MODEL-BASED EVALUATION OF ANTIMICROBIAL AGENTS IN CHILDREN

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MODEL-BASED EVALUATION OF ANTIMICROBIAL AGENTS IN CHILDREN

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EDITORIAL
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Editorial: Model-Based Evaluation of Antimicrobial Agents in Children

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Keywords: pharmacokinetics, pharmacometrics, developmental pharmacology, children, antimicrobial agents

Editorial on the Research Topic

Model-Based Evaluation of Antimicrobial Agents in Children

INTRODUCTION

Globally, the rational use of drugs in pediatrics has received more and more attention from the regulatory agencies and public health professionals, because pediatric patients have, together with pregnant women, the highest off-label drug use, which may lead to treatment failure due to underdosing or toxicity due to overdosing (Mei et al., 2019). Antimicrobial agents are the most commonly prescribed medications and are very often used in an off-label manner. More than 35% of hospitalized children received antimicrobial agents and more than 70% of hospitalized neonates receive these agents on or before day 3 of postnatal life (Versporten et al., 2013; Oliver et al., 2017).

Children are not "little adults". These young individuals are constantly changing, and together with the impact of intercurrent diseases such as infections and hematological malignancies, the disposition of antimicrobial agents in children will be different with adults. The unwanted side effects or toxicity caused by supratherapeutic drug exposure and treatment failure caused by subtherapeutic drug exposure may occur (Imani et al., 2017; Kullar et al., 2011). Therefore, the dosage for adults cannot be extrapolated to children. It is urgent to optimize dosing regimens and individualize therapy of antimicrobials in pediatrics using an innovative methodology, pharmacometrics.

In this topic "*Model-Based Evaluation of Antimicrobial Agents in Children*", the articles focus on studies of model-based drug development of antimicrobial agents in the pediatric population; model-based individualized antimicrobial therapy in neonates, infants, children, and adolescents.

MODEL-BASED INDIVIDUALIZED ANTIMICROBIAL THERAPY

Individualized Antimicrobial Therapy Based on Developed PopPK or PBPK Models

In this topic, model-based individualized antimicrobial therapy was recommended. Zhang et al. developed a population pharmacokinetic (PopPK) model of teicoplanin using retrospective data in Asian pediatric patients. By using two dose-optimized indicators, C_{min} and pharmacokinetics/pharmacodynamics (PK/PD) targets, they found that the standard dose regimen of three loading

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doses of 10 mg/kg every 12 h, followed by 6–10 mg/kg/day might result in underdosing, except for moderate infection with a standard loading dose. Weight and serum creatinine were found to have a strong effect on drug exposure, and model-based individualized dosing regimens for patients with different weight and serum creatinine values were recommended. Similarly, in the PopPK study of Li et al., body weight and renal function index (estimated glomerular filtration rate) were also significant covariates in the PopPK analysis of ganciclovir in critically ill pediatric patients. The current empiric regimen (10 mg/kg/d) may result in subtherapeutic exposure, and dose regimens were optimized based on the PopPK model. Du et al. focused on the pharmacokinetics (PK) behavior of cefathiamidine in infants with augmented renal clearance (ARC), which may result in subtherapeutic antibiotic concentrations. According to the PopPK analysis, a higher model-based dosing regimen for bacteria with MIC $\geq$ 0.5 mg/L was obtained in ARC patients. From the above studies, it can be seen that renal function plays an important role in the excretion of antibiotics. Is there a better renal marker for the model to predict the optimized dose? Leroux et al. studied whether serum Cystatin C (S-CysC) could be an alternative renal marker to SCr for estimating vancomycin clearance in neonates. The results showed that S-CysC is also a relevant renal marker for individualization of vancomycin therapy. Shen et al. established the PopPK model of vancomycin for Chinese pediatric patients, Chinese adult patients and the entire population, respectively. Based on this unified PopPK model of vancomycin for adults and pediatric patients, the optimal dosage regimen for the treatment of Chinese pediatric patients with Gram-positive infections was 60–80 mg/kg/day every 6 or 8 h (<12 years old), and 50–60 mg/kg/day every 6 or 8 h (>12 years old). In the study of Liu et al., 18 published vancomycin PopPK models were externally evaluated at two clinical centers. They found that for dose simulation, there were large deviations between observations and simulations, but the predicted performance improved significantly after Bayesian forecasting with one or two prior observations, which demonstrated the necessity of combining the PopPK models with therapeutic drug monitoring (TDM) in clinical practice. In addition, disease status often affects the disposal of antimicrobials in human body. Zhang et al. studied voriconazole plasma exposure in the pediatric population and developed a physiologically based pharmacokinetic (PBPK) model by integrating auto-inhibition of cytochrome P450 3A4 and CYP2C19 gene polymorphisms. According to the results, dosing regimens were established based on fungal species and metabolic enzyme type. Leroux et al. reviewed the PopPK studies available for glycopeptides and antifungals in pediatric hematological malignancies. In this population, the optimal dose of the drug needs more attention, and the PK/PD target for dose optimization needs still to be established.

Clinical Practice of Model-Informed Precision Dosing

Model-informed precision dosing (MIPD) is a valid and precise tool to predict individual drug exposure and optimize dosing regimens in pediatrics by collecting information of patient characteristics, disease, administration, sampling, laboratory tests and drug concentrations, which is usually used in conjunction with TDM (Avent et al., 2013; Pea et al., 2002). Abdulla et al. reviewed the workflow and application of MIPD implementation in clinical practice. The four studies (1 study of amikacin, 3 studies of vancomycin) included in this review confirmed that MIPD administration was superior to conventional dosing strategies, even if the evidence of MIPD from clinical practice was not sufficient. Hartman et al. developed model-informed doses of piperacillin and amikacin in critically ill children using published pharmacokinetic data. Three studies of piperacillin and one of amikacin were used to generate the model-informed doses. Qi et al. designed a randomized controlled trial of latamoxef to compare the efficacy and safety differences between model-based dosing regimens and conventional regimens. Wu et al. reported a premature neonate with carbapenem-resistant enterobacteriaceae (CRE) infection who was successfully cured using model-based dosing regimen and this study emphasized the utility of model-based TDM of high-dose meropenem therapy for CRE infection. D'Agate et al. obtained a simplified fixed dose regimen of gentamicin through dose optimization by using a previously published PopPK model, which was externally validated with TDM data. The fixed dose regimen was 10 mg for patients with body weight <2.5 kg, 16 mg for patients with body weight between 2.5 and 4 kg, and 30 mg for those with body weight >4 kg, which was easier to implement in the clinic.

MODEL-BASED EVALUATION AND PREDICTION OF ADVERSE DRUG EVENTS

The off-label use of drugs in pediatrics not only may lead to treatment failure, but also potentially exposes this vulnerable population to an increased risk of adverse drug reactions. In addition to promoting drug development and individualized therapy of antimicrobial agents, the innovative methodologies of PK/PD modelling and machine learning are continuously improving and are currently applied to the evaluation, management and prediction of adverse drug events. Elzagallaai et al. focused on model-based evaluation of hypersensitivity reactions induced by antimicrobial agents. They reviewed the challenges in implementing the model-based evaluation due to a lack of an animal model to study the molecular pathophysiology of these hypersensivity reactions as well as a very small number of validated *in vitro* tests with good predictive values. On the other hand, Yu et al. explored risk factors associated with adverse drug events, using machine learning methods in a large pediatric population of 1,746 patients aged 28 days to 18 years. Gradient Boosting Decision Tree was used to establish a predictive model with the best predictive power after comparing 7 algorithms, which provided a novel idea for accurately predicting adverse drug events in pediatric inpatients.

To summarize, this research topic "*Model-Based Evaluation of Antimicrobial Agents in Children*" will provide sufficient information and ideas for model-based drug development and

individualized therapy of antimicrobial agents, which we hope can promote improved rational drug use in the pediatric population.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Carbapenem-Resistant Enterobacteriaceae Bloodstream Infection Treated Successfully With High-Dose Meropenem in a Preterm Neonate

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Carbapenem-resistant enterobacteriaceae (CRE) bloodstream infections have been rapidly spreading worldwide with a high mortality and pose a challenge to therapeutic decision-making, especially in premature neonates because insufficient empirical antimicrobial therapy is independently associated with high mortality. This case reported that a premature infant with CRE bloodstream infection was treated successfully with high-dose meropenem treatment with model-based therapeutic drug monitoring (TDM). In clinical settings, treatment target attainment of meropenem can be improved by increasing the frequency of administration, prolonging the infusion time, and using a high dose. This case report shows a successful regimen for CRE infection in a premature neonate and emphasizes the utility of model-based TDM of high-dose meropenem treatment. The adequate antimicrobial benefit provided by innovative techniques could ensure the efficacy and safety of high-dose meropenem therapy for CRE infection.

Keywords: meropenem, high dose regimen, carbapenem-resistant enterobacteriaceae infection, model-based therapeutic drug monitoring, preterm neonate

INTRODUCTION

Carbapenem-resistant enterobacteriaceae (CRE) bloodstream infections have been rapidly spreading worldwide with a high mortality rate of about 30–70% (Tumbarello et al., 2012). One of the most frequent CRE pathogens is *K. pneumoniae*. Carbapenems have been used successfully for the treatment of severe infections with sensitive Gram-negative bacteria (Fritzenwanker et al., 2018). However, the prevalence of CRE poses a challenge to therapeutic decision-making, especially

in premature neonates. The optimal antimicrobial therapeutic regimen for CRE bloodstream infections is still a matter of debate in clinical practice, but it is clear that insufficient empirical antimicrobial therapy is independently associated with high mortality (Tumbarello et al., 2012). Several retrospective studies have reported that in adult patients improved outcomes could be achieved with a combination therapy of carbapenems and other antibiotics (Tumbarello et al., 2012; Giannella et al., 2018) along with higher doses and/or prolonged infusion strategies (Giannella et al., 2018). However, there is still hardly any experience in neonatal clinical practice.

CASE DESCRIPTION

A neonate born prematurely at 27 weeks' gestation with a birth weight of 970 g was admitted to the neonatal intensive care unit. Apgar scores were 5, 7, and 7 at 1, 5, and 10 min. On arrival, clinical examination did not show any abnormal findings, and the neonate had an unremarkable clinical course during the first 2 weeks of life with normal repeated clinical and laboratory evaluations.

