



## Research article

# A systemic review of vancomycin population pharmacokinetic models in children

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## ARTICLE INFO

### Article history

Received 25 April 2025

Revised 26 May 2025

Accepted 26 May 2025

### Keywords

Vancomycin

PopPK

Children

Pediatric

Therapeutic drug monitoring

Modeling

Pharmacokinetics

## ABSTRACT

Vancomycin has been extensively used to treat infections caused by Gram-positive bacteria. This antibiotic has a narrow therapeutic range, requiring therapeutic drug monitoring (TDM) to determine the dose to maximize therapeutic efficacy and minimize toxicity [1]. Due to significant variability inter and intra-individuals of pediatric population, determining the right dose for each patient could become more complicated. Recently, numerous population pharmacokinetic (popPK) models have been established to guide the dosing scheme in this population. This article aimed to systemically review published pediatric popPK models and covariates responsible for pharmacokinetic variability and dosage choices for pediatric patients. A systemic literature search was conducted in PubMed from the inception to August 2024 for pharmacokinetic research used popPK approaches in 1 month to 21 years old patients who were prescribed intravenous vancomycin. This review included 37 eligible studies, which were built on groups of children diverse in age and comorbid conditions. The majority were one-compartment models (30/37). CL and Vd varied in a wide range, 0.06 to 0.286 L/h/kg and 0.285 to 4.63 L/kg, respectively. Pharmacokinetics parameters were described by numerous covariates, of which age, weight, and serum creatinine are the most common ones. This study provided a big picture of established data on vancomycin popPK models in children. Application of these data to identify the optimal dose needed for individual child should be done in future researches.

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<http://doi.org/10.59882/1859-364X/309>

## INTRODUCTION

Since 1958, vancomycin has been widely used to treat infections caused by Gram-positive bacteria in both adults and children. In addition to its high bactericidal efficacy on Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus*, other notable features was its remarked nephrotoxicity and ototoxicity. Vancomycin showed dose-dependent efficacy and toxicity with narrow therapeutic index feature [2]. In addition, pharmacokinetic studies showed large inter- and intra-individual variability when using vancomycin in adults and children [3, 4]. Therefore, despite its use for nearly seven decades, optimal dosing of vancomycin remains a challenge. These characteristics led to the need for TDM to ensure effectiveness and safety during the treatment course [5]. Guidelines have been developed for decades to guide the monitoring of TDM treatment in both adults and children [6]. Recently, a consensus among the American Society of Hospital Pharmacists, the American Society of Infectious Diseases, the Society of Pediatric Infectious Diseases, and the Society of Infectious Diseases Pharmacists was issued in 2020, recommending the implementation of TDM aimed at reaching the target AUC/MIC with AUC in the range of 400-600 mg.h/L in children of all ages. In addition, the Bayesian method based on pharmacokinetic models was also noted as a preferred approach due to the advantage of requiring fewer blood samples [1]. However, many pharmacokinetic models have been developed for pediatric populations in decades. Among them, which model would be best to include as an *a priori* model for Bayesian estimates in such a variable population as children remains a question.

This systematic review therefore was conducted with the aim of synthesizing population pharmacokinetic models that have been developed in children, including subgroups of children with specific characteristics, and identifying the most important covariates which can affect vancomycin pharmacokinetic and dosing regimen in general pediatric population as well as each group.

## METHODS

The literature screening was conducted on the PubMed database, according to MeSH terms appeared in any part (Any fields) of the article. The groups of terms were determined by the PICO question. Terms are connected by "OR" within the same term group and "AND" between groups. We used the filter tool to retain full-text articles, written in English and published before 31<sup>st</sup>, August 2024 with the searching syntax as below:

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("pediatric"[Title/Abstract] OR "children"[Title/Abstract] OR "infant"[Title/Abstract] OR "adolescent"[Title/Abstract] OR "toddler" [Title/Abstract] OR "neonate"[Title/Abstract] OR "paediatric" [Title/Abstract] OR "neonatal" [Title/Abstract] OR "neonates" [Title/Abstract] OR "infants") AND ("Vancomycin"[Title/Abstract]) AND ("kinetic"[Title/Abstract] OR "pharmacokinetics" [Title/Abstract] OR "population pharmacokinetic" [Title/Abstract] OR "population pharmacokinetics" [Title/Abstract] OR "pharmacokinetic model"[Title/Abstract] OR "pharmacokinetic analysis"[Title/Abstract] OR "pharmacokinetic modeling" [Title/Abstract] OR "popPK"[Title/Abstract] OR "pop PK"[Title/Abstract] OR "PK analysis"[Title/Abstract] OR "PK model" [Title/Abstract] OR "compartmental pharmacokinetic" [Title/Abstract] OR
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"pharmacokinetic and pharmacodynamic analysis"[Title/Abstract] OR "PK/PD analysis"[Title/Abstract] OR "non-linear mixed effect model"[Title/Abstract] OR "NLME"[Title/Abstract] OR "NLMIXED"[Title/Abstract] OR "NONMEM"[Title/Abstract] OR "Monolix"[Title/Abstract] OR "ADAPT"[Title/Abstract] OR "WinNonMix"[Title/Abstract] OR "Phoenix"[Title/Abstract] OR "MWPHARM"[Title/Abstract] OR "P-PHARM"[Title/Abstract] OR "Kinpop" [Title/Abstract] OR "Pmetrics"[Title/Abstract] OR "pharmacometrics"[Title/Abstract] OR "simulation"[Title/Abstract] OR "dosing guidance"[Title/Abstract])

All relevant articles were reviewed and included if they developed at least one vancomycin population pharmacokinetic (popPK) model using nonlinear mixed-effect (NLME) modeling approach; study subjects were children 1 month to 21 years old using intravenous vancomycin. Articles were excluded if they were: (1) reviews, case reports, guidelines; editorials, commentaries, etc. (2) studies on other antibiotics (3) studies on oral or inhaled vancomycin (4) full text version not in English (5) they were inaccessible or not downloadable (6) all information of popPK model were not fully provided. Risk of bias was independently assessed by two research team members using the National Heart, Lung and Blood Institute Study Quality Assessment Tool for Case Series Studies [7], which was considered suitable for systematic reviews that include observational studies [8, 9]. The research team also screened the searched reviews' to identify all related articles. Relevant articles were also included in the review if they met all the criteria mentioned above.

Data was extracted by one research team member into data collection sheets and then were double-checked by another. Any disagreement in bias accessing and data extracting process was discussed to reach final agreement. Collected data include: publication information (author, year and country of publication, study design), population characteristics (population size, age, weight, serum creatinine, patient status), vancomycin dosing regimen and sampling scheme, analytical assays, modeling method (modeling software, structural models, covariate selection method, validation method) and the final model, typical value of clearance and volume of distribution, inter-individual variability (IIV), inter-occasion variability (IOV) and residual unexplained variability (RUV).

This article was within the framework of the research conducted with approval from the Vietnam National Children's Hospital (Decision No. 5582/QD-BVNTW on December 8th, 2023).

