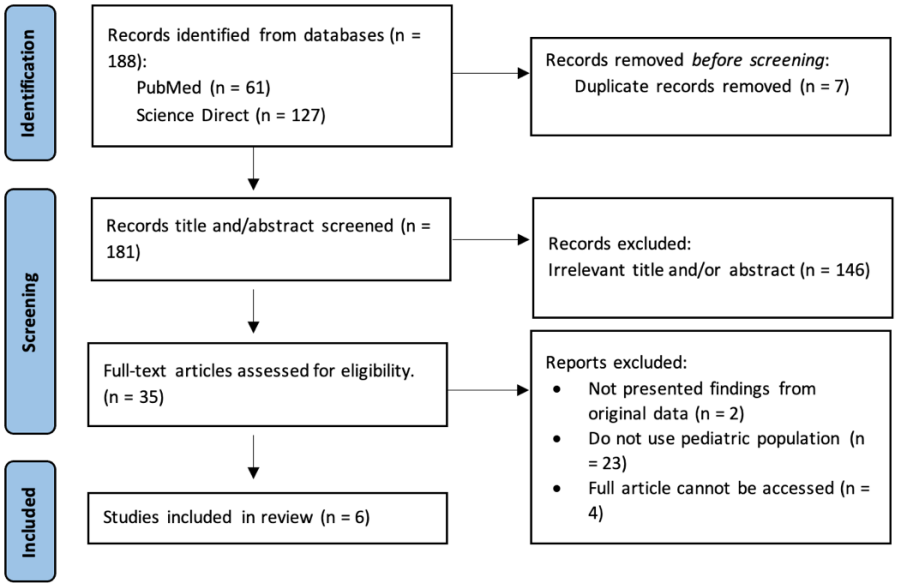

Figure 1. PRISMA diagram of study screening and selection

Table I. Summary of Patients' Demographic for Pharmacokinetic Studies in This Review

Study	Publication Year	Sample Size	Country	Population Characteristics					
				Patient Group	Sex (M/F)	Age (Year)	Weight (kg)	Clcr (mL/min)	Albumin (g/dL)
Tian et al.	2025	80 patients	China	Children with bacterial infections	48/32	3.3 (0.1-12.6) years	12.5 (5.3-45.9) [a]	190.1 (97.0-350.2) (mL/min/1.73m^2) [a]	34.0 (25.5-43.5) [a]
Yang et al.	2023	63 patients	China	Children (critically ill patients with staphylococcal infections)	43/20	5.21 ± 4.22 [b]	22.28 ± 15.00	136.46 ± 80.50	30.44 ± 5.06
Li et al.	2019	112 patients	China	Children (age 0-12 years) who confirmed or suspected multiresistant Gram-positive bacterial infections	65/47	2.9 (3.4) [c]	13.9 (10.2) [c]	136.5 (50.0) (mL/min/1.73m^2) [c]	NR
Duan et al.	2024	54 patients	China	Premature neonates (neonates hospitalized in NICU who underwent linezolid with TDM, premature infants treated with linezolid)	32/22	Gestational age (wk) 31.00 ± 2.74 [b]	Current weight 1.57130 ± 0.50381 [b]	29.46(24.79, 40.41) [d]	31.95 (29.33, 34.43) [d]
Garcia-Prats et al.	2019	48 patients	South Africa	Children with multidrug resistant tuberculosis	24/24	4.6 (0.6-15.3) [e]	NR	NR	NR
Ogami et al.	2019	from 15 patients	Japan	Children (0-13 years) who received linezolid	10/5	Postnatal age: 2 (0-13) [e]	9.9 (3.0; 49.7)	NR	NR

Notes: [a]: median (5th-95th); [b]: mean ± standard deviation (SD); [c]: mean (SD); [d]: median (IQR); [e]: median (range); NR: Not reported