On the 15th day of life the neonate developed signs of neonatal sepsis based on clinical signs including oxygen fluctuations and abdominal distension and a clearly abnormal laboratory work-up that showed metabolic acidosis (blood pH 7.15) (normal range: 7.35–7.45) and several abnormal inflammatory indices such as elevated procalcitonin (PCT) concentration (12.6 ng/ml) (normal range:<0.5 ng/ml), C-reactive protein (CRP) (14.8 mg/l) (normal range: <8 mg/L), white blood cell count (WBC) (2.19×10^9/L) (normal range: 5×10^9/L–20×10^9/L), and platelets (PLT) (51×10^9/L) (normal range: 100×10^9/L–300×10^9/L). Antibacterial treatment was started immediately and consisted of meropenem (20 mg/kg, q12h) and vancomycin (15 mg/kg, single dose). On the same day neonatal sepsis with Gram-negative bacteria was confirmed by blood culture using BacT/Alert 3D Blood Culture Systems, and also a rapid increase in levels of PCT (116.1 ng/ml) and CRP (54 mg/l) was seen. Cerebrospinal fluid could not be obtained due to the neonate's poor clinical condition and intolerance to the attempted lumbar puncture. Nevertheless, neonatal meningitis was suspected and the meropenem dose was increased from 20 to 40 mg/kg; meanwhile, vancomycin was discontinued. A high-dose meropenem regimen (40 mg/kg, q12h) was given off-label by intravenous infusion over 30 min for a week (days 15 to 21). In order to monitor the effectiveness of treatment and avoid occurrence of adverse reactions, model-based therapeutic drug monitoring (TDM) was performed. The covariate values of albumin and serum creatinine were 33.8 g/L and 80 μmol/L, respectively. The sample for TDM was obtained using an opportunistic sampling approach before and during the high-dose meropenem treatment. The concentration of meropenem was measured by high performance liquid chromatography (Sun et al., 2011). A previously reported population pharmacokinetic model was used to calculate the time of free drug concentration exceeding the minimal inhibitory concentration (fT > MIC) (Smith et al., 2011).

On day 18, an antimicrobial susceptibility test (AST) was conducted using VITEK® 2 system after 3 days' blood culture, and the results of AST showed *K. pneumoniae* resistant to carbapenems (MIC 8 mg/L), indicating CRE infection. The isolate was also resistant to other antibiotics, such as imipenem, piperacillin/tazobactam, cefoperazone/sulbactam, cefotaxime, ceftazidime, aztreonam, ertapenem, and cefuroxime. The isolate was sensitive to levofloxacin and amikacin, but the use of fluoroquinolones and aminoglycosides is not allowed for use in neonates in China. The meropenem concentrations of samples obtained 0.4 h (day 15) and 0.9 h (day 19) post dose were 37.9 and 26.6 ug/ml, respectively. The model-based pharmacokinetic–pharmacodynamic analysis by NONMEM software according to the population pharmacokinetic model of meropenem in premature and term infants reported by *P. Brian* et al. (Smith et al., 2011) showed that this patient with CRE infection had 53% fT > MIC when given 20 mg/kg meropenem on day 15 and 72% fT > MIC when given 40 mg/kg on day 19. Using 70% fT > MIC (the drug concentration was above the MIC during 70% of the dosage interval) as the pharmacokinetic–pharmacodynamic target, the probable target attainment was 99.2% by giving the high-dose regimen after 1,000 Monte Carlo simulations. The simulated pharmacokinetics profile with 95% confidence intervals after giving the high-dose regimen is presented in **Figure 1**. The high-dose regimen ensured acceptable pharmacokinetic–pharmacodynamic target for CRE infection. Subsequently, with the treatment of high-dose meropenem, the condition of the baby improved with normalization of PCT, CRP, WBC, and PLT levels (**Figure 2**) and negative blood culture. The cerebrospinal fluid was examined on day 20, and it showed no obvious abnormality [WBC: 10×10^6/L (normal range: 0×10^6/L–29×10^6/L), protein: 1.56 g/L (normal range: 0.65–1.5 g/L), glucose: 2.35 mmol/L (normal range: 1.344–3.53 mmol/L)]. Adverse effects possibly due to meropenem were not observed during the treatment. Written informed consent was obtained from the minor's legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

DISCUSSION

This case reported that a premature infant with CRE bloodstream infection was treated successfully by high-dose meropenem treatment with model-based TDM. Insufficient empirical antimicrobial therapy is independently associated with high mortality (Tumbarello et al., 2012). In clinical settings, treatment target attainment of meropenem can be improved by increasing the frequency of administration, prolonging the infusion time, and using a high dose (van den Anker et al., 2009). This case report shows a successful regimen for CRE infection in a premature neonate and emphasizes the utility of model-based TDM of high-dose meropenem treatment. Premature neonates with underlying disease such as chronic lung disease, esophageal atresia, and congenital heart disease are extremely vulnerable who need more precise medication to avoid inadequate or excessive drug exposure. The approach of model-based TDM of drugs can directly reflect the drug exposure levels in patients by integrating drug concentrations, ontogenetic factors, and laboratory test results, which can

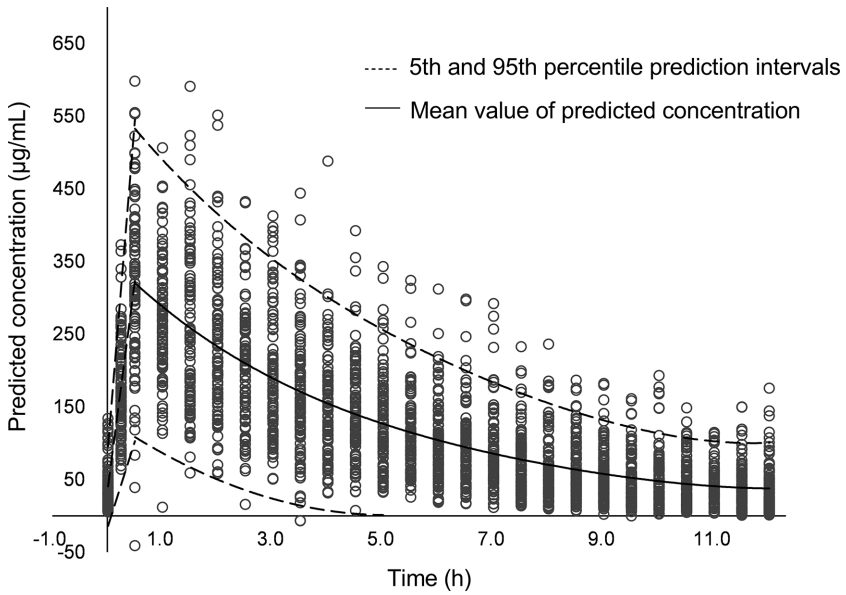

FIGURE 1 | The simulated pharmacokinetics profile with 95% confidence intervals after giving the high-dose meropenem.

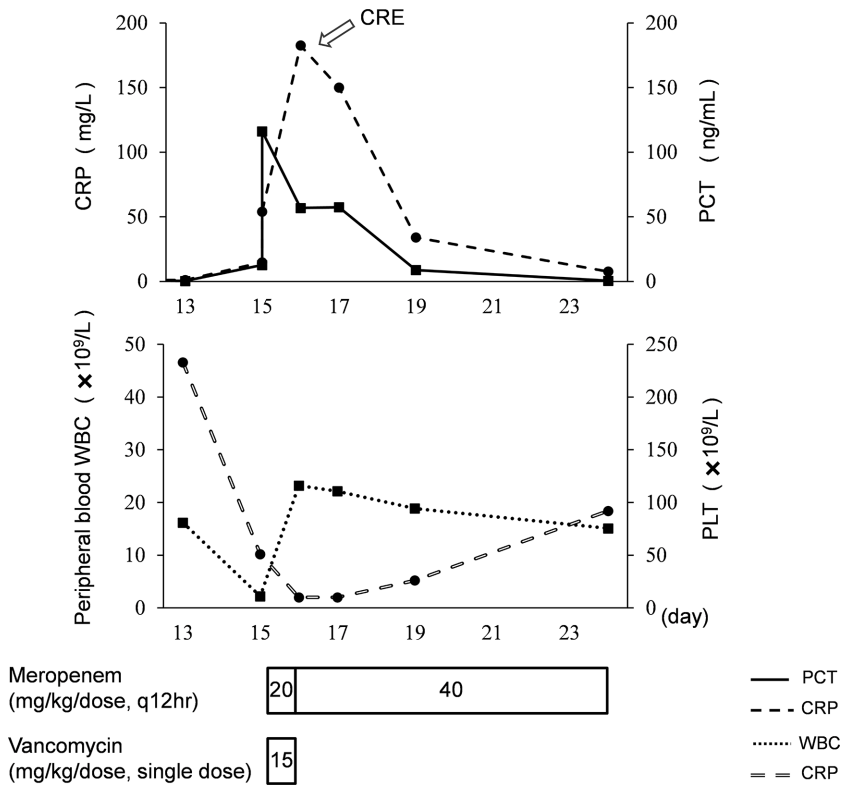

FIGURE 2 | Clinical course of the premature neonate with CRE infection. PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count; PLT, platelet.

extrapolate to premature infants mentioned above. The adequate antimicrobial benefit provided by innovative techniques could ensure the efficacy and safety of high-dose meropenem therapy for CRE infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical ethics committee of The First Affiliated Hospital of Shandong First Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor's legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WZ and X-YC coordinated and supervised data collection and critically reviewed and revised the manuscript. Y-EW performed TDM and data analysis and drafted the initial manuscript. H-YX and H-YS managed the patient, collected the clinical data, and reviewed the manuscript. JA provided advice, critically reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Population Pharmacokinetics and Model-Based Dosing Optimization of Teicoplanin in Pediatric Patients

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Zhang T, Sun D, Shu Z, Duan Z, Liu Y, Du Q, Zhang Y, Dong Y, Wang T, Hu S, Cheng H and Dong Y (2020) Population Pharmacokinetics and Model-Based Dosing Optimization of Teicoplanin in Pediatric Patients. Front. Pharmacol. 11:594562. doi: 10.3389/fphar.2020.594562

Objectives: The pharmacokinetics (PK) of teicoplanin differs in children compared with adults. Our aim was to determine the PK of teicoplanin in an Asian pediatric population and to optimize dosage regimens.

Methods: This was a retrospective PK study and all the data were collected from hospitalized children. We developed a population PK model using sparse data, and Monte Carlo simulation was used to assess the ability of standard teicoplanin regimen and other different dosage regimens. The optimal dosing regimens were defined as achieving the target trough concentration (C_{min}) of 10 mg/L and pharmacokinetic/pharmacodynamic (PK/PD, [AUC_{24}/MIC]) of 125 for moderate infection. For severe infection, the optimal dosing regimens were defined as achieving the target 15 mg/L and AUC_{24}/MIC of 345.