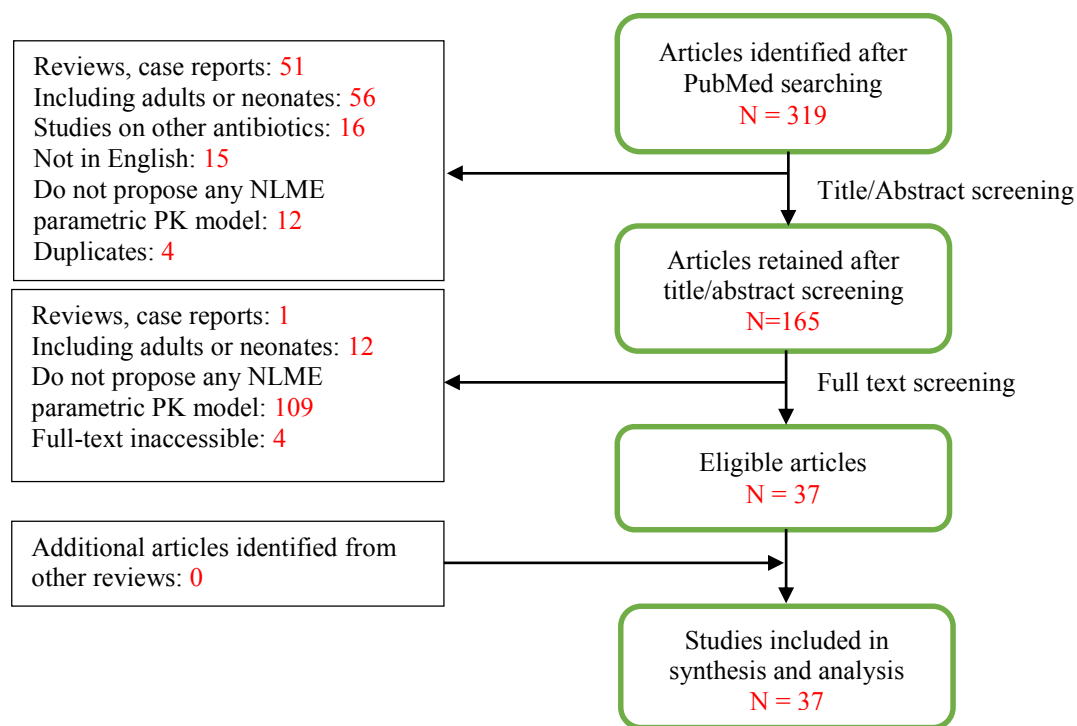
## RESULTS AND DISCUSSIONS

### RESULTS

Of the 319 articles identified using PubMed screening tools, 37 articles met the research criteria (see Figure 1). All of these studies were rated as good or fair when assessing risk of bias and were included in the analysis.

#### *Study design and population characteristics*

Of 37 included studies, 20/37 were published from 2020-2024 (Table 1). Three fourth of the studies (29/37) retrieved data retrospectively from therapeutic drug monitoring practice, while 7 other studies were conducted prospectively, and the newest study was a clinical trial. These studies were conducted in the U.S (13), China (12), other



**Figure 1.** Screening and selecting article process

developed countries (Canada: 3, France: 2, Japan: 1, Saudi Arabia: 1, Iran: 1, Bahrain:1) or other low to middle income countries (Thailand: 2, Jordan: 1). Sample sizes ranged from 6 to 1892 patients, in which the studies of Le et al. (2013) and Smit et al. (2021) enrolled a significantly higher number of patients than other studies, with 702 and 1892 patients [10, 11].

Two thirds included children of all ages (25/37), some studies focused on specific age groups. Zhang et al. (2016) and Li et al. (2021) targeted the group of infants (2/37) [12, 13] while some researched on older children (9/37) including Lanke et al. (2016) study, which recruited only adolescents 12 to 18 years old into the model [14]. In addition, besides nearly half of studies included children in general (16/37), others analyzed groups with varying medical conditions. Some models were established on patients

with special physical status (obesity: 2, augmented renal clearance: 3) or treatment status (in pediatric intensive care unit: 5). Others studies were conducted on patients with infectious diseases (skin and soft tissue infection or bone and joint infection: 1; meningitis: 1, febrile neutropenia: 2) and/or other comorbidities affecting pharmacokinetic processes (cancer: 5, renal failure: 1; cardiac diseases: 1) and/or having interventions (ventricular assist device: 1, hematopoietic stem-cell transplant: 1, liver transplant: 1, neurosurgery: 1, continuous renal replacement therapy (CRRT):1, hypothermia: 1). The weight of study populations varied in a wide range, notably, the study by Lanke et al. (2016) had significantly higher weight than other studies with a median weight of 58.9 kg [14]. The distribution of serum creatinine concentrations in the studies was quite large,

especially in the study by Moffet et al. (2020) on CRRT patients with median of serum creatinine concentration values of 0.72 mg/dL (Table 1) [15].

### ***Dosing and sampling scheme***

Vancomycin was administered as intermittent infusion (36/37) and continuous infusion (2/37), in which the clinical trial of Roshan et al. (2024) compared pharmacokinetic target achievement between intermittent and continuous infusion groups [16]. The common dose was 40-60mg/kg/day with a dose interval of 6h/8h/12h. Blood samples for vancomycin quantitative assays were typically drawn at steady state within 1 hour before the next dose (C<sub>trough</sub>) and/or within 2 hours after infusion (C<sub>peak</sub>). The exceptions were the samples collected right after the first dose in the study of Issaranggoon et al. (2020) [17] or the only preoperative dose for surgical site prophylaxis in the study of Brooks Peterson (2020) [18]. The average number of samples per patient during the vancomycin course was 1.35-7.19. Sparse-sampling strategy was commonly applied while the dense sampling strategy were conducted in some studies as the study of Wrishko RE (2000) and Issaranggoon (2020), collecting 10 samples per patients, including 1 sample at 30 minutes before infusion and 9 other samples after infusion of the final dose and the first dose, respectively [17, 19]. Vancomycin concentrations were measured mostly via immunoassays such as enzyme multiplied immunoassay technique (11/37), fluorescence polarization immunoassay (6/37) and chemiluminescent microparticle immunoassay (4/37) (Table 1).

### ***Modeling characteristics***

Most of the studies used NONMEM software (30/37 studies) to build models

while the remaining used Phoenix software (4/17 studies) or Monolix (3/17 studies). The first-order pharmacokinetic elimination hypothesis was used in all analyses. Most of the papers reported one-compartment models (30/37) while two-compartment models were reported in 7 other papers. All studies described the variability in pharmacokinetic parameters through inter-individual variability (IIV), while inter-occasion variability (IOV) was only mentioned in Alsultan et al. study (2018) [20]. IIV and IOV values are both expressed in exponential functions in studies. The residual unexplained variability (RUV) values were expressed through a variety of different expressions, including proportional (18/37), combined additive and proportional (8/37), additive (6/37), and exponential error model (5/37).

30/37 studies used the stepwise method to determine factors that significantly affected pharmacokinetic parameters, except for 7 studies that did not mention. Values of p-index and  $\Delta$ OFV were used to decide to select or eliminate covariates to models. The most commonly cut-off value for decreased OFV was  $\geq 3.84$  ( $p < 0.05$ ) (20/30 studies) in forward inclusion, while for backward elimination, OFV needed to increase more than 6.63 or 10.83 ( $p < 0.01$  or  $< 0.005$ ) (17/30 studies).

The typical value of popPK parameters varied over a wide range. In 30 one-compartment models, estimated vancomycin clearance (CL) values ranged from 0.06 to 0.286 L/h/kg, and volume of distribution (V<sub>d</sub>) ranged from 0.285 to 4.63 L/kg. The interindividual variability (IIV) of vancomycin CL ranged from 14 to 58%, and the IIV of V<sub>d</sub> ranged from 12 to 77%. For studies establishing two-compartment pharmacokinetic models, estimated CL

values ranged from 0.072 to 0.19 L/h/kg, intercompartmental clearance (Q) ranged from 0.13 to 8.49 L/h. Reported central compartment volume of distribution ( $V_c$ ) fluctuated from 5.3 to 81 L and peripheral volume of distribution ( $V_p$ ) widely varied in a range from 2.6 to 37.8 L with an extra elevated value of 550 L in the study of Moffet et al. (2019) on CRRT patients [15]. In two-compartment models, IIV of CL ranged from 6-50%, IIV of  $V_c$  from 5-147% while IIV of Q and  $V_p$  were rarely reported (Table 2).