Table II. Summary of the Clinical Protocols for Studies included in This Review

Study	Study Type	Dose	Samples' Time	Assay
Tian et al., 2025	Prospective, multicenter study	IV infused: 10mg/kg, q8h for children under 12 years 600mg, q12h for children aged 12 years and above	At the steady-state linezolid concentration (at least 48 h from the start of treatment)	High-Performance Liquid Chromatography method with ultraviolet detection
Yang et al., 2023	Prospective, single center study	IV infusion: 10 mg/kg three times per day for children under 12 years, 12 years and 600 mg twice daily for those aged 12 to 18 years.	Four samples were collected at steady state from each patient half an hour before the infusion (trough concentration) and after the end of the infusion (peak concentration). Another two sample time points were constantly changed between peak and trough times (intermediate concentration).	Ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS)
Li et al., 2019	Prospective study	10.00 mg/kg/dose, q8h, 1 hour IV infusion	At the steady-state linezolid concentration (at least 3 days from the start of treatment) 5.8 (2.6) hours after the last dose [b] At the trough concentration, peak concentration (0.5 h after the end of infusion) and at the time between peak and trough concentration	High-performance liquid chromatography
Duan et al., 2024	Retrospective study	10 mg/kg, q12h for preterm neonates with a GA <34 weeks and a PNA <7 days 10 mg/kg, q8h for preterm neonates with a GA ≥ 34 weeks and preterm neonates with GA <34 weeks and a PNA >7 days	At the steady-state trough linezolid concentration (after the fourth maintenance dose and 30 minutes prior to the next dose) and opportunistic concentration (after the fourth maintenance dose, one or two blood samples (at least one trough concentration) were taken from each patient	Liquid chromatography-tandem mass spectrometry (LC-MS/MS)
Garcia-Prats et al., 2019	Prospective study	10mg/kg/dose twice daily for children <10 years and 10mg/kg/dose once daily for children >10 years, up to a maximum total daily dose of 600mg, given orally	MDRPK1: prior to- and then at 1, 2, 4, 8, and either 6 or 11 hours after the anti-TB medications' dose MDRPK2: prior to- and at 1, 4, and 10 hours after the observed dose	Liquid chromatography tandem-mass spectrometry (LC-MS/MS)
Ogami et al., 2019	Prospective study	10 mg/kg, q8h, given orally and/or IV injection	NR	High-performance liquid chromatography

Notes: NR: not reported

Table III. Population Pharmacokinetic Modeling Methods, Tested, and Retained Covariates by the Studies Included in This Review

Study	Compartments	Software	Covariates Tested	Covariates Included in Final Model	Model Validation
Tian et al., 2025	One-compartment model with first-order elimination	NONMEM	Gender, age, weight, height, ALT, AST, albumin, direct bilirubin, total bilirubin, serum creatinine concentration, eGFR, and blood urea nitrogen	Weight and eGFR	Bootstrap analysis, NPDE test, and VPC test
Yang et al., 2025	Two-compartment models with first elimination	Phoenix NLME	Age, gender, weight, body mass index, albumin, alanine aminotransferase, aspartate aminotransferase, creatinine clearance, total bilirubin, direct bilirubin, pediatric critical illness score, CRRT/ECMO	Body weight and AST	Bootstrap analysis
Li et al., 2019	One-compartment model with first-order elimination	NONMEM	Gender, age, weight, height, BSA, BUN, serum creatinine concentration, urin acid concentration, serum cystatin-C concentration, eGFR, total bilirubin, ALT, AST, γ-glutayltranspeptidase concentration	Body weight and eGFR	Goodness-of-fit plots, bootstrap analysis, NPDE test, and VPC
Duan et al., 2024	One-compartment with first order elimination	Phoenix NLME	Gender, gestational age, postnatal age, postmenstrual age, birth weight, current weight, body surface area, the apgar score, hemoglobin, platelet, ALT, AST, total bilirubin, serum albumin, serum creatinine, and creatinine clearance	BSA	Bootstrap analysis and pc-VPC
Garcia-Prats et al., 2019	One compartment disposition model	NONMEM	Weight, height, age, sex, race, HIV status, linezolid administration method (oral versus nasogastric tube), formulation (whole versus crushed versus suspension), linezolid given as single dose versus at steady state, and interactions with concomitant drugs	Weight	VPC analysis
Ogami et al., 2019	One-compartment with first order absorption	NONMEM	Weight and age	Weight and age (postnatal age)	Bootstrap analysis

Notes: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSA: body surface area; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; VPC: visual predicted check