Results: 159 children were included and 1.5 samples/children on average were provided. Estimated clearance of teicoplanin was 0.694 L/h (0.784/L/h/70 kg) and volume of distribution was 1.39 L. Teicoplanin standard loading dose was adequate for moderate infection, while 13 mg/kg was needed for severer infection. With standard maintenance doses, both patients with moderate and severe infection failed to achieve the target C_{min}. 12 and 16 mg/kg/day were required to achieve a $C_{min} \geq 10$ and 15 mg/L, respectively. However, standard maintenance dose was adequate to achieve AUC_{24}/MIC ≥ 125 for moderate infection, and 12 mg/kg/day was needed to achieve AUC_{24}/MIC ≥ 345 for severe infection. Lower weight and serum creatinine were associated with higher dose.

Conclusion: Optimal doses based on the target C_{min} were higher than that based on the PK/PD target. To achieve the C_{min} and PK/PD targets simultaneously, a standard loading dose was adequate for moderate infection based on simulation, while dosing higher than standard doses were required in other situation. Further clinical studies with rich sampling from children is required to confirm our findings.

Keywords: teicoplanin, pediatrics, population pharmacokinetics, dosing optimization, Monte Carlo simulation

INTRODUCTION

Teicoplanin is a glycopeptide antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Traina and Bonati, 1984). The marketed drug is hydrophilic predominantly bound to albumin in plasma (>90%) (Lukas et al., 2004) and has a longer elimination half-life than vancomycin (Kasai et al., 2018). Teicoplanin trough concentration (C_{min}) is closely associated with clinical efficacy. For the moderate (such as respiratory tract infections, urinary tract infections and skin and soft-tissue infections) and severe infection (such as sepsis, infective endocarditis, bone and joint infections), C_{min} of at least 10 and 15 mg/L are recommended, respectively (British Medical Association, 2015-2016). However, the standard dosage regimens appear to be inconsistent with the emerging scientific evidence. In previous clinical studies, the proportion of children failing to achieve the target C_{min} were 48–89% (Sanchez et al., 1999; Strenger et al., 2013; Zhao et al., 2015). The mean C_{min} of teicoplanin were 4.8/5.7/5.9 mg/L at 24/72/168 h, respectively, after the first dose (Sanchez et al., 1999). Even though higher doses were prescribed, 14.1% still had C_{min} <10 mg/L (Strenger et al., 2013), and the overall mean C_{min} was 9.0 mg/L (Lukas et al., 2004). Yet, the optimal dose of teicoplanin remains to be determined.

Antibiotic dosing determined by pharmacokinetics/pharmacodynamics (PK/PD) data also has been recommended (Kalil et al., 2016). The index that best correlates with teicoplanin antibacterial activity is the ratio of 24-h area under the concentration-time curve to the minimum inhibitory concentration (AUC_{24}/MIC) (Ramos-Martin et al., 2017a). AUC_{24}/MIC goals of ≥ 125 and 345 could predict successful outcomes for moderate and severe infection, respectively (Kuti et al., 2008; Ahn et al., 2011). To date, no data has provided a comprehensive understanding the ability of standard dosage regimens of teicoplanin to achieve the suggested PK/PD targets in children.

Previous studies investigated the impact of covariates on pharmacokinetics of teicoplanin in children. A trend of clearance decreasing with increasing age has been observed (Reed et al., 1997). It is considered to be at high risk of PK variability because less fat, higher volume of water and immature renal function in neonate and infant (<1 year) (Friis-Hansen, 1971), especially in the presence of various pathophysiological conditions such as sepsis, fluid overload, effusions, hypoalbuminaemia, and altered renal function, making drug dosing requirements can be difficult to predict. Moreover, it has been demonstrated that nearly 60% of children in pediatric intensive care unit (PICU) exhibit augmented renal clearance (ARC), resulting in low drug exposure due to enhanced excretion (Van Der Heggen et al., 2019). Little is known about the PK of teicoplanin in children (eight studies in total), which greatly hinder the dosing optimization of teicoplanin in children, and only one of them involves Asian children (**Supplementary Table S1**) (Terragna et al., 1988; Reed et al., 1997; Aarons et al., 1998; Sanchez et al., 1999; Lukas et al., 2004; Ramos-Martin et al., 2014; Zhao et al., 2015; Gao et al., 2020). The objectives of this analysis were to: 1) determine the PK of teicoplanin in Asian children by using a population approach; 2) evaluate the standard dosage regimens of teicoplanin; and 3) establish a simulation-based dosage regimens in this vulnerable population.

METHODS

Study Design and Patient Population

This was a retrospective PK study performed in two hospitals in China according to the principles of the current Declaration of Helsinki and Good Clinical Practice (Hospital 1: the First Affiliated Hospital of Xi'an Jiaotong University; Hospital 2: the Affiliated Children Hospital of Xi'an Jiaotong University). The protocol was approved by the institutional review board of each study site (No.XJTU1AF2017LSK-28). All patients aged 1 month to 18 years old receiving teicoplanin (Targocid, Sanofi-Aventis) for proven or suspected MRSA infection were selected for the study over 33-month period (March 2017 and November 2019). Children were excluded if a complete teicoplanin dosing history or precise sampling time was not available. The demographic variables with potential impact on the PK of teicoplanin and details of teicoplanin administration (dose and infusion start and stop times) were extracted from medical records retrospectively by a trained research assistant. If serum creatinine (SCr) readings were unavailable around the teicoplanin dosing (±48 h), the closest available SCr reading would be imputed. Creatinine clearance (CLcr) was estimated by Cockcroft formula: CLcr = (140 – age (years)) ×weight (WT, kg) × 0.85 (if female)/0.818 × SCr (μmol/L), instead of Schwartz formula due to the lack of height data in most children (Cockcroft and Gault, 1976).

Teicoplanin Dosing, Blood Sampling, and Measurement

Teicoplanin was administered at three loading doses of 10 mg/kg every 12 h, followed by 6–10 mg/kg/day. Types of blood samples included therapeutic drug monitoring (TDM) sample, and opportunistic sample. TDM was typically performed within 30 min preceding a dose at steady state. Samples were centrifuged for 10 min. Serum was separated and stored at −80°C until analysis. The laboratory staff were allowed to identify the opportunistic samples with the timings of blood taking documented and store them at −80°C after routine testing and pretreatment. Teicoplanin concentrations were determined with a validated high performance liquid chromatography method. The calibration curve ranged from 2.5 to 100 mg/L, and lower limit of detection (LLOQ) of this assay was 2.5 mg/L. Intra- and inter-day precision values were 3.5 and 6.2%, respectively (Wang et al., 2015). For the samples below the LLOQ, concentration values were recorded as LLOQ of 2.5 mg/L.

Population Pharmacokinetic Analysis

Population pharmacokinetic (PPK) analysis was performed using NONMEM (version 7.2). A one-compartment PK model with first-order elimination (ADVAN1 TRANS2) was implemented. The concentration-time data for teicoplanin were modeled by first-order conditional estimation with interaction (FOCE-I). We evaluated inter-individual variability using an exponential error model. Residual variability was selected from additive, proportional, exponential, and combined additive and proportional error models according to acceptable standard

errors, physiological plausibility of population clearance (CL) and distribution volume (V_d) estimates, improvement of the objective function value (OFV) and good visual representation of standard diagnostic plots. Demographic characteristics (age, gender, WT), renal functions (blood urea nitrogen, SCr, CLcr), biochemical data (total protein, albumin), status of disease (sepsis, endocarditis), and nephrotoxic medications received during teicoplanin therapy were investigated as potential variables on PK parameters. CLcr was calculated by the Cockcroft formula (Cockcroft and Gault, 1976). A covariate model was developed using a standard stepwise forward-addition backward deletion procedure to ascertain the statistical significance of each covariate. The effects of continuous covariates were modeled using linear, power and exponential models. For categorical covariates, the effect on PK parameter was described by an exponential model. During forward selection, a covariate would be retained if a decrease in objective function value (OFV) was > 3.84 [$p < 0.05$, χ^2 distribution, degree of freedom (df) = 1] after addition to the basic model, and then all the covariates selected were added simultaneously into a full model. A more stringent criterion was used for the backward elimination step, where a covariate was independently removed from the full model if the increase in OFV was < 10.83 ($p < 0.001$, χ^2 distribution, df = 1). If the 95% confidence interval of the covariate coefficient included zero, the particular form was rejected.

Model Evaluation

Evaluation of the model was first based on goodness-of-fit plots. To evaluate the accuracy and stability of the final model, a bootstrap, normalized prediction distribution errors and visual predictive checking (VPC) were performed (PsN). Additionally, the predictive performance of the final model was externally evaluated in a separate patient cohort by calculating the prediction error (PE) and absolute prediction error (APE). The separate patient cohort and patients used for model development come from the same two hospitals. The model with PE value within ± 15% and ± 20% for concentration ≥ 10 and < 10 mg/L, respectively, were considered acceptable. PE and APE are calculated by the following equations (Menichetti et al., 1994; Svetitsky et al., 2009).

$$\mathrm{PE} = \frac{\text{Model predicted concentration} - \text{Observed concentration}}{\text{Observed concentration}} \times 100\%$$

$$\mathrm{APE} = \frac{\left|\text{Model predicted concentration} - \text{Observed concentration}\right|}{\text{Observed concentration}} \times 100\%$$

Simulation of Dosage Regimens

Monte Carlo simulations were performed to generate 5,000 virtual children. The PK parameters obtained from final model of each patient were used to predict the concentration-time profiles for different teicoplanin weight-based loading and maintenance dosage regimens. Three loading doses were simulated and C_{min} were predicted by the day 3 of therapy. C_{min} at steady state was predicted for maintenance dosing (by the day 5). A dosage regimen was defined as optimal if mean C_{min} reaches 10 and 15 mg/L for moderate and severe infection, respectively. The proportion of patients with potentially toxic concentration (>60 mg/L) were also calculated (Ramos-Martin et al., 2017b).

Based on the discrete MIC distributions for the MRSA released by the European Committee on Antimicrobial Susceptibility Testing (0.032–16 mg/L, https://mic.eucast.org/Eucast2/regShow.jsp?Id=20922), the cumulative fraction of response (CFR) was also calculated as the weighted average of the probability of target attainment across the MIC strata to define the optimal dosage regimens able to attain the AUC_{24}/MIC target of 125 and 345. AUC_{24} was calculated in this study by the formula: AUC_{24} = Daily Dose/CL, which refers to the AUC at steady state. A CFR value of ≥ 90% was considered to be the minimum for achieving optimal empirical therapy (Masterton et al., 2005).