Weight, age, estimated glomerular filtration rate (eGFR) and serum creatinine were the most common covariates recorded in models. Weight was the selected covariate in 35/37 studies as actual weight (33/35) or fat free mass (FFM) in 2 studies of Moffet et al. in 2019 on obese and CRRT patients [15, 21]. Age was included in the final model of 9/37 studies as actual age (7/9) or post menstrual age (2/9). 10 studies identified serum creatinine (Scr) as a factor that significantly influenced vancomycin clearance, while eGFR was recorded as a covariate on clearance in 14 studies. Other factors have also been retained in popPK models, including gender, blood urea nitrogen (BUN) concentration, serum cystatin C, temperature, intravenous administration route (intermittent or continuous infusion), body surface area (BSA), ultrafiltration rate (CRRTUF), dialysate rate (DILYSTE) and days from liver transplant.

Internal validation was applied to all models of which 7/37 studies were further validated externally with independent data. Internal validation was mainly performed through goodness of fit (GOF), visual predictive check (VPC), prediction-corrected visual predictive check (pcVPC), and normalized prediction distribution error

(NPDE) charts. 29/37 studies used the bootstrap method to determine the variation range in population pharmacokinetic parameters. Models were externally validated based on bias and accuracy metrics.

## **DISCUSSIONS**

The article is a compilation of research studies focused on vancomycin pharmacokinetics and in pediatric populations with varying conditions, including renal function differences, obesity, critical illness, and specific diseases such as infections, cancers, etc. These studies collectively aim to improve vancomycin usage by using population pharmacokinetic models and Bayesian estimation to ensure efficacy and minimizing toxicity in children. The number of studies published in the 2020-2024 period is higher than during the previous 20 years 2000-2020, in which most of newer studies were conducted in Asian countries rather than in American and European countries as previously. This trend suggests a global growing interest in optimizing vancomycin treatment in children following the 2020 consensus guideline [1].

### **Pharmacokinetic models**

Most studies proposed one-compartment model, generated from sparse sampling strategy which may lead to not fully describing the distribution phase of the drug [10]. One-compartment models were largely accepted to describe the vancomycin pharmacokinetics in pediatric patients due to the difficulties in collecting blood sample in this vulnerable population [10, 22]. The 2-compartment models were identified in several studies by assuming 2-compartment structural model when establishing study methods [23] or employing dense sampling strategy [17, 19] or collecting a wide range of

concentrations at different time after dose within a dosing interval [11, 15].

The estimated weight-adjusted clearance values of the studies ranged from 0.06 to 0.286 L/h/kg, similar to the values recorded in the previously reviews in children of Chung et al. (2021) and Aljutayli et al. (2021) [3, 8], but higher than the adult values (0.0054-0.1279 L/h/kg) [4]. The most common reported covariates on vancomycin clearance were total body weight or FFM (72%), estimated glomerular filtration rate (38%), serum creatinine (27%), and chronological age or postmenstrual age (PMA) (24%). Although weight was the most common predictor for CL, higher weight-adjusted clearance in children may not reflect true higher drug clearance than in adult due to the influence of organ maturation [24], presented by complex maturation functions of weight on CL, from a simple linear relation to a more complex sigmoidal function (Table 2). It was also demonstrated by allometric scaling approach, using the theoretical power 0.75 or 1, or estimated powers, for actual body weight, FFM or body weight corrected to 70 kg, or the mean/median body weight of modeling data. In addition, kidney function (expressed through Scr and eGFR) was commonly reported as a covariate on vancomycin clearance, in which eGFR estimated by modified Schwartz or Traub formula was proved to have high correlation [25]. Recently, cystatine C attracted more attention as a reliable predictor for vancomycin clearance due to the stability of this renal function biomarker [26, 27]. Le et al. noted that age in linear function was also a covariate of vancomycin clearance in their serial studies [10, 25, 28-30]. In other studies, age was also appeared in final

model, in linear, power or exponential functions, or sigmoid function of PMA in models for infants or younger children, to reflect the effect of maturation on vancomycin clearance [31].

Estimated value of the weight-adjusted volume of distribution ranged from 0.285 to 4.63 L/kg, similar to the range published previously [3, 8], but more largely when compared with adult data of 0.4-1 L/kg [32]. This high variability could be attributed to the wide range of total water content and extracellular fluid volume in different ages from birth to 18 years, in addition to the diversity of disease states and renal function in each study population. In critically ill pediatric patients, Vd can be further altered due to interventions that affected body fluid during intensive care treatment [33]. Weight was the only covariate retained on Vd in most studies, in form of linear formula (65%) or power formula (24%). Total body weight or FFM itself or standardized to the study median or to 70 kg, were utilized to express the effect of size scaling on Vd. Based on these results, although a 40-70 mg/kg/day dose regimen was recommended in the general pediatric population [34-36], other dose regimens may be suggested in different subgroups (see below).

#### ***Abnormal renal function***

Several studies have been compared vancomycin pharmacokinetic between renal failure vs. normal renal function children, showing that CL vancomycin in children with impaired renal function is 30–80% lower than normal group [13, 25, 34, 37]. Consequently, AUC increased up to 1.9-2.8 times in renal failure children, raising the ability to reach the treatment target, but posing the patient to the higher risk of nephrotoxicity [13]. Besides serum creatinine and BUN, which reflect

residual renal function, this study showed the impact of renal replacement interventions via dialysis flow rate, ultrafiltration rate on CL. CL value were relatively low compared with other studies, whereas larger Vd may be explained by sparse sampling, large priming volumes in continuous veno-venous hemofiltration (CVVH), and fluid overload in this population [15]. The results suggested that appropriate initial dosing and aggressive TDM should be considered in pediatric patients with renal failure and dialysis [13, 15, 37].

On the other hand, the value of CL vancomycin of augmented renal clearance (ARC) children was 2-fold than the CL value of normal group [38]. Covariates of CL on ARC children included weight, age and eGFR [12, 38, 39]. Based on these results, He et al. (2021) proposed the initial dose 75 mg/kg/day in children 1 month - 12 years old and 70 mg/kg/day in children 12-18 years old [39]. For patients who had both underlying diseases, including pediatric cancer patients, pediatric intensive care patients and ARC status concurrently, a series of pharmacokinetic models have also been built to optimize the dose regimen (see below).

### **Obesity**

Pharmacokinetic studies of vancomycin in obese children have yielded inconsistent results. A matched case-control study between obese and normal-weight children conducted by Le et al. (2015) showed that the weight-adjusted CL and Vd of obese children were lower than those of normal-weight patients, by 10.8% and 2.2%, respectively. Therefore, the authors suggested that dose adjustment may not be necessary in obese children. In addition, the study results also suggested the use of  $\text{weight}^{0.75}$  in vancomycin popPK models of obese children [28]. When building a model  $\geq 70$  kg children, Moffet et

al. (2019) found the advantage of FFM over actual weight in estimating pharmacokinetic parameters. From the simulation results, the research group proposed a dose regimen of 20 mg/kg/dose every 6 hours [21]. With a large dataset of 1892 patients with various degree of obesity and renal function, Smit et al. (2021) noted the influence of actual weight and renal function on the pharmacokinetics of vancomycin. They recommended a dose regimen based on both weight and eGFR to ensure efficacy and safety when using vancomycin, in which the dose for children weighing  $\geq 70$  kg ranged from 3-6-12-18 mg/kg every 12 hours, corresponding to eGFR 10-30, 30-50, 50-90 and  $>90$  ml/min/1.73 m<sup>2</sup> [11].