Table IV. Summary of Final Models and Estimated Population Pharmacokinetics

Study	Fixed Model	Estimate Parameters	Variability
Tian et al., 2025	$CL = 1.91 \times (WT/12.5)^{0.696} \times (eGFR/190.1)^{0.291}$	CL: 1.91 L/h VD: 10.5 L	BSV CL: 33.02 % BSV VD: 82.28 %
Yang et al., 2023	CL (L/h) = 2.34 x (weight/15) ^ 0.8 x (AST/45.9) ^ (-0.16) x exp(ηCL) VD (L) = 5.22 x exp(ηV)	CL: 2.35 L/h Vc: 5.22 L	BSV CL: 52.51% BSV Vc: 55.78%
Li et al., 2019	$CL = 1.31\ x(\frac{\ln WT}{2.40})^{0.83}\ x\ (\frac{\ln eGFR}{4.89})^{0.60}$ $V = 4.24\ x\ (\frac{\ln WT}{2.40})^{0.86}$	CL: 1.31 L/h VD: 4.24 L	BSV CL: 39.10% BSV VD: 28.09%
Duan et al., 2024	$CL = 0.154\ x\ (\frac{BSA}{0.127})^{1.186}\ x \exp(\eta CL)$ (L/h) $VD = 0.783\ x\ (\frac{BSA}{0.127})^{1.066}\ x \exp(\eta VD)$	CL: 0.154 L/h VD: 0.783 L	ω^2_{CL}: 0.132
Garcia-Prats et al., 2019	Ka (h^{-1}) = θ_Ka + (CL/V) CL/F (L/h) = θ_CL × 〖"(WT/70")〗 ^0.75 V/F (L) = θ_V × (“WT/70”)	CL: 4.73 L/h/70 kg VD: 54.8 L/70 kg Ka: 0.77/h	$BSV_{CL/F}$: 37% $BSV_{V/F}$: 32%
Ogami et al., 2019	$CL = 5.82\ x\ \left(\frac{WT}{70}\right)^{0.75}\ x\ \left(\frac{PNA^{46.0}}{2.06^{46.0}\ x\ PNA^{46.0}}\right)$ $VC = 41.3\ x\ \frac{WT}{70}$	CL: 5.82 L/h Vc: 41.3 L T_{abs}: 3.61 h $T_{1/2}$ elimination: 3 h (based on weight 9.9 kg and age of 24 months)	BSV CL: 52.3% BSV VC: 121%

Notes: BSV: between subject variability; CL: clearance; Vc: central volume of distribution; VD: volume of distribution; NR: not reported; WT: weight; θ: typical parameter, ω^2_{CL}: inter-individual variation

Although children with various age were the main subjects of all studies, one study specifically explored population pharmacokinetic only in premature neonates.[19] All children included in all studies got linezolid administered orally or by intravenous injection for treating the bacterial infections. Five studies did not limit the type of infection, while Garcia-Prats et al. only focused on children with multidrug-resistant tuberculosis.[16]

Study Designs and Analysis Method

Studies collected in this review contain of five prospective studies and one retrospective study. Among the prospective studies, Tian et al.'s study was multicenter study which data collection was done in several hospitals.[11] The manufacturer recommends the standard dose in using linezolid at 10mg/kg three times daily for children under 12 years and 600mg/dose twice daily for children aged 12 years and above. Mostly, all studies used the same dose regimen, nevertheless Garcia-Parts et al.'s study had different dose regimen preference, which was 10mg/kg/dose twice daily for children less than 10 years old and 10mg/kg/dose once daily for children more than 10 years old with the maximum total daily dose 600mg.[16] In addition, since Duan et al. focused on premature neonates' population, they had different dose regimen given to the patient which was also based on the manufacturer in their study which were 10mg/kg twice daily for preterm neonates with gestational age <34 weeks and postnatal age <7 days and 10mg/kg three times daily for preterm neonates with gestational ages ≥34 weeks and preterm neonates with gestational age <34 weeks and postnatal age >7 days.[19] For the drug administration, linezolid was given by intravenous infusion in five studies and orally (tablet or suspension, if available) in two studies. The time of sample collection was also varied in each study. For instance, Yang et al. collected four sample at the steady state, which were trough concentration (half an hour before the infusion), peak concentration (after the end of infusion), and two additional sampling times were consistently varied between peak and trough periods, representing intermediate concentrations.[10]

Differently, in Garcia-Prats et al.'s study, blood samples were collected before dosing and subsequently at 1, 2, 4, 8 hours, and at either 6- or 11-hours post-administration of anti-TB drugs in the first observational study group and samples were taken pre-dose and then at 1, 4, and 10 hours following the observed drug administration in the second observational study.

The amount of linezolid concentration was quantified using several methods. High-performance liquid chromatography, ultraperformance liquid chromatography-tandem mass spectrometry, and liquid chromatography tandem-mass spectrometry were used in these studies. All information regarding general characteristic of clinical protocol from each study can be seen in table II.