RESULTS

Patient Population

An overview of the entire study flow chart is shown in **Figure 1**. After excluding eight patients due to lack of sampling time, 159 children with 236 drug concentrations were included for model development eventually. The demographics and clinical characteristics are summarized in **Table 1**; **Supplementary Table S2**. Out of the 236 teicoplanin concentrations, 212 (89.8%) were drawn for TDM. Six plasma concentrations fell below the LLOD. 12 (5.1%) had imputed SCr readings. Nine and four children from Hospital 1 were included in model-building and evaluation, respectively. Nine children developed nephrotoxicity during hospitalization and all of them occurred this after the last sample was collected.

Population Pharmacokinetic Analysis and Model Evaluation

A one-compartment PPK model with an exponential error model for inter-individual variability and additive error model for residual variability resulted in the lowest in OFV for the base model. In the final PK model (OFV = 971.014), WT and SCr were identified as significant covariates for CL, while the OFV of a reduced model without this WT or SCr increased to 1067.599 and 971.000, respectively. WT was also a significant covariate for V_d, while the OFV of a reduced model without WT on V_d increased to 987.532. **Supplementary Table S3** summarizes details of the model development process and the population values for CL and V_d are derived as follows:

$$CL\ (L/h) = 0.0694 \times \left(1 + \theta_1 \times \frac{WT}{16.71}\right) \times \theta_2^{(SCr/29.075)} \times e^{\eta 1}$$

$$V_d\,(L) = 1.39 \times \theta_3^{(WT/16.71)} \times e^{\eta 2}$$

The coefficient of variation decreased from 123.3% to 65.9% for CL and from 128.1% to 61.0% for V_d after adding the covariates, indicating that the final model accounts for 46.6%

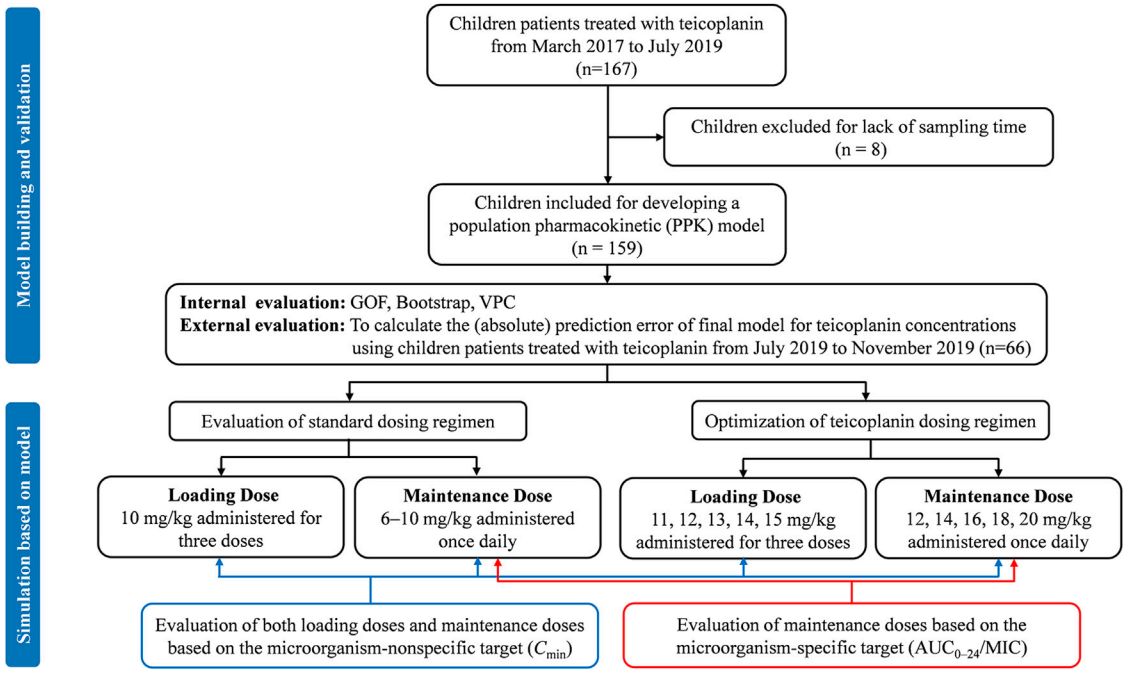

FIGURE 1 | Study flow chart and simulation workflow. GOF, goodness-of-fit; VPC, visual predictive check.

and 52.4% of the variability of CL and V_d in the data, respectively. The shrinkage were 26.9% and 19.8% for CL and V_d, respectively, and 24.4% for residual error.

Graphical and statistical model evaluation showed well stability and robustness of the final model (**Figures 2**, **3** and **Table 2**). The external validation dataset for teicoplanin consisted of 89 concentrations from 66 children with similar demographics to those of the subjects in the PPK analysis (**Table 1**). The predictive performance was acceptable with a mean PE of −0.24%, and with a mean APE of 10.48%. The percentage of population prediction error within ± 20% for C_{min} < 10 mg/L was 94.8% (55/58), and within ±15% for C_{min} ≥ 10 mg/L was 89.1% (27/31).

Simulation of Dosage Regimens

Based on final model, the simulated population was stratified by the various WT and renal function groups to evaluate the effect of these two variates on the optimal dosage regimens. In order to clarify the trend of the effect of SCr on the dosing regimen, the lower limit of SCr range in adult with normal renal function (44 μmol/L) was selected as the typical cut-off value for the simulation due to the lack of standard level of SCr for children.

Figure 4A shows the mean C_{min} achieved with different loading dose regimens. A standard loading dose of 10 mg/kg achieved a mean C_{min} of 12.0 mg/L, which is sufficient for moderate infection, while 13 mg/kg (15.6 mg/L) would be effective in achieving mean C_{min} of 15 mg/L for severe infection. All the optimal dosage regimens are summarized in **Table 3**. Higher loading dose correlated with lower WT and SCr according to subgroup analysis (**Figure 5**).

At maintenance doses of 6–10 mg/kg/day proposed by specification, at best, only a mean C_{min} of 9.4 mg/L was achieved, which were inadequate both for moderate and severe infection (**Figure 4B**). 12 and 16 mg/kg/day could achieve mean C_{min} of 10 and 15 mg/L, respectively. Higher maintenance doses were required in the patients with lower WT and SCr (**Figure 6** and **Table 3**).

<2% of patients had potentially toxic concentrations (>60 mg/L) across the dosage regimens simulated, indicating that all the dosing strategies involved in our study had acceptable exposures.

Figures 4C,D display the CFR of different dosage regimens. The standard maintenance doses had overall CFR of 94.6–98.0% for AUC_{24}/MIC ≥ 125. However, with an AUC_{24}/MIC ≥ 345, only CFR of 68.7–85.7% were obtained. A higher maintenance dose of 12 mg/kg/day achieved a CFR ≥90% for severe infection. In the subgroup analysis, no obvious effect of SCr on the optimal regimens was observed, while maintenance dose presents increase with the decrease of WT in the patients with severe infection (**Figure 7**).

DISCUSSION

We developed a PPK model of teicoplanin in Asian children. A highlight in this study is that dosing regimens in children were first optimized using two methods, providing two sets of optimal dosing regimens. On the one hand, the advantage of such way was to compare the results directly from two kind of targets widely adopted in dosing optimization, and understand the differences between them. We deed found that optimal doses based on the

TABLE 1 | Demographic and clinical information for all patients included in model building and evaluation analysis.

Patient characteristic	Values	
	Model-building data (*n* = 159)	**Model evaluation data (*n* = 66)**
Samplings	236	89
Male/female patients (n, %)	87 (54.7)/72 (45.3)	38 (57.6)/28 (42.4)
Age (yr)	4.1 ± 3.4 (3.7, 0.2–14.0)	4.6 ± 3.8 (3.8, 0.2–13.7)
Patients aged (n, %)	—	—
<2	51 (32.1)	20 (30.3)
2–10	98 (61.6)	37 (56.1)
≥10	10 (6.3)	9 (13.6)
Weight (kg)	16.7 ± 10.1 (14.8, 2.9–69.0)	17.9 ± 12.1 (16.0, 3.0–67.0)
Serum creatinine concentration (μmol/L)	29.1 ± 17.3 (26.0, 10.0–139.0)	25.5 ± 20.1 (22.0, 11.0–176.0)
Creatinine clearance (ml/min)[a]	87.8 ± 47.2 (89.6, 11.0–295.5)	98.0 ± 34.3 (94.9, 11.9–190.4)
Antibiotic indication (n, %)	—	—
Sepsis	39 (24.5)	18 (27.3)
Respiratory tract infection	155 (97.5)	45 (68.2)
Bacteremia	20 (12.6)	10 (15.2)
Bone and joint infection	11 (6.9)	20 (30.3)
Comorbidities (n, %)	—	—
Congenital heart disease	24 (15.1)	6 (9.1)
Myocardial injury	22 (13.8)	1 (1.5)
Malignant hematological disease	91 (57.2)	36 (54.5)
Ventilation (n, %)	48 (30.2)	19 (28.8)
Intensive care unit admissions (n, %)	40 (25.2)	19 (28.8)
Co-medicated with other anti-bacterial drugs (n, %)[b]	—	—
Ceftriaxone	68 (42.8)	12 (18.2)
Meropenem	54 (34.0)	16 (18.2)
Imipenem-cilastatin	72 (45.3)	20 (30.3)
Cefoperazone-sulbactam	31 (19.5)	10 (15.2)
Co-medicated with loop diuretic (n, %)	68 (42.8)	16 (24.2)
Pathogens (n, %)	—	—
Staphylococcus aureus	2 (1.3)	3 (1.9)
methicillin-Resistant *Staphylococcus aureus*	6 (3.8)	2 (1.3)
Staphylococcus epidermidis	6 (3.8)	1 (0.6)
E. faecalis	4 (2.5)	0
E. faecium	7 (4.4)	0
Teicoplanin loading dose (mg/kg)[c]	9.8 ± 1.4 (10.0, 5.2–16.0)	9.8 ± 1.5 (10.0, 3.0–14.3)
Teicoplanin daily maintenance dose (mg/kg)	9.5 ± 1.2 (10.0, 5.2–12.9)	9.6 ± 1.9 (10.0, 3.7–12.3)
Teicoplanin concentration (mg/L)	8.6 ± 12.1 (10.3, 2.5–82.3)	9.6 ± 5.6 (8.6, 2.5–29.5)

Data are expressed as n (%) or mean ± standard deviation unless specified otherwise.