### **Pediatric intensive care unit (PICU)**

With rapidly changing pathophysiological characteristics, including changes in plasma protein levels, extracellular fluid volume, and renal clearance, the intensive care pediatric population often has higher CL and Vd than the general population [26, 38, 40, 41]. Augmented renal clearance was often observed in PICUs, occurring in 1 in 10 children according to a review by Avedissian et al. (2017) [40]. As a result, vancomycin CL in the ARC group increased up to 2-fold in infants and 1.5-fold in older children compared to the non-ARC group [38, 40], lowering the ability to achieve trough concentration and AUC targets in PICU patients [16, 38, 40]. To address this issue, Sridharan et al. (2021) proposed a dose of 60–80 mg/kg/day to achieve  $\text{AUC/MIC} \geq 400$  [41]. Huang et al. (2022) suggested a higher dose for infant population, up to 100 mg/kg in the group with  $\text{eGFR} > 210$  ml/min/1.73 m<sup>2</sup> and noted that for premature and low birth weight infants, the dose should be individualized based on gestational age and

weight [38]. Another concern raised from some studies was the renal function assessment formula as commonly used Schwartz bedside formula renal did not perform superior than others when establishing vancomycin popPK models in PICU patients [26, 40]. Based on a comparison of eGFR estimates from different formulas in the development of a suitable pharmacokinetic model for vancomycin in pediatric intensive care patients, Downes et al. (2020) recommended that the use of cystatin C-based renal function assessment formulas may provide a better estimate of vancomycin CL [26]. Taking a different approach, Roshan et al. (2024) built a model showing that continuous infusion of vancomycin maintained a more stable AUC and increased the likelihood of achieving the target AUC  $\geq 400$  mg.h/L to 82% compared to 23% with intermittent infusion [16].

### **Cancer**

In studies on children with cancers, vancomycin CL and Vd were high and varied over a wide range. Abdel Hadi et al. (2015) reported CL 0.381 L/h and Vd 0.663 L in pediatric cancer patients and suggested that the dose should be increased higher than the usual dose of 60 mg/kg/day [42]. In children with hematological malignancies, both research groups of Zhao and Wang noted CL with high typical value and were affected by renal clearance and weight, from which the authors suggested increasing doses for this group of patients, respectively 80-90 mg/kg/day and 73-106 mg/kg/day [36], [43]. Lv et al. (2020) built a popPK model on a group of hematological cancer patients with ARC status also found that CL vancomycin was elevated and proposed an initial dose of 50-75 mg/kg/day [43]. Conducting a study on both hematological and solid tumor patients,

Guilhaumou et al. (2016) found that Vd ranged from 0.48 to 0.72 L/kg and CL ranged from 0.08 to 0.14 L/h/kg, depending on each subgroup of subjects (hematological malignancies using cyclosporine and not using cyclosporine and solid tumors), thereby proposing a weight-based dose for each group [10].

### **Other populations**

Some authors have developed pharmacokinetic models for groups of children with specific infectious diseases. Xu et al. (2022) developed a popPK model in a group of children with meningitis, noting that only 10.7% of cases reached the target trough concentration. They also reported that weight and BUN were covariates of CL and should be considered in optimizing vancomycin doses in children with meningitis [44]. Lv et al. (2023), when developing an optimal dose regimen for children with skin and soft tissue infections and bone and joint infections, noted that CL and Vd values were within the common range of studies and proposed a high dose regimen of 75-80 mg/kg/day to optimize the ability to reach the therapeutic target [45]. Shinamoto et al. (2021) conducted a study on pediatric patients with febrile neutropenia after hematopoietic stem cell transplantation and found more than one-third of patients had ARC and CL were affected by weight, age, eGFR, and fever. The research team therefore proposed to individualize the initial dosing regimen for each patient subgroup divided by these factors [23].

Other researchers have developed vancomycin popPK models in pediatric populations undergoing medical interventions. Zane et al. (2017) developed a PopPK model for pediatric populations

Table 1: Study population characteristics

Author (year)	Country	Study design	Study population	Patients (samples)	Age (years)	Weight (kg)	Creatinin (mg/dL)	Dosage	Sampling scheme	Assays
Wrishko RE (2000)[19]	Canada	Pro- spective	Children	6 (60)	6.9 ± 3.0	21.2 ± 6.8	n.s	40–60 mg/kg/d	At ss (final dose), 0.5h before dose, and 1,2,3,4,5,6,8,10,12h after starting infusion.	FPIA (Abbott)
Le J (2013)[10]	US	Retro- spective	3m-21y	702 (1660)	6.6 (2.2-13.4)	22.8 (12.6-46.0)	0.4 (0.3-0.6)	n.s	n.s	FPIA
Le J (2014)[29]	US	Retro- spective	3m-21y	138 (712)	6.1 (2.2-12.2)	22.2 (13.2-37.9)	0.37(0.30-0.50)	n.s	At ss (96h): Cp: 1-3h after ending infusion; Ct and C near trough: within 2h before the next dose	n.s
Le J (2014)[25]	US	Retro- spective	3m-21y, RF	63 (319)	13 ± 6	51 ± 25 <sup>b</sup>	0.6 ± 0.2		At ss	FPIA (Siemens)
Zhao W (2014)[48]	France	Retro- spective	<18y, hematologic cancer	70 (98)	6.8 ± 4.8	25.7 ± 15.5	0.36 ± 0.19	40 – 60 mg/kg/d q6h	n.s	FPIA (Roche)
Le J (2015)[30]	US	Retro- spective	3m-21y	680 (1576)	6.7 (2.2–13.7)	23.1 (12.8–46.7)	0.4 (0.3–0.5)	n.s	n.s	n.s
Le J (2015)[28]	US	Retro- spective	3m-21y, BMI >85%	87 (389)	10.0 [4.8–15.2]	31.3 [16.8 – 47.1]	0.48 ± 0.20	47.4 ± 13.0 mg/kg/d	n.s	n.s
Abdel Hadi O (2016)[42]	Jordan	Retro- spective	Children, cancer	49 (120)	G1: 9.1 ± 5.7; G2: 7.1 ± 5.4	G1: 31.6 ± 18.6; G2: 25.0 ± 16.4	G1: 0.37 ± 0.23; G2: 0.32 ± 0.17	Continuous infusion: 10mg/kg, then 30mg/kg/24h	At ss (24h after the 1 <sup>st</sup> dose)	n.s
Guilhaumou R (2016)[49]	France	Retro- spective	3y-13y, cancer	121 (301)	6 ± 2.5	19.6 ± 6.9	0.4 ± 0.11	40 – 120 mg/kg/d q6-8h	At ss: Cp, Ct	FPIA (Roche)
Zhang H (2016)[13]	China	Pro- spective	1m-2y	110 (253)	0.5 (0.1-2.0)	7.9 [5.0-11.2]	N/A	n.s	At ss (after the 4 <sup>th</sup> dose): Cp: 1h after ending infusion; Ct: 1h before the next dose	n.s
Avedissian SN (2017)[40]	US	Retro- spective	1y-21y, ARC, PICU	250 (658)	9.8 [3.2 – 14.0]	30.0 [15.0 – 50.0]	0.4 [0.30 – 0.54]	n.s	During 48h after the 1 <sup>st</sup> dose: Cp 2h after infusion, Ct 2h before the next dose	n.s
Lanke S (2017)[14]	US	Retro- spective	12y-18y	463 (1107)	15.6 (14.0-17.5)	58.9 (45.8-72.2)	0.62 (0.50-0.79)	n.s	Cp: 0.5h after ending infusion; Ct: 0.5h before the next dose	n.s
Zane NR (2017)[37]	US	Retro- spective	1m-17y, cardiac diseases	52 (154)	G1: 3.6 [0.3-17.6]; G2: 1.9 [0.1-17.5]	G1: 16.4 [7-88.3]; G2: 12 [3.8 – 77.5]	G1: 0.2 [0.1 – 2.0]; G2: 0.4 [0.1 – 3.9]	40 mg/kg/d q6h	n.s	n.s