Population Pharmacokinetic Models of Linezolid

Population pharmacokinetic (PopPK) is a quantitative method which useful in describing the pharmacokinetic parameters of a drug at the population level.[20] This popPK modeling can provide the pharmacokinetic properties of a drug and identify intrinsic and extrinsic aspects of variability that affect the drug's pharmacokinetic. This review revealed that most studies of pharmacokinetic modeling of linezolid in pediatric patients employed a one-compartment model. Detail information of final models and estimated population pharmacokinetic parameters from each study can be seen in table IV. Body weight emerged as the most consistent and influential covariate affecting clearance, while body surface area was significantly associated with the volume of distribution in neonates.

As can be seen in table III, there are five studies adopted the one-compartment model for developing the popPK modeling. However, there is one study which found that a two-compartment model provided a better fit.[10] This discrepancy may be due to differences in sampling time, study populations (e.g., critically ill vs stable patients), or modeling approaches. The use of NONMEM in most studies included in this review reinforces its role as the standard software for population pharmacokinetic modeling.

The high variability in clearance underscores the risk of both underdosing and overdosing in pediatric patients when using fixed-dose regimens. Weight-based dosing remains essential, yet it may not be sufficient in specific subgroup such as neonates, patients with augmented renal clearance (ARC) or hepatic dysfunction, where eGFR and AST were also found to significantly affect pharmacokinetics.

Discussion

This systematic review included six studies that developed population pharmacokinetic (popPK) models of linezolid in pediatric patients. The majority of the included studies adopted one-compartment model with first-order elimination to describe the pharmacokinetics of linezolid, consistent with prior findings in both pediatric and adult populations. Only Yang et al.'s study which utilized two-compartment model, likely due to more intensive sampling and the inclusion of critically ill patients, whose altered physiology may affect drug distribution and elimination.[21] This align with previous study which stated that linezolid has typically been described using either one- or two-compartment structural models.[7] Differences in compartment models were also found in the adults group. For instance, one compartment was found fit as best model in patients with COVID-19-associated acute respiratory distress syndrome on veno-venous extracorporeal membrane oxygenation and also patients with tuberculosis meningitis.[22,23] Meanwhile, in studies involving critically ill and postoperative neurological patients, a two-compartment model was applied.[24,25]

Linezolid clearance in children showed substantial interindividual variability, ranging from 0.068 to 5.82 L/h. Linezolid clearance, in order from the highest to the lowest, was found in study included 15 Japanese children patients aged 0-13 years, critically ill pediatric patients infected by Staphylococcal in China, two studies included children with bacterial infections in Beijing and Wuhan, China, premature neonates with bacterial infections in Nanjing, China, and children with multidrug resistant tuberculosis in South Africa. Similarly, the volume of distribution ranged widely from 0.783-10.5 L which the lowest value of 0.783 L was obtained in two studies by Duan et al. and Garcia-Prats et al. and the highest value was found in Tian et al. study.[11,16,19] However, study by Yang et al. and Ogami et al. did not present volume distribution value but gave information 5.22 L and 41.3 L as the volume of central compartment, respectively.[10,17] These broad ranges may reflect differences in age, body composition, disease states, renal function, and study design. One study mentioned that the pharmacokinetic profile of linezolid shows age-dependent differences in pediatric population. Children under 12 years old have faster clearance and shorter elimination half-life compared to adults. Although newborns initially have clearance rates similar to adults, it rises rapidly during the first week of life, reaching two to three times adult values by day seven. Clearance then gradually declines in young children, eventually aligning with adult levels by adolescence.[26]

Across all studies, body weight emerged as the most consistent and significant covariate influencing clearance, included in the final model of five out of six studies. This finding underscores the importance of weight-based dosing to optimize therapeutic exposure and avoid subtherapeutic or toxic concentrations. In addition to body weight, several studies identified other relevant covariates. Duan et al. found that body surface area (BSA) to be significantly associated with both clearance and volume of distribution of linezolid in premature neonates.[19] This finding highlighted the need for special consideration in this subpopulation. Tian et al. and Li et al. reported that estimated glomerular filtration rate (eGFR) significantly influenced clearance.[11,18] Clearance was higher in patients with augmented renal clearance (ARC) (eGFR > 130 mL/min/1.73 m^2) compared to patients with normal renal function (90 ≤ eGFR ≤ 130 mL/min/1.73 m^2) in Tian et al.'s study.[11] This finding is similar to study in adult populations that reported higher clearance values in patients with augmented renal clearance which supports the notion that changes in renal function may affect the pharmacokinetics of linezolid in both adult and pediatric patients.[27] Furthermore, aspartate aminotransferase (AST) was found to impact the clearance in Yang et al.'s study, reflecting the role of hepatic metabolism in linezolid elimination. Additionally, Ogami et al. demonstrated that age, postnatal aged particularly, was associated with increased clearance, supporting the notion that maturation processes in infants affect pharmacokinetic behavior.[17] This is in line with prior studies showing substantial variation in linezolid pharmacokinetics during the first postnatal week. The mean clearance observed in 7-day-old infants was considerably lower than that in older infants. Clearance continued to be substantially increased throughout the first two to three months of life.[26] Developmental and maturational changes in children are key contributors to the pharmacokinetic variability observed in pediatrics.[28]