[a]*Creatinine clearance was calculated by the Cockcroft formula.*

[b]*The number of patients co-medicated with at least one other anti-bacterial drug were summarized.*

[c]*Administered for three doses at the start of teicoplanin therapy.*

target C_{min} were higher than that based on the PK/PD target. On the other hand, it is helpful for clinicians and pharmacists to determine the optimal dosing regimens, avoiding the doubts about which optimal dosing regimens are reliable. According our simulation, doses higher than currently recommended in children should be used to achieve both targets of C_{min} and PK/PD.

This is the largest PK study of teicoplanin in children (**Supplementary Table S1**). The covariate analysis revealed that WT and SCr were the significant covariates influencing teicoplanin PK, accounting for around 50% of the observed PK variability, which is higher than other PPK studies in children and adults (Byrne et al., 2015; Ramos-Martin et al., 2017; Zhao et al., 2015). CLcr of children is likely to be overestimated due to young age and small body weight when estimated by Cockcroft formula, and this might be the main reason why the CLcr showed no significant influence on PK parameters of teicoplanin in our study (Cockcroft and Gault, 1976).

Great variation for PK parameters of teicoplanin was presented in children. The typical population values of CL in our study (0.014 L/h/kg) was similar to the range of 0.015–0.024 L/h/kg reported in non-PICU Caucasians previously, but lower than that in PICU Caucasians (0.03–0.074 L/h/kg) (Aarons et al., 1998; Lukas et al., 2004; Ramos-Martin et al., 2014; Reed et al., 1997; Sanchez et al., 1999; Terragna et al., 1988; Zhao et al., 2015). Due to widespread systemic inflammation, patients may often have an ARC in PICU patients (Van Der Heggen et al., 2019), and increased volume of distribution and drug clearance has been observed for hydrophilic drugs, resulting in sub-therapeutic trough concentrations (Hirai et al., 2016). Consequently, higher doses may be required. Lukas, et al. reported that the typical population values of CL and V_d were 0.16 L/h/kg and 2.14 L/h/kg, respectively, which are far higher than results from other studies (Lukas et al., 2004). Consistent with Lukas, two studies were also conducted in patients admitted to the PICU, and reported only 0.045 and 0.03 L/h/kg for

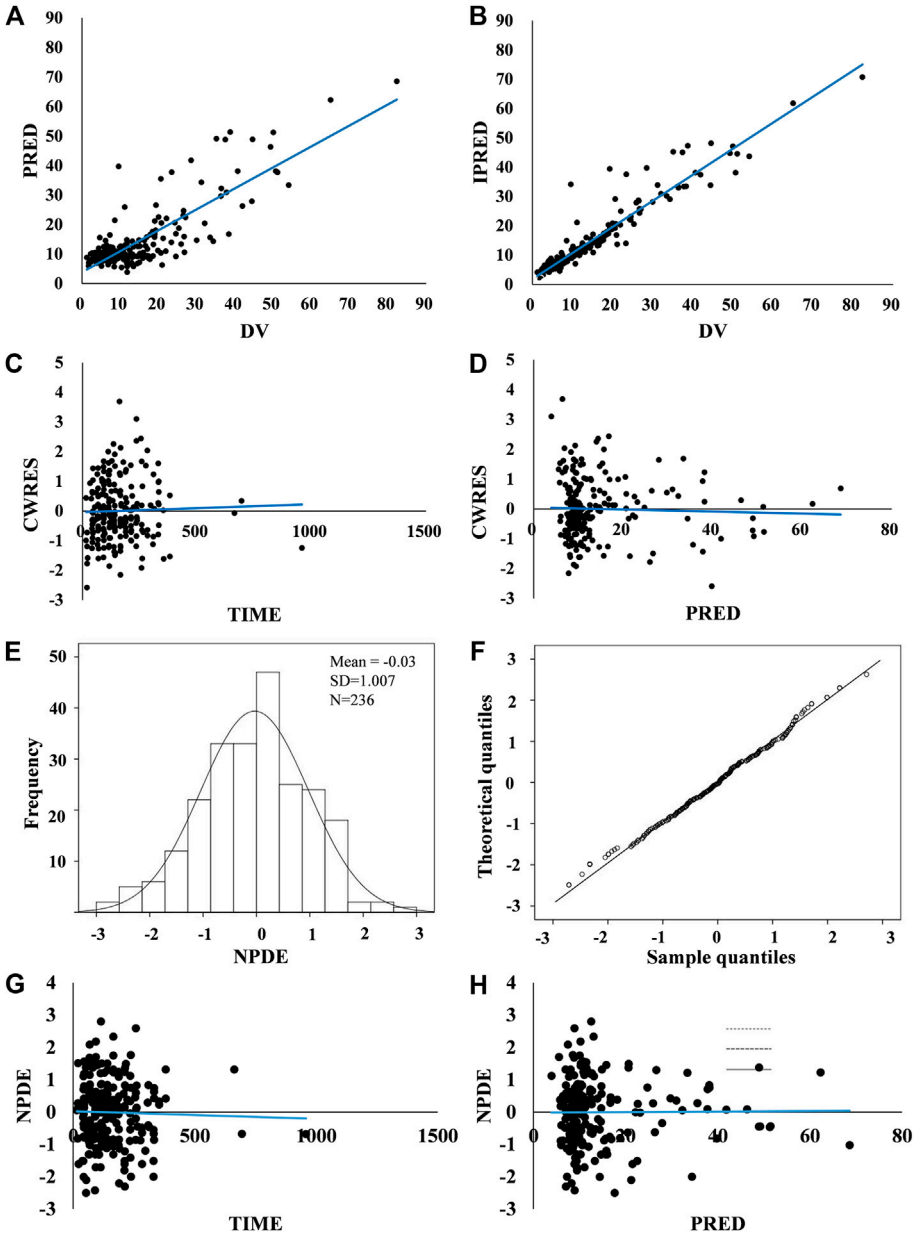

FIGURE 2 | Model evaluation. **(A,B)** Routine diagnostic goodness-of-fit plots: population predicted (PRED) vs. observed concentrations (DV) and individual predicted (IPRED) vs. observed concentrations (DV). **(C,D)** Conditional weighted residuals (CWRES) vs. time and conditional weighted residuals (CWRES) vs. population predicted concentrations (PRED). A solid blue line indicates a trend line. Standard goodness-of-fit of the model showed no obvious systematic bias. There were no trends in conditional weighted residuals distributions. **(E–H)** Normalized prediction distribution errors (NPDE): Q-Q plot of the distribution of the NPDE vs. the theoretical N–(0, 1) distribution and a histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid. NPDE distribution with the mean of 0.03 met well the theoretical N – (0, 1) distribution, and no trend in the scatterplots was observed, indicating that the fit of the model to the data was acceptable.

CL (Reed et al., 1997; Sanchez et al., 1999). A small sample size in Lukas's study might be one of the reasons for this difference. CL estimate (0.013 L/h/kg) from a most recent study involved Chinese children is almost equal to ours, while much difference in V_d (1.85 L/kg) was showed compared with our and other studies (0.2–1.02 L/kg). The estimate of V_d in this study (0.15 L/kg) was closest to that published by Ramos-Martin et al. (0.2 L/kg), which could be explained by the similar patients characteristics between our studies (Ramos-Martin et al., 2014) (**Supplementary Table S1**). Overall, our study provides an important addition to the PK characteristics of teicoplanin and essential foundation for optimizing teicoplanin dosing regimen in this special population.

Loading dose regimen is necessary to reach the effective drug exposure rapidly (Kollef, 2013). However, the standard loading dose was insufficient for severe infection with a mean C_{min} of only 12 mg/L achieved in this study. Sanchez reported that the mean

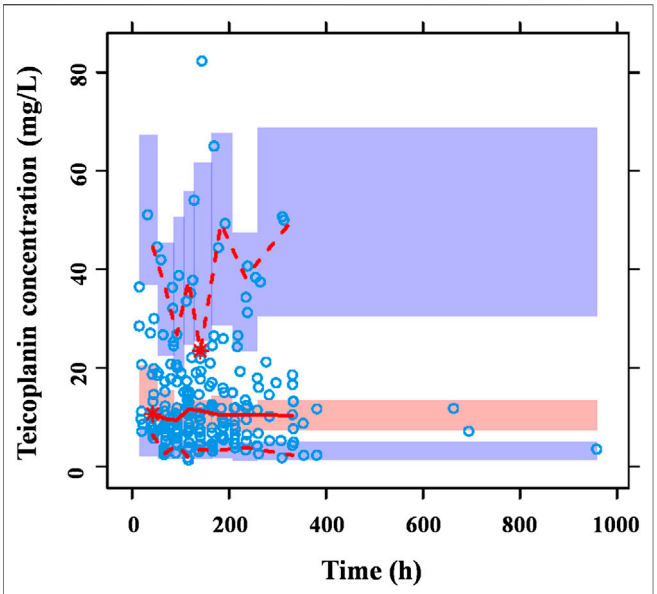

FIGURE 3 | Prediction-corrected VPC generated from a Monte Carlo simulation (n = 1,000) for patients used in model development. The blue circles represent the prediction-corrected observed concentrations. The red solid line represents the median prediction-corrected observed concentrations and pink field represents simulation-based 95% confidence intervals for the median. The observed 5% and 95% percentiles are presented with red dashed lines and the 95% intervals for the model-predicted percentiles are shown as corresponding purple fields. VPC demonstrated that 90.7% observations fell within the 90% prediction interval of simulated concentrations out of 1,000 simulated data sets, indicating that the model-based simulated quantities were in good agreement with teicoplanin measured concentration.

C_{min} by 48 h were 4.8 mg/L (Sanchez et al., 1999). With higher loading doses of 10–15 mg/kg, the proportion of children with C_{min} of <10 mg/L was 14.4% (Strenger et al., 2013). Higher initial loading dose could provide higher drug exposure at the start of treatment. However, the difference appeared to vanish after 14 days when different loading doses were followed by the same dose administered once daily, illuminating the importance of sufficient maintenance dose (Ahn et al., 2011). Our results showed that the current maintenance doses in children only achieved mean C_{min} of 5.6–9.4 mg/L, which are in agreement with the C_{min} of 4.8–5.9 mg/L achieved in another study (Sanchez et al., 1999). Although a few studies evaluated teicoplanin standard dosage regimens in children, none of them focused on the probability of target attainment according to PK/PD targets (Reed et al., 1997; Sanchez et al., 1999; Zhao et al., 2015). Interestingly, we found that the current maintenance doses of teicoplanin showed sufficient for moderate infection, but not for severe infection in term of PK/PD targets. In summary, the current dosage regimens are associated with a high risk of underdosing in this particular group of patients, and higher doses are needed to improve the probability to achieve the target of C_{min} or PK/PD. Zhao et al. suggested a maintenance dose of 15 mg/kg/day in children (Zhao et al., 2015). Even higher doses of 15–20 mg/kg/day were recommended to assure C_{min} above 10 mg/L and all patients attain C_{min} > 10 mg/L only when a maintenance dose of 20 mg/kg/day was administrated (Dufort et al., 1996). These findings provide additional support to our results to increase the dose of teicoplanin. Although several other studies did not perform optimization for the teicoplanin dosage regimens, they also proposed that children may require relatively higher doses (Reed et al., 1997; Lukas et al., 2004).