Author (year)	Country	Study design	Study population	Patients (samples)	Age (years)	Weight (kg)	Creatinin (mg/dL)	Dosage	Sampling scheme	Assays
Alsultan A (2018)[20]	Saudi Arabia	Retro-spective	1y-12y	76 (122)	5.8 ± 2.9	18.1 ± 8.5	0.38 ± 0.12	n.s	At ss: Cp: 1h after ending infusion; Ct: 0.5h before the 5 <sup>th</sup> dose	n.s
Moffett BS (2019)[15]	US	Retro-spective	<19y, CW/HDF	138 (828)	4.9 [1.0-14.5]	31.0 ± 25.8 <sup>b</sup>	0.72 (0.41 - 1.29)	40 - 50 mg/kg/d q8-12h	n.s	EMIT (Ortho)
Moffett BS (2019)[21]	US	Retro-spective	<19y, ≥70 kg	196 (555)	15.9 [9.3 - 18.9]	91.8 ± 20.6	0.90 ± 0.48	10-15 mg/kg/dose q6-8h	n.s	n.s
Wang Y (2019)[34]	China	Retro-spective	1m-18y	155 (351)	2.16 ± 2.94	10.9 ± 6.9	0.38 ± 0.20	n.s.	After the 4 <sup>th</sup> dose	HPLC (Agilent)
Brooks Peterson M (2020)[18]	Canada	Pro-spective	Children, neuro-surgery	59 (237)	7.8 ± 5.9	33.7 ± 25.5	n.s	15 mg/kg (max 1g) ≤2h before incision	Skin biopsies, blood samples at incision & skin closure, blood samples at 2h&4h in long surgery	LC/MS/MS (Sciex)
Downes KJ (2020)[26]	US	Pro-spective	2y-18y, PICU	20 (83)	12.7 (8.8-15.5)	33.9 (25.9-45.9)	0.4 (0.3-0.7)	10-15 mg/kg every 6-8 hours	<0.5h before the 4 <sup>th</sup> dose; 1h±0.5h&3.5h±0.5h after ending infusion; <0.5h before the next dose	CMIA (Abbott)
Issarangoon Na Ayuthaya S (2020)[17]	Thailand	Pro-spective	2y-18y	14 (140)	6.3 (3.3-10.8)	16.5 (12.8-29.2)	0.35 (0.28-0.40)	60-80 mg/kg/d q6h	1 <sup>st</sup> dose: 0.5h before; 0.5h, 1h during infusion; 1h15, 1h30, 2.3, 4, 5, 6h after.	CMIA (Abbott)
Lu JJ (2020)[27]	China	Retro-spective	2y-18y	170 (346)	9.36 ± 4.59	28.7 ± 14.8	n.s	15 mg/kg/dose	At ss	EMIT (Siemens)
Lv CL (2020)[43]	China	Retro-spective	2y-18y, hematologic cancer, ARC	53 (106)	8.62 ± 4.13	28.1 ± 14.7	0.33 ± 0.15		At ss: Ct	EMIT (Siemens)
Moffett BS (2020)[46]	US	Retro-spective	<19y, VAD	69 (337)	7.1 (2.4, 11.9)	26.1 (12.7, 53.5)	0.38 (0.30, 0.55)	14.8±1.8 mg/kg/dose+irrigation dose	n.s	EMIT (Ortho)
Wang H (2020)[50]	China	Retrospective	1m-18y, hematologic cancer	92 (144)	7.5 ± 3.8	26.4 ± 12.6	0.5 ± 0.12	40-60 mg/kg/d q6-12h	Ct: 0.5-1h before the 4 <sup>th</sup> or 5 <sup>th</sup> dose	CMIA (Abbott)
Zhang T (2020)[51]	China	Retro-spective	1m-18y	201 (383)	2.5 (0.7-6.1)	13.0 (0.8-20.8)	0.28 (0.21-0.37)	n.s	At ss: Cp: 0.5h after ending infusion; Ct: 0.5h before the next dose	HPLC
He CY (2021)[39]	China	Retro-spective	1m-18y, ARC	113 (242)	4.50 [0.44 - 14.88]	15.00 [6.00-62.00]	0.28 [0.16 - 0.56]	58.82 [11.69 - 133.93] mg/kg/d	n.s	n.s
Li DY (2021)[12]	China	Retro-spective	1m-24m	61 (139)	0.19 ± 0.33	2.9 ± 2.2	0.35 ± 0.37	n.s	At ss (5 <sup>th</sup> dose): Cp: 0.5h after ending infusion; Ct: 0.5h before dose	EMIT
Shimamoto Y (2021)[23]	Canada	Retro-spective	<18y, HSCT, febrile neutropenia	165 (276)	n.s	20.7 [13.5-46.5]	0.34 [0.25-0.45]	53.5 ± 10.0 mg/kg/d	Mostly Ct	EMIT (Ortho)

Author (year)	Country	Study design	Study population	Patients (samples)	Age (years)	Weight (kg)	Creatinin (mg/dL)	Dosage	Sampling scheme	Assays
Shoji K (2021)[47]	Japan	Retro-spective	<18 y, liver transplant	161 (1158)	1.11 [0.08 – 15.50]	9.1 [3.1 – 61.0]	0.16 [0.06 – 5.43]	1m-12y: 60 mg/kg/d q6h 13y-17y: 45 mg/kg/d q8h	Ct before the 4 <sup>th</sup> or 5 <sup>th</sup> dose	n.s
Smit C (2021)[11]	US	Retro-spective	1y-18y	1892 (3968)	G1:6.9(2.9-13.2); G2:7.2(3.0-12.6); G3:3.0(2.5-13.2)	G1:20.6(13.0-38.8); G2: 25.0 (13.8-51.4); G3:30.0(14.0-78.1)	G1:0.40 (0.30-0.54); G2:0.40 (0.30-0.57); G3:0.44 (0.30-0.61)	n.s	Cp: 0.5h after ending infusion; Ct: 0.5h before the next dose, or at other time points	n.s
Sridharan K (2021)[41]	Bahrain	Retro-spective	Children, PICU	58 (145)	1.6 [0.04-17]	9.2[1.68-60]	0.21 [0.0-0.59]	n.s	Ct: before the 3 <sup>rd</sup> dose	EMIT 2016, TIIA 2017
Chuphan C (2022)[36]	Thailand	Retro-spective	1m-18y	212 (348)	3.5 (0.9–10.9)	14.0 (7.2–30.4)	0.38 (0.25–0.59)		At ss and non-ss, Cp: 1-2h after ending infusion; Ct: ≤1h before the next dose	CMIA (Abbott)
Huang GM (2022)[38]	China	Retro-spective	1m-12m, PICU, eGFR≥80ml/min/m <sup>2</sup>	66 (169)	0.45 [0.10-0.98]	6 (1.1-10)	0.2 (0.045-0.53)	30-60mg/kg/d, q6-8h	After the 4 <sup>th</sup> dose: Cp:1h after infusion, Ct: just before the next dose	EMIT (Siemens)
Xu J (2022)[44]	China	Pro-spective	<60 m, meningitis	82 (155)	1.13 ± 1.39	8.27 ± 3.54	0.58 ± 0.31	10-15 mg/kg/dose q6, 8, 12h	Ct: 0.5h before the 5 <sup>th</sup> dose; Ct: 30 mins after the 5 <sup>th</sup> dose	EMIT, SYVA Viva-E
Lv M (2023)[45]	China	Pro-spective	1m-18y, SSTI or BJI	25 (73)	2.68 [0.1-10.8]	12.25 [4.9-51.0]	0.25 [0.14-0.65]	40mg/kg/d q6-8h	At ss (≥day2), at time of routine biochemical test	EMIT, SYVA Viva-E
Roshan N S B (2024)[16]	Iran	Clinical trial	2m-15y, PICU	68 (136)	3.25 ±3.65	13.19 ±10.50	GFR 96.02 ± 39.52 ml/min	60mg/kg/d q6h or continuous infusion 15mg/kg, then 60mg/kg/24h	Day 3: Ct: 0.5h before infusion, C2: 1.5h after starting infusion	FPIA (Cobas)
Shen X (2024)[35]	China	Retro-spective	>1m	386 (521)	2.22 [0.08-17.45]	11.95 [0.88-49.5]	0.29 [0.09-1.26]	n.s	Ct: 0.5h before the 4 <sup>th</sup> -5 <sup>th</sup> dose, Cp: 0.5-1h after infusion	EMIT (Siemens)