The variability in pharmacokinetic parameters observed among the included studies also reflects differences in sampling schemes, assay techniques, and modeling software. NONMEM and Phoenix NLME are the software widely used in population pharmacokinetic modelling.[29] In the articles included in this study, while four studies used NONMEM, two applied Phoenix NLME. Validation strategies of population pharmacokinetic which has been developed also differed, with bootstrap analysis being the most employed, yet no study performed external validation. Bootstrap methods utilize repeated sampling to provide an alternative framework for quantifying the uncertainty of parameter estimates.[20]

Clinically, these findings have significant implications. Fixed dose regimens, particularly in vulnerable subpopulations such as neonates or children with organ dysfunction, may result in underexposure or overexposure of linezolid. PopPK models that incorporate relevant covariates such as weight, renal function, or

liver enzymes offer a more individualized approach to dosing and may improve therapeutic outcomes while minimizing adverse effects, for instance thrombocytopenia. Tian et al. found that the standard linezolid dosage can reach good efficacy and safety target when MIC is equal to and less than 2 µg/mL.[11] Meanwhile, in study by Garcia-Prats et al., linezolid exposure was higher than expected in children with multi-resistant drug tuberculosis (MDR-TB).[16] It results in severe adverse event occasionally happen. Additionally, higher minimum concentration of linezolid is associated with risk of thrombocytopenia in Japanese children who treated with linezolid.[17] Other studies provide recommended dosing regimens that can be administered to the children population. Yang et al. suggest that dose regimen should consider the number of AST, a dose of 10mg/kg every 12 hours is appropriate for children aged <12 years and 600 mg every 48 hours is suitable for those aged 12 to 18 years with an AST of >200 U/L at a MIC of 1 mg/L.[10] Whereas, from study conducted by Li et al., it is known that approved dosage of 10mg/kg every 8 hours may lead to a risk of underdosing for children in the presence of bacteria with MIC $\geq$ 2 mg/L.[18] Therefore, they suggest elevating the dose become 15 or 20mg/kg every 8 hours to attain the pharmacokinetic target. Additionally, study by Garcia-Prats et al. proposed a new weight-banded once daily doses of linezolid for children treated for MDR-TB with several weight-band categories, start from 5 kg to more than 44 kg, and optimal dose from 80 mg to 600 mg to get exposure similar to the 600 mg daily in adult population.[16]

Strength, Limitations, and Recommendation

To the best our knowledge, this is the first review which summarizes the literature knowledge on population pharmacokinetics of linezolid, especially in children population. Despite these insights, the small number of studies and the heterogeneity in study design (sample sizes, clinical conditions, assay methods) limit the generalizability of the findings. Additionally, this study does not limit population pharmacokinetic studies to one type of linezolid dosage form**.** Furthermore, most studies focused on total plasma concentrations, only one study explored unbound (free) linezolid level, which is more directly related to the pharmacologic activity. Future studies should aim to include more diverse pediatric populations, standardize sampling and modeling protocols, and incorporate pharmacodynamic outcomes.

CONCLUSION

This systematic review identified six studies that investigated the population pharmacokinetics of linezolid in pediatric populations. Most of the included studies utilized one-compartment models to describe linezolid disposition. Body weight consistently emerged as the most influential covariate affecting drug clearance, while body surface area influenced volume of distribution in certain subpopulations such as neonates. These findings highlight the importance of incorporating patient-specific covariates into dosing strategies to optimize therapeutic outcomes and minimize adverse effects. Given the variation in study designs, routes of administration, and limited data on unbound drug concentrations, further research is needed to refine population models for both oral and intravenous formulations of linezolid in children. Future studies should also explore pharmacodynamic correlations and validate model-based dosing recommendations in clinical practice.

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