There are large differences in the optimal dosage regimens provided by the two methods (**Table 3**). Taken together, optimal dosage regimens based on the C_{min} targets in our study are recommended, which are three loading doses of 10 mg/kg every 12 h, followed by a maintenance dose of 12 mg/kg/day for C_{min} of > 10 mg/L and three loading doses of 13 mg/kg every 12 h, followed by a maintenance dose of 16 mg/kg/day for C_{min} of > 15 mg/L. The reasons are as follows: 1) The maintenance dose based on the C_{min} targets are higher than that based PK/PD targets. In other words, maintenance dose based on the C_{min} targets could achieve both microorganism-nonspecific and microorganism-specific targets simultaneously. It is worthy to be noticed that the two evaluation criteria, mean C_{min} of 10 (15) mg/L and $AUC_{24}/MIC \geq 125$ (345), are not in correspondence. It

TABLE 2 | Population pharmacokinetic parameter estimates of final model and bootstrap results from final model.

Parameters	Final model		Estimates based on 1,000 bootstrap replicates[a]	
	Estimate values	Relative standard deviation (%)	Mean	95% confidence interval
CL (L/h)	0.0694	11.3	0.0718	0.0453–0.0983
V_d (L)	1.39	11.0	1.77	1.34–2.20
θ_{wt} on CL	2.82	20.6	3.62	1.21–6.03
θ_{SCr} on CL	0.882	5.0	0.794	0.688–0.9
θ_{wt} on V_d	1.75	6.3	1.76	1.29–2.23
IIV (%)				
CV-CL	65.9	17.6	64.1	57.3–71.9
CV-V_d	61.0	42.5	69.6	43.8–90.5
Residual variability (%)				
CV-σ	7.0	21.9	8.5	5.1–11.9

Abbreviations: CL, clearance; V_d, volume of distribution; WT, weight; SCr, serum creatinine; IIV, inter-individual variability; CV, coefficient of variation.
[a]*Bootstrap success rate = 96.5%.*

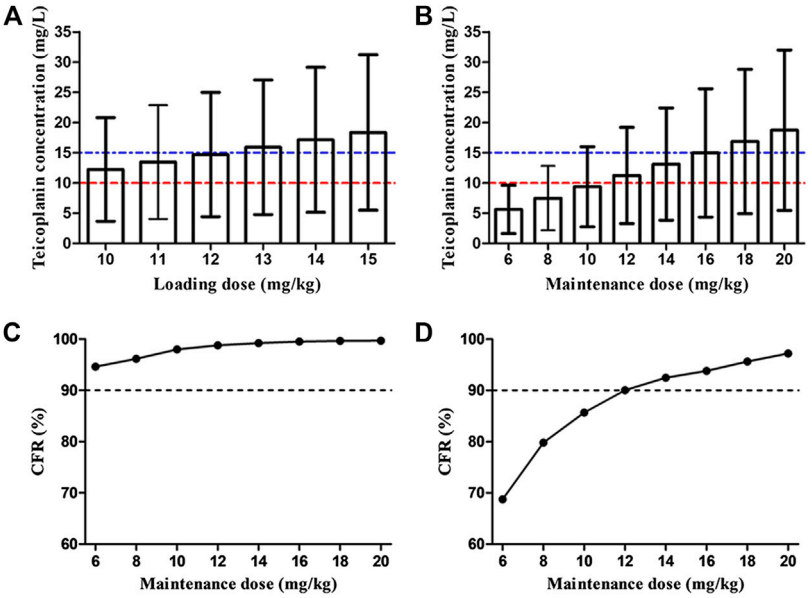

FIGURE 4 | Overall teicoplanin C_{min} with different loading doses **(A)** and maintenance doses **(B)**. Each bar represents the mean ± standard deviation. The dashed red line and blue line indicate the targets C_{min} of 10 mg/L (moderate infection) and 15 mg/L (severe infection), respectively. Cumulative fraction of response (CFR) of different maintenance doses for AUC_{24}/MIC ≥ 125 **(C)** and 345 **(D)**. AUC_{24}/MIC ≥ 125 and 345 were defined as the target values for moderate and severe infection, respectively. The MIC range and distribution are based on the EUCAST data published in 2019 (https://mic.eucast.org/Eucast2/regShow.jsp?Id=20922). Loading doses were administered every 12 h for three doses and C_{min} was simulated by day 3 (48 h). Maintenance doses were administered once daily and C_{min} was simulated by day 5 (96 h).

TABLE 3 | Optimal dosing regimens achieving target teicoplanin C_{min} at 48 h for loading dose regimens and at day 5 for maintenance dose regimens, and AUC_{24}/MIC for moderate and severe infection[a].

Subgroup		Moderate infection			Severe infection		
		C_{min} ≥ 10 mg/L		AUC_{24}/MIC ≥ 125	C_{min} ≥ 15 mg/L		AUC_{24}/MIC ≥ 345
WT	SCr	Loading dose	Maintenance dose	Maintenance dose	Loading dose	Maintenance dose	Maintenance dose
<10	<44	10 mg/kg q12h × 3	14 mg/kg q24h	6 mg/kg q24h	15 mg/kg q12h × 3	20 mg/kg q24h	16 mg/kg q24h
	≥44	10 mg/kg q12h × 3	10 mg/kg q24h	6 mg/kg q24h	11 mg/kg q12h × 3	16 mg/kg q24h	14 mg/kg q24h
10 ≤ WT < 20	<44	10 mg/kg q12h × 3	12 mg/kg q24h	6 mg/kg q24h	14 mg/kg q12h × 3	18 mg/kg q24h	12 mg/kg q24h
	≥44	10 mg/kg q12h × 3	10 mg/kg q24h	6 mg/kg q24h	10 mg/kg q12h × 3	14 mg/kg q24h	12 mg/kg q24h
20 ≤ WT < 30	<44	10 mg/kg q12h × 3	12 mg/kg q24h	6 mg/kg q24h	13 mg/kg q12h × 3	18 mg/kg q24h	10 mg/kg q24h
	≥44	10 mg/kg q12h × 3	8 mg/kg q24h	6 mg/kg q24h	10 mg/kg q12h × 3	12 mg/kg q24h	10 mg/kg q24h
WT ≥ 30	<44	10 mg/kg q12h × 3	10 mg/kg q24h	6 mg/kg q24h	10 mg/kg q12h × 3	14 mg/kg q24h	10 mg/kg q24h
	≥44	10 mg/kg q12h × 3	6 mg/kg q24h	6 mg/kg q24h	10 mg/kg q12h × 3	8 mg/kg q24h	10 mg/kg q24h
Overall		10 mg/kg q12h × 3	12 mg/kg q24h	6 mg/kg q24h	13 mg/kg q12h × 3	16 mg/kg q24h	12 mg/kg q24h

Abbreviations: C_{min}, trough concentration; WT, weight (kg); SCr, serum creatinine (μmol/L). AUC_{24}/MIC, the ratio of the 24-h area under the curve to the minimum inhibitory concentration.
[a]C_{min} ≥10 mg/L and AUC_{24}/MIC ≥ 125 were defined as the target values for moderate infection; C_{min} ≥ 15 mg/L and AUC_{24}/MIC ≥ 345 were defined as the target values for severe infection.

would be more reasonable to define a dose achieving 90% of patients with a C_{min} of 10 (15) mg/L as the optimal dose. However, the proportion of patients achieving the desired exposure is far below 90% both in clinical study (Sanchez et al., 1999; Strenger et al., 2013; Zhao et al., 2015; Sanchez et al., 1999; Strenger et al., 2013; Zhao et al., 2015) and our simulation (**Supplementary Figures S1, S2**). Increasing the magnitude of doses is always the first step to improve the C_{min} target attainment rates in such situation. Gao et al. reported dosing regimens for Chinese pediatrics to achieve the C_{min} of > 10 mg/L. Three loading doses of 6–12 mg/kg every 12 h, followed by a maintenance doses of 8–10 mg/kg/day were required, which is similar to three loading doses of 10 mg/kg every 12 h, followed by a maintenance dose of 6–14 mg/kg/day in our study (Gao et al., 2020). 2) Although antibiotic dosing as determined by PK/PD data was suggested, lack of practitioner familiarity, unclear benefit, time allocation and training requirements are the biggest obstacles to make it in clinical

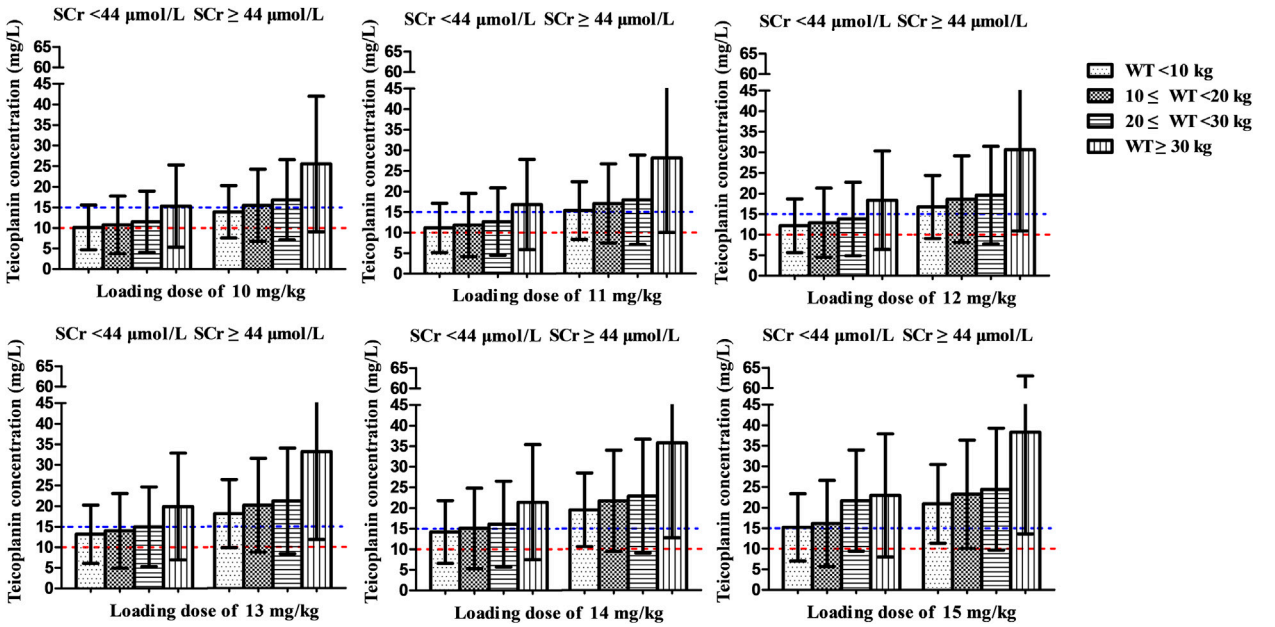

FIGURE 5 | Mean teicoplanin Cmin with different loading doses in subgroups stratified by weight (WT, kg) and serum creatinine (SCr, μmol/L). Each bar represents the mean ± standard deviation. Loading doses were administered every 12 h for three doses and C_{min} was simulated by day 3 (48 h). The dashed red line and blue line indicate the target C_{min} of 10 mg/L (moderate infection) and 15 mg/L (severe infection), respectively.