Note: Data are expressed as median [range] or median (IQR) or mean±standard deviation. Abbreviations: d: day/days; m: month/months; y: year/years; BMI: body mass index; RF: renal failure; ARC: augmented renal clearance, PICU: pediatric intensive care unit, CWHDF: continuous veno-venous hemodiafiltration, VAD: ventricular assist device therapy, HSCT: hematopoietic stem cell transplantation, SSTI: skin and soft tissue infection; BJI: bone and joint infection, n.s: not specified, ss: steady state, FIPA: Fluorescence-based immunoprecipitation assay, EMIT: Enzyme multiplied immunoassay technique, CMIA: chemiluminescence microplate immunoassay, HPLC: High Performance Liquid Chromatography, LC/MS/MS: Liquid chromatography–mass spectrometry, Cp: peak concentration, Ct: trough concentration, G1: group 1, G2: group 2, G3: group 3

**Table 2:** Population pharmacokinetic models

Author (year)	Modelling software	Compartments	Covariate selection	Final model	CL (L/h/kg)	Vd (L/kg)	IV (CL,Vd)	RUV	Validation
Wrishko RE (2000)	NONMEM, n.s	2	n.s	$CL(L/h)=0.1^{*}wt; Q(L/h)=2.43;$ $Vc(L)=0.36^{*}wt; Vp(L)=0.29^{*}wt$	CL0.1; Q 2.43L/h	Vc 0.36; Vp 0.29	16%; 12% (Vc)	Exponential: 7%	Internal: ME, MAE
Le J (2013)	NONMEM, FOCE	1	Stepwise: forward OFV ↓>4(p<0.05); backward OFV ↑>8(p<0.005)	$CL(L/h)=0.248^{*}wt^{0.75}$ $*(\ln(\text{age})/7.8)^{0.995}*(0.4/5cr^{*a})^{0.361};$ $V(L)=0.636^{*}wt$	0.248	0.636	35%; 18%	Proportional: 29%	Internal: GOF, BO, CWRES
Le J (2014)	NONMEM, FOCEI	1	Stepwise: forward p<0.05; backward p<0.005	$CL(L/h)=0.258^{*}wt^{0.75}$ $*(\ln(\text{age})/7.7)^{0.808}*(0.4/5cr^{*a})^{0.431};$ $V(L)=0.644^{*}wt$	0.258	0.644	41%; 12%	Proportional: 32%	Internal: ME, MAE
Le J (2014) (RF)	NONMEM, FOCE	1	Stepwise: forward p<0.05; backward p<0.005	$CL(L/h)=0.235^{*}wt^{0.75}$ $*(\ln(\text{age}(d))/8.6)^{1.09}$ $*(\ln(5cr)/0.407); V(L)=0.564^{*}wt$	0.235	0.564	39%; n.s	28%	Internal: GOF, BO
Zhao W (2014)	NONMEM, FOCEI	1	Stepwise: forward OFV ↓>3.84(p<0.05); backward OFV ↑>7.88(p<0.005)	$CL(L/h)=4.37^{*}(wt/20.2)^{0.677}$ $*(\ln(\text{age})/191)^{1.03};$ $V(L)=119^{*}(wt/20.2)^{0.838}$	0.17	4.63	35%; 77%	Combined: (a) 1.17 mg/L, (p) 5.3%	Internal: GOF, BO, VPC,NPDE; External: PE%,APE%
Le J (2015)	NONMEM, FOCEI	1	n.s	$CL(L/h)=0.105^{*}wt^{0.75}$ $*(\ln(\text{age})/3.4)^{1.12}*(0.39/5cr)^{0.457};$ $V(L)=0.628^{*}wt$	0.105	0.628	34%; 22%	Combined: (a)1.29mg/L; (p) 26.4%	Internal: BO
Le J (2015) (Obese)	NONMEM, FOCEI	1	Weight measures that reduce MOF ≥ 4(p<0.05)	$CL(L/h)=0.286^{*}wt^{0.75}$ $*(\ln(\text{age})/8.3)^{0.755}*(0.4/5cr)^{0.290};$ $V(L)=0.574^{*}wt$	0.286	0.574	30%; 29%	24%	Internal: BO
Abdel Hadi O (2016)	NONMEM, FOCE	1	Stepwise: forward p<0.05; backward p<0.005	$CL(L/h)=0.381^{*}wt^{0.75}; Vd=0.663^{*}wt$	0.02	0.66	19%; n.s	Additive: 0.109	Internal: BO
Guilhaumou R (2016)	NONMEM, FOCE	1	n.s	$CL(L/h)=\theta^{*}(wt/70)^{0.75}(\theta=3.49; 4.66;$ 4.97 for hematological cancers with/without cyclosporine and for solid tumors); $V(L)=34.8$	0.084	1.76	32%; 67%	Combined: (a) 4.45 mg/L, (e) 0.238	Internal: GOF, BO, NPDE
Zhang H (2016)	NONMEM, FOCEI	1	Stepwise: forward OFV ↓>3.8(p<0.05); backward OFV ↑>6.6(p<0.01)	$CL(L/h)=0.83^{*}(wt/7)^{0.97}$ $*(\ln(\text{age})/108)^{0.42};$ $V(L)=4.22^{*}(wt/7)^{0.93}$	0.1	0.6	29%; 22%	Additive: a=0.01	Internal: GOF, BO, VPC
Avedisian SN (2017)	NONMEM, FOCE	1	n.s	$CL(L/h)=0.118^{*}wt^{*e^{(-1.13^{*}(Scr-0.40))}}; V(L)=0.624^{*}wt$	0.118	0.624	39%; 35%	Combined: (a): 2.96, (p) 21%	Internal: BO
Lanke S (2017)	NONMEM, FOCEI	1	Stepwise: forward OFV ↓>3.84(p<0.05); backward OFV ↑>10.83(p<0.001)	$CL(L/h)=4.85^{*}(wt/58.9)^{0.84}$ $*(\ln(\text{age})/108.1)^{0.78};$ $V(L)=31^{*}(wt/58.9)^{0.52}$	0.082	0.526	28%; 25%	Combined: (a) 37.1%, (p) 20.7%	Internal: BO, VPC

Author (year)	Modelling software	Compartments	Covariate selection	Final model	CL (L/h/kg)	Vd (L/kg)	IV (CL,Vd)	RUV	Validation
Zane NR (2017)	NONMEM, FOCEI	2	n.s	$CL(L/h)=4.48 \cdot (wt/70)^{0.75} \cdot (GFR/90)^{1.01} \cdot (U/37)^{1.96}; Vc = 12.7 \cdot (wt/70); Vp = 35.5 \cdot (wt/70); Q = 8.49 \cdot (wt/70)^{0.75}$	CL 0.19; Q 0.121	Vc 0.181; Vp 0.507	CI 50% Q71% Vc 136% Vp 33%	Proportional: 20.9%	Internal: GOF
Alsultan A (2018)	Monolix, SAEM	1	Stepwise regression	$CL(L/h)=2.99 \cdot (wt/20); V(L)=9.55 \cdot (wt/20)$	0.06	0.47	15%; 12%	Proportional: 11.9%	Internal: VPC; External: GOF, bias, precision
Moffett BS (2019) (CVHDF)	NONMEM, n.s	2	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 10.83$ (p<0.001)	$CL(L/h)=2.24 \cdot (FFM/70)^{0.75} \cdot 0.535 \cdot \ln(Scr/0.56) \cdot 0.92 \cdot \ln(BUN/30) \cdot 1.88 \cdot ((CRRTUF/500) \cdot 1.12 \cdot DILYSTE/60); Vc(L)=81 \cdot (FFM/70); Vp(L)=550 \cdot (FFM/70); Q=0.93 \cdot (FFM/70)^{0.75}$	CL 0.072; Q 0.03	Vc 2.61; Vp 17.74	32%; 28% (Vc)	Proportional: 20.5%	Internal: BO
Moffett BS (2019)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 10.83$ (p<0.001)	$CL(L/h)=18.6 \cdot (FFM/70)^{0.75} \cdot 0.582 \cdot \ln(Scr/0.67); V(L)=102 \cdot (FFM/70)$	0.203	1.111	33%; 41%	Proportional: 21.7%	Internal: BO, NPDE; External: MPE, APE, NPDE
Wang Y (2019)	Phoenix, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 6.63$ (p<0.01)	$CL(L/h)=0.004 \cdot wt^{0.858} \cdot (\ln GFR)^{2.367}; V(L)=0.558 \cdot wt^{1.027}$	0.133	0.65	25%; 22%	Additive: 0.52 mg/L	Internal: GOF; pc-VPC; BO.
Brooks Peterson M (2020)	Phoenix, FOCE	2	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 6.63$ (p<0.01)	$CL(L/min/1.73m2)=0.09 \cdot BSA^{1.69} \cdot \exp(\eta); Vp(L/35kg)=5.3 \cdot wt^{1.01} \cdot \exp(\eta); Vc=2.56L; Q(L/min)=0.12$	CL (L/min /1.73m2) 0.09; Q(L/min) =0.12	Vp(L/35kg) =5.3; Vc (L)=2.56	13%; 147% (Vc)	Relative (plasma) 0.23, additive (skin) 7.5mg/L	Internal: GOF
Downes KJ (2020)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ ; backward OFV $\uparrow > 7.88$	$CL(L/h)=4.02 \cdot (wt/34)^{0.75} \cdot (eGFR/145)^{0.903} \cdot (0.699 \text{ if female}); V(L)=16.4 \cdot (wt/34)$	0.29	0.48	23%; n.s	Combined: (a) 2.44, (p) 0.179	Internal: GOF
Issaranggoon Na Ayuthaya S (2020)	Phoenix, FOCEI	2	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.01); backward OFV $\uparrow > 10.83$ (p<0.001)	$CL(L/h)=0.16 \cdot wt^{0.97}; Vc(L)=3.86; Vp(L)=0.19 \cdot wt^{1.07}; Q=0.13 \cdot wt^{1.19}$	0.16; 0.13	Vc 3.86; Vp 0.19	6%; 5%	Multiplicative 0.12	Internal: GOF, BO
Lu JJ (2020)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 10.83$ (p<0.001)	$CL(L/h)=2.25 \cdot 1.95^{(9.36/age)} \cdot 0.742 \cdot (CysC/0.71); V(L)=8.17 \cdot 2.25^{(9.36/age)}$	0.078	0.285	40%; n.s	Proportional: 37.4%	Internal: GOF, VPC, BO, NPDE
Lv CL (2020)	NONMEM, n.s	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 10.83$ (p<0.001)	$CL(L/h)=6.32 \cdot (wt/70)^{0.75} \cdot e^{-0.0467}; V(L)=39.6 \cdot (wt/70)$	0.09	0.566	22%; n.s	Exponential: 29.82%	Internal: GOF, BO, VPC, NPDE

Author (year)	Modeling software	Compartments	Covariate selection	Final model	CL (L/h/kg)	Vd (L/kg)	IV (CL, Vd)	RUV	Validation
Moffett BS (2020)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 10.83$ (p < 0.001)	$CL(L/h) = 4.35 * (wt/70)^{0.75} * (0.33^{\wedge} \ln(Scr/0.58)); V(L) = 87.8 * (wt/70); Ka(1/h) = 0.0012$	4.35 L/h for 70kg patient	V=87.8L for 70kg patient	48%; 51%	Proportional 19.7%	Internal: GOF, BO
Wang H (2020)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 6.63$ (p < 0.01)	$CL(L/h) = 4.18 * (eGFR/145)^{0.741} * (wt/25)^{\wedge} K; K = (wt^{\wedge} - 0.856) / (wt^{\wedge} - 0.856 + 6.53^{\wedge} - 0.856); V(L) = 22.3$	0.17	0.845	26%; n.s	Proportional 26.96%	Internal: GOF, BO, VPC, NPDE
Zhang T (2020)	NONMEM, FOCE	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 10.83$ (p < 0.001)	$CL(L/h) = 1.44 * wt^{\wedge} 0.683; V(L) = 15.7 * (wt/15.44)^{\wedge} 0.507$	0.09	1.02	14%; 52%	Additive: 0.438 mg/L	Internal: GOF, pcVPC, BO, CWRES
He CY (2021)	NONMEM, FOCE	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 6.635$ (p < 0.01)	$CL(L/h) = 2.27 * (wt/15)^{\wedge} 0.75 * (age/4.5)^{\wedge} 0.11; V(L) = 6.82 * (wt/15)$	0.14	0.45	23%; 15%	Exponential: 31.8%	Internal: GOF, BO, VPC, NPDE
Li DY (2021)	NONMEM, n.s	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 10.83$ (p < 0.001)	$CL(L/h) = 0.407 * (wt/2.25)^{\wedge} 1.24 * e^{\wedge} (-0.533 * Scr^{\wedge} b/27.1); V(L) = 1.86 * (wt/2.25)^{\wedge} 1.28$	0.18	0.82	31%; n.s	Proportional: 0.335 (all)	Internal: GOF, pcVPC, BO; External: IMPE, MAE %RMSE
Shimamoto Y (2021)	NONMEM, n.s	2	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05)	$CL(L/h) = 5.94 * (wt/70)^{\wedge} 0.75 * (PMA^{\wedge} 3.4) / (47.7^{\wedge} 3.4 + PMA^{\wedge} 3.4) * (eGFR/120)^{\wedge} 0.626 * 1.12^{\wedge} t$ (t=1 if $\geq 38^{\circ}C$ , t=0 if not); $Vc = 39.9L/70kg; Vp = 37.8L/70kg; Q = 3.85L/h$	CL 0.085; Q 0.55	Vc 0.57; Vp 0.54	23%; n.s	Proportional 0.0855	Internal: GOF, BO, pcVPC
Shoji K (2021)	Phoenix, FOCE	1	n.s	$CL(L/h) = 0.29 * wt^{\wedge} 0.75 * (Scr/0.16)^{\wedge} -0.70 * (DFLT/17)^{\wedge} (-0.09) * e^{\wedge} 0.46 * V(L) = 1.00 * wt^{\wedge} e^{\wedge} 0.48$	0.18	1.01	49%; 51%	Proportional 56.5%	Internal: GOF, VPC, BO
Smit C (2021)	NONMEM, n.s	2	n.s	$CL(L/h) = 2.12 * (wt/22.1)^{\wedge} 0.745 * (eGFR/100); Q(L/h) = 1.55 * (wt/22.1)^{\wedge} 0.599; Vc(L) = 8.9 * (wt/22.1); Vp(L) = 12.3 * (wt/22.1)$	CL 0.096; Q 0.07	Vc 0.4; Vp 0.55	29%; 110% (Vp)	Proportional: 0.0789	Internal: GOF, pcVPC, NPDE
Sridharan K (2021)	Monolix, SAEM	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05)	$CL(L/h) = 1.23 * (wt/11.75)^{\wedge} 0.87 * (eGFR/91.175)^{\wedge} 0.67; V(L) = 13.3 * (wt/11.75)^{\wedge} 0.79$	0.134	1.446	58%; 75%	Proportional: 0.4	Internal: pcVPC, BO, IWRES
Chuphan C (2022)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p < 0.05); backward OFV $\uparrow > 10.83$ (p < 0.01)	$CL(L/h) = 1.66 * (wt/14)^{\wedge} 0.75 * eGFR/108.9; V(L) = 12.7 * (wt/14)$	0.13	0.88	35%; 40%	Combined: (a) 1.4, (p) 17.8%	Internal: GOF, pcVPC, bootstrap