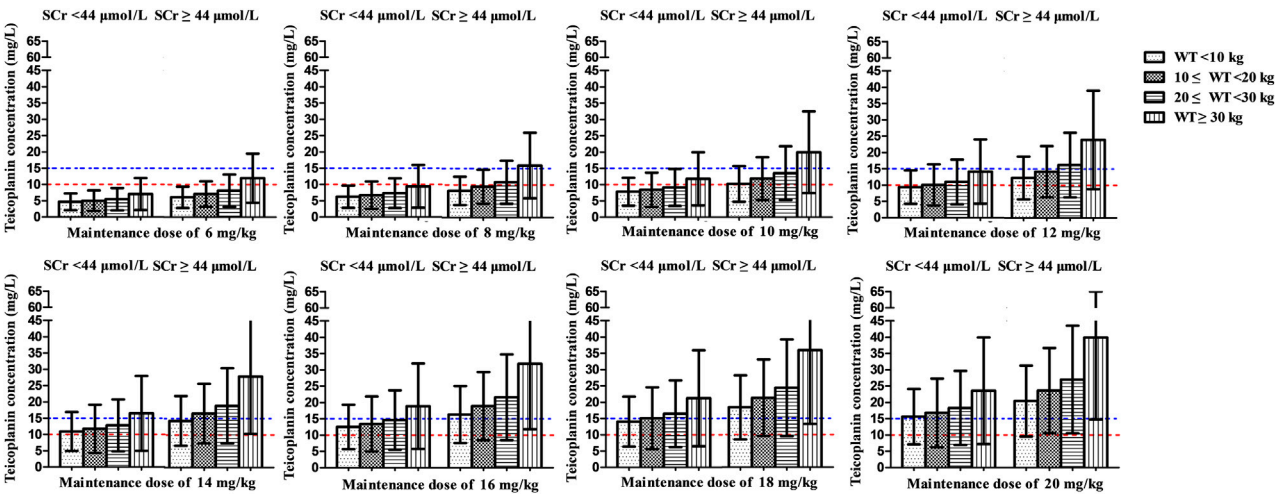

FIGURE 6 | Mean teicoplanin C_{min} with different maintenance doses in subgroups stratified by weight (WT, kg) and serum creatinine (SCr, μmol/L). Each bar represents the mean ± standard deviation. Maintenance doses were administered once daily and C_{min} was simulated by day 5 (96 h). The dashed red line and blue line indicate the target C_{min} of 10 mg/L (moderate infection) and 15 mg/L (severe infection), respectively.

practice (Kufel et al., 2019). Considerable extra costs for the levels monitoring using AUC is another dilemma (Meng et al., 2019). Teicoplanin exhibits linear PK (Rowland, 1990) and C_{min} correlates with AUC_{24} strongly (Cazaubon et al., 2017; Zhao et al., 2015), which make it possible for C_{min} as a surrogate of AUC_{24}. In the present study, the mean C_{min} increased 1.2 and 0.9 mg/L with each 1 mg/kg increase in loading and maintenance dose, respectively. However, the necessity of TDM for teicoplanin is still controversial. TDM for teicoplanin is not performed routinely in clinical practice (Darley and MacGowan, 2004). Even so, exposure control to maximize efficacy should not be neglected and the relatively higher pediatric PK variability supports the use of routine TDM to reduce the risk of clinical failure and the development of drug resistance due to suboptimal drug exposure. Therefore, the situation of low teicoplanin concentration in children is the predominant argument for the

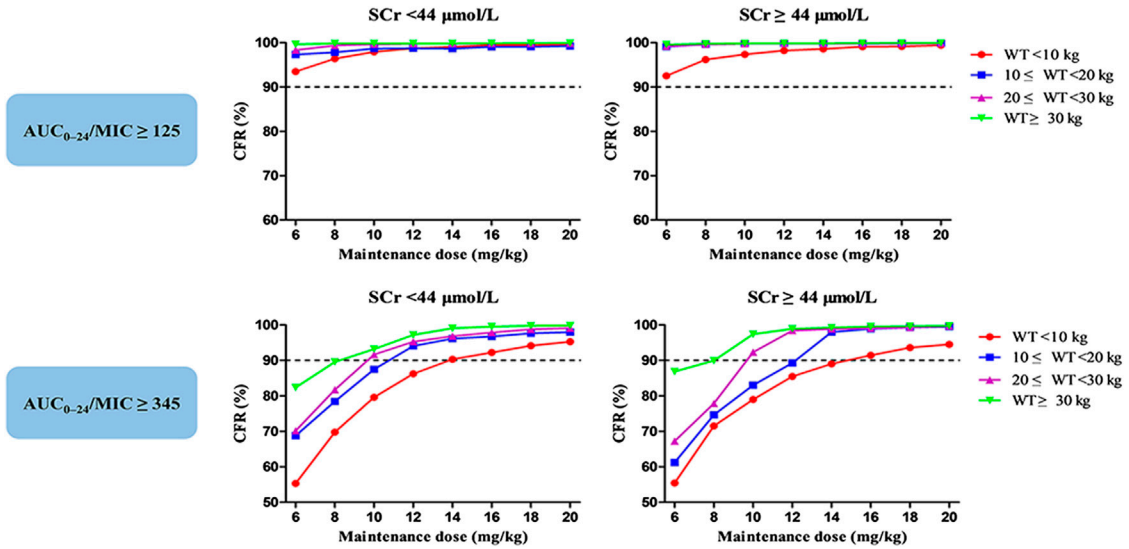

FIGURE 7 | Cumulative fraction of response (CFR) of different maintenance doses for MRSA in subgroups stratified by weight (WT, kg) and serum creatinine (SCr, μmol/L). The pharmacodynamic index was the 24-h area under the plasma concentration–time curve over the minimum inhibitory concentration ratio (AUC_{24}/MIC). AUC_{24}/MIC ≥ 125 and 345 were defined as the target values for moderate and severe infection, respectively. The MIC range and distribution are based on the EUCAST data published in 2019.

routine monitoring of teicoplanin concentrations. A retrospective analysis over a 13 year period indicated that the TDM of teicoplanin has been paid more attention and played an important role in improving the C_{min} target attainment rate (Tobin et al., 2010). 3) Children have demonstrated a higher CL of teicoplanin than adults (Rowland, 1990; Tarral et al., 1988). In the adults study published previously, seven out of ten of the teicoplanin CL reported were lower than 0.01 L/h/kg (Byrne et al., 2018; Cazaubon et al., 2017; Kasai et al., 2018; Lamont et al., 2005; Soy et al., 2006; Yamada et al., 2012; Yu et al., 1995), which is similar with that in the normal healthy male volunteers (Thompson et al., 1992) and lower than that in children (0.015–0.074 L/h/kg) (Aarons et al., 1998; Lukas et al., 2004; Ramos-Martin et al., 2014; Reed et al., 1997; Sanchez et al., 1999; Terragna et al., 1988; Zhao et al., 2015). The standard doses for adult were lower compared to that for children before the update of teicoplanin information form (3–6 mg/kg vs. 6–10 mg/kg). However, the standard doses for adult has been increased to 2-fold, but no modification was made for pediatrics (**Supplementary Table S4**). In fact, the standard doses are not only insufficient for adults (Brink et al., 2008; Matsumoto et al., 2010; Kato et al., 2016), but also for children (Sanchez et al., 1999; Lukas et al., 2004; Strenger et al., 2013; Zhao et al., 2015). 4) Teicoplanin is associated with a lower adverse event compared with vancomycin (Svetitsky et al., 2009) and the proportion of patients achieving C_{min} ≥ 60 mg/L is < 2%, showing well safety of all doses simulated. Although nephrotoxicity, hepatotoxicity and drug fever have been reported previously in adults (Greenberg, 1990; Kato et al., 2016), whether higher doses for children would lead to safety concern is still not determined, which remind us to closely monitor the adverse reaction induced by teicoplanin when higher doses are administered.

There are some limitations of this study. First, sparse sampling is not an optimal but very useful method to determine the PK characteristic of drugs in pediatric populations. Although the current final PPK model was developed based on the biggest sample size so far, only 1.5 samples/children on average was provided due to practical reasons. Caution needs to be exercised when interpreting our results in this very variable population. Second, the evaluation and optimization of loading doses were conducted only based on the C_{min} targets. The formula used for calculating AUC_{24} is unable to calculate it in a specific period, not like the integral method used by other researchers (Byrne et al., 2017; Cazaubon et al., 2017). However, it could be speculated that the loading doses based on the C_{min} targets might obtain sufficient for achievement of the PK/PD target due to lower maintenance doses based on the PK/PD targets. Third, AUC_{24}/MIC goals of ≥ 125 and 345, two PK/PD indexes of teicoplanin for efficacy, were used in this study. Additional PK/PD indexes also have been reported, such as 750, 900, and 1800 (Rose et al., 2008; Kanazawa et al., 2011; Matsumoto et al., 2016). Considering that there is not enough evidence to support the correlation of efficacy with 750, 900, and 1800 is suggested to prevent the teicoplanin-resistant *S. aureus*, these target PK/PD ratio were not adopted. We did not evaluate the correlation of AUC_{24}/MIC or C_{min} with efficiency, because 78% of children had microbial culture results but no specific MIC values and this study was not designed to relate efficacy indicators to clinical outcomes. However, the teicoplanin C_{min} and PK/PD targets of children are referred to that for adults, which are largely based on retrospectively studies (Kuti et al., 2008; Ramos-Martin et al., 2017). Other research efforts should evaluate whether these targets could be extrapolated to pediatric patients and compare the AUC_{24}/MIC methodology with trough measurement in children.

CONCLUSION

In conclusion, we successfully developed and externally validated a PPK model for teicoplanin based on a large cohort of Asian pediatric patients. Under standard protocol, the expected C_{min} for children might be undertherapeutic, especially for the children with lower WT and SCr. Dosage regimens of three loading doses of 10/13 mg/kg every 12 h, followed by 12/16 mg/kg/day for moderate/severe infection, respectively, might be required in this particular patient population. Additional well-designed prospective studies with intensive sampling strategy are warranted to evaluate the potential clinical outcome and safety of these optimized dosage regimens.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the first affiliated hospital of Xi'an Jiaotong University Ethics committee of the Affiliated Children Hospital of Xi'an Jiaotong University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YD and TZ helped design the study. YD, TZ, DS, ZS, and ZD helped conduct the study collected the data. All authors helped analyze and interpret the data, contributed to the preparation of the manuscript, and approved the final manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.594562/full#supplementary-material.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A New Framework to Implement Model-Informed Dosing in Clinical Guidelines: Piperacillin and Amikacin as Proof of Concept

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Background: Modeling and simulation is increasingly used to study pediatric pharmacokinetics, but clinical implementation of age-appropriate doses lags behind. Therefore, we aimed to develop model-informed doses using published pharmacokinetic data and a decision framework to adjust dosing guidelines based on these doses, using piperacillin and amikacin in critically ill children as proof of concept.

Methods: Piperacillin and amikacin pharmacokinetic models in critically ill children were extracted from literature. Concentration-time profiles were simulated for various dosing regimens for a virtual PICU patient dataset, including the current DPF dose and doses proposed in the studied publications. Probability of target attainment (PTA) was compared between the different dosing regimens. Next, updated dosing recommendations for the DPF were proposed, and evaluated using a new framework based on PK study quality and benefit-risk analysis of clinical implementation.

Results: Three studies for piperacillin (critically ill children) and one for amikacin (critically ill pediatric burn patients) were included. Simulated concentration-time profiles were performed for a virtual dataset of 307 critically ill pediatric patients, age range 0.1–17.9 y. PTA for unbound piperacillin trough concentrations >16 mg/L was >90% only for continuous infusion regimens of 400 mg/kg/day vs. 9.7% for the current DPF dose (80 mg/kg/6 h, 30 min infusion). Amikacin PTA was >90% with 20 mg/kg/d, higher than the PTA of the DPF dose of 15 mg/kg/d (63.5%). Using our new decision framework, altered DPF doses were proposed for piperacillin (better PTA with loading dose plus continuous infusion), but not for amikacin (studied and target population were not comparable and risk for toxicity with higher dose).

Conclusions: We show the feasibility to develop model-informed dosing guidelines for clinical implementation using existing pharmacokinetic data. This approach could

complement literature and consensus-based dosing guidelines for off-label drugs in the absence of stronger evidence to support pediatricians in daily practice.

Keywords: pharmacokinetics, model-informed dosing, clinical implementation, critically ill children, piperacillin, amikacin

INTRODUCTION

The Dutch Pediatric Formulary (DPF) provides pediatric dosing recommendations for all drugs used in children the Netherlands (van der Zanden et al., 2017). This includes drugs used off-label by indication and/or age group, but also drugs approved for use in children. If emerging evidence suggests the labelled dose to be suboptimal, the DPF adjusts the dose to reflect up-to-date evidence. These best-evidence doses are based on a standardized benefit-risk analyses using literature data, including doses used in clinical trials and expert opinion. The DPF overcomes the current information gap for physicians when a medical need to prescribe a drug to children is evident and the registered pediatric dose is lacking or believed suboptimal due to emerging new data.

Drug disposition rapidly changes during growth and development, due to maturation of the processes involved in absorption, distribution, metabolism and excretion (Kearns et al., 2003). Not addressing these differences between adults and children might cause suboptimal exposure, lack of efficacy or adverse effects in children (Kearns, 2010; Tuleu and Breitkreutz, 2013). Pediatric pharmacokinetic (PK) data, reflecting these age-related changes can be used to simulate dosing regimens reaching therapeutic and safe exposures. Indeed, model-informed dosing is increasingly used to support dosing recommendations, but implementation in clinical care of such dosing guidelines is lagging behind (Darwich et al., 2017; Keizer et al., 2018). Moreover, many pediatric PK publications do not include dosing simulations and/or proposals for dosing.

We hypothesized that existing, published PK data can also be used to generate dosing recommendations and be used to optimize existing dosing recommendations for children, to be implemented in clinical dosing guidelines, such as the DPF. The aim of our study was to develop a framework using model-informed doses based on published PK studies, as a complementary tool to generate model-informed, evidence-based dosing guidelines.

MATERIALS AND METHODS

Literature and Selection of Drugs

As proof of concept, we focused on the dosing regimens of antibiotics in critically ill children, as concentration targets are available, to enable concentration-based simulations (Tsai et al., 2015). Moreover, these drugs are relatively well studied in children with published pharmacokinetic data ranging from well-validated population PK (pop-PK) studies including dose simulations, to more basic studies simply reporting drug concentrations (Hartman et al., 2019).

We selected publications using pop-PK modelling as these models include interindividual variation (IIV) as a parameter. This provided the possibility to study the full target range and identify the risk of over- or underdosing with the simulated doses. We extracted any information on model structure of the final model, differential equations, covariate relationships, PK-parameter estimates (volume of distribution (Vd) and clearance (Cl)), IIV, and residual error model. Additionally, we evaluated concentration-time profiles in the publications for peak (Cmax) and trough (Cmin) concentrations in order to compare our results to the published studies. Lastly, we identified whether the publication provided a dose advice for critically ill children.

This information was used to select suitable drug candidates aiming to study one drug with and one drug without dosing simulations and recommendations in the manuscript. Both drugs had to have dosing recommendations in the DPF.

Generating Dosing Regimens

PK models were implemented in R and R-studio using the published PK parameters (R version 3.6.2, R-studio version 1.2.1335, R Core Team 2013) with additional package "mrgsolve" and evaluated using "ggplot2" (ggplot2, 2016; Mrgsolve, 2020). Model codes were requested from the authors of the included publication. We only received the model code from De Cock et al. which was used to verify our version of the model (De Cock et al., 2017). The models were written in line with the "mrgsolve user guide." Development and evaluation of the rebuilt models was performed in three steps (detailed in *Step 1: Implementation of Models in a Standardized R-Script*, *Step 2: Extrapolation; Generating a Dosing Advice*, and *Step 3: Decision Framework for Best Evidence Dosing Guidelines*):

Step 1: Implementation of Models in a Standardized R-Script

The first step consisted of rebuilding the model as described in the original article for a specific antibiotic. This step was performed to check validity of the models, as rebuilding the original models should provide similar concentration-time outcomes to the published article. We used the dosing advices in the original articles as input for the model.

R-scripts of the models were written in a fixed format including covariate relationships, PK-parameter values, population characteristics and specific dosing regimens (as described above). Other model-specific characteristics such as model structure, differential equations and error-models were dependent on the number of compartments and the type of error model presented in the article.

The R-scripts were checked for purposes of quality control by two experienced pharmacokinetic modelers (RTH and SVB).

This ensured the models in the script were correctly adapted and represented the models of the original articles.

Step 2: Extrapolation; Generating a Dosing Advice

After evaluating the implementation of the model in step 1, a dosing advice was generated based on simulated concentration-time profiles, toxicity thresholds and the PK targets of efficacy and/or safety.

Simulation Patient Population

For our simulations we used a virtual PICU patient dataset with anonymous demographic and relevant covariate data of critically ill children, 1 m–18 y of age, admitted to the PICU of the Radboudumc in 2018. This was done to ensure we had a virtual patient population that closely mimics the target population for the new dosing regimen. Data were obtained from the electronic patient records and included weight, height, postmenstrual age, postnatal age, gender and eGFR calculated with the creatinine-based revised Schwartz formula (Schwartz et al., 2009). Patients were excluded if more than two of the requested demographic characteristics were missing.

Based on the Dutch Law on Human Drug Research, formal ethical approval by an institutional review board or informed consent were not needed as anonymized clinical patient data were used.

Concentration (PK) Targets

Different PK targets for the efficacy and safety of antibiotics are used, dependent on the properties of the drug. Based on the drugs chosen for the simulation we identified the optimal PK targets. We used epidemiological cut-off values of minimal inhibitory concentrations (MIC) as target values aiming for a clinically relevant, worst-case scenario. For this we used the epidemiological cut-off for MIC values provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for each drug. The relevance of protein binding was evaluated and obtained from literature data of comparable patient populations.

Dose Simulations

Using 100 iterations of the PICU simulation dataset, concentration-time curves were created and compared to Cmax, Cmin and IIV presented in the original articles. Subsequently, simulations of concentration-time profiles were performed for different dosing regimens.

First, the current dose in the Dutch Pediatric Formulary (DPF) was simulated (Dutch Pediatric Formulary-Amikacin; Dutch Pediatric Formulary-Piperacillin). For the drug with dose advice in the paper(s) we also used the advised dose as input for these simulations. For the drug without a dose advice in the paper, several dosing regimens were examined for reaching the determined PK-targets, using a "trial and error"-principle with predefined dose increments, based on the drug's DPF dose and dose intervals of at least 12 h. We compared the simulation results between the DPF dose and these "trial and error" doses.

Cross-checks of these doses were performed between the different models for additional insight in applicability and robustness. Additionally, probability of target attainment (PTA) was determined by the proportion of patients that reach selected target concentrations for safety and/or efficacy. PTA was determined for current and selected optimal dosing regimens, in order to quantify the improvements in PTA of a new dosing regimen.

Step 3: Decision Framework for Best Evidence Dosing Guidelines

In order to aid the possible implementation of our model-informed doses as best-evidence dosing guidelines of our simulations, we determined the following framework to evaluate the models. The following questions were aimed to evaluate the level of uncertainty of the model-informed doses and determine the doses with the best benefit-risk ratio for the intended population:

(1) What is the level of certainty of the target concentrations?
(2) What is the clinical risk of over- or underdosing?
(3) What is the level of certainty of the model output?
(4) Does the currently advised DPF dose result in adequate (simulated) target exposure?
(5) Which dose results in better target exposure, is this a significant improvement?
(6) Is the proposed dose practical?
(7) Is the population in the published PK model comparable to the simulated population (e.g., with respect to demographics, severity of illness, underlying disease)? If not, will this impact the dosing requirements?
(8) Overall conclusion

RESULTS

Literature and Selection of Drugs