Author (year)	Modelling software	Compartments	Covariate selection	Final model	CL (L/h/kg)	Vd (L/kg)	IIV (CL;Vd)	RUV	Validation
Huang GM (2022)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 10.83$ (p<0.01)	$CL(L/h) = 5.7 * (wt/70)^{0.75} * (eGFR/168)^{0.872} * (PMA \wedge 3.97) / (PMA \wedge 3.97 + 33.3 \wedge 3.97); V(L) = 54 * (wt/70)$	5.7 L/h	54L	32%; 33%	Exponential: 34.7%	Internal: GOF, pc-VPC, NPDE, BO
Xu J (2022)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 6.63$ (p<0.01)	$CL(L/h) = 1.87 * (wt/8.27)^{1.2} * (2.68/BUUN)^{0.415} * e^{0.238}; V(L/kg) = 0.63$	0.226	0.63	24%; n.s	Exponential: 45.5%	Internal: BO, NPDE; External: MPE, APE, NDPE
Lv M (2023)	NONMEM, FOCEI	1	Stepwise: forward OFV $\downarrow > 3.84$ (p<0.05); backward OFV $\uparrow > 6.63$ (p<0.01)	$CL(L/h) = 2.53 * (wt/17.5)^{0.771} * e^{0.182}; V(L) = 8.84 * (wt/17.5)^{0.957}$	0.14	0.5	18%; n.s	Combined: 2.7; 1.07%	Internal: GOF, pcVPC, BO; External: GOF
Roshan N S B (2024)	Monolix, SAEM	1	Stepwise	$CL(L/h/kg) = 0.11 * e^{(0.48 * route)} * e^{0.33}$ (route=1 if intermittent IV infusion, =0 if continuous infusion); $V(L/kg) = 0.88 * e^{0.33}$	0.11	0.88	34%; 34%	Proportional 0.032%	Internal: GOF
Shen X (2024)	NONMEM, FOCEI	1	Stepwise forward OFV $\downarrow > 6.64$ and backward OFV $\uparrow > 10.8$	If age>2y: $CL(L/h) = 2.59 * (wt/12)^{0.38} * (eGFR/75)^{0.517} * e^{0.319}$ ; if age<=2y: $CL(L/h) = 1.98 * (wt/12)^{0.739} * (eGFR/75)^{0.517} * e^{0.319}$ ; $V(L) = 22.4 * wt/12$	0.216 if age > 2 yrs; 0.165 if age ≤ 2 yrs	1.87	33%; n.s	Additive: 4.46 mg/L and 4.53 mg/L	Internal: GOF; pc-VPC; BO. External: MPE%, MAPE%

Abbreviations: d: day/days; m: month/months; y: year/years; t: temperature; wt: weight; Scr: serum creatinin; eGFR: estimated glomerular filtration rate, DFLT: days from liver transplant, FFM: fat free mass, CRRTUF: ultrafiltration fluid rate (mL/h), DILYSTE: dialysate flow rate (mL/h); CysC is serum cystatin C (mg/L), IV: intravenous, (a): additive, (p): proportional, (e): exponential, GOF: goodness of fit, BO: bootstrap, VPC: visual predictive check, pcVPC: prediction-corrected visual predictive check, NPDE: normalized prediction distribution error, PE%: prediction error, APE%: absolute prediction error; MPE%: mean prediction error, MAPE%: mean absolute prediction error, IMRES: individual weighted residuals, CWRES: conditional weighted residuals.

undergoing hypothermia for cardiac arrest, finding that hypothermia could result in a 25% reduction in vancomycin CL in pediatric patients with normal renal function and up to 84% in pediatric patients with impaired renal function [37]. Moffet et al. (2020), in a study of pediatric patients with ventricular assist devices (VADs), found that this group had a 2-fold higher vancomycin Vd than other children, suggesting that high-dose regimens may be considered [46]. Similarly, Shoji et al., when studying the group of children after liver transplantation, noted a high Vd of vancomycin, which could be explained by the large infusion volume and the common cirrhosis after liver transplantation, and proposed a dose regimen of 45-80 mg/kg/day [47]. The authors all recommended that strict TDM be performed when using vancomycin in these special patient groups [37, 46, 47].

#### ***Appropriate model and dosing regimen for Vietnamese pediatric patients***

From the above results, it seemed complex to select a single popPK model and dosing regimen for the general pediatric population. The reasons for this include: (1) large differences in different pediatric patient groups in terms of age and maturity (2) discrepancies between pediatric patient groups with concomitant pathological conditions and medical interventions (3) lack of external validation studies of the constructed models. To select an appropriate model, further research is needed in which models should be examined using TDM data from local hospitals. The suitable dosage regimens for targeted population should be proposed based on factors related to age, growth, physiological and pathological

factors to find a suitable dosage regimen. In addition, Bayesian softwares and other covariates that can be collected in medical practice yet commonly available in routine care such as cysteine C test results or PMA values in Vietnam should be considered in coming studies.

#### **CONCLUSION**

This study provides an overview of the pharmacokinetic model of vancomycin in children, including different pediatric subgroups with different age, physiology and pathology. The results show that besides the common influencing factors including age, weight, renal function with CL and weight with Vd, there are many factors that can influence the pharmacokinetics of vancomycin in pediatric groups, leading to widely different estimates of CL and Vd between studies. Selecting and validating a specific popPK model into clinical practice to optimize vancomycin dosage in children should be carefully considered based on the similarity of patient characteristics as well as the model's predictive performance for the population of interest.

#### **ACKNOWLEDGMENTS**

We would like to thank the Vietnam National Center of Drug Information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy and the Institute of Child Health Training and Research, Department of General Planning, Vietnam National Children's Hospital for method supporting when carrying out the manuscript.

#### **CONFLICTS OF INTEREST**

None.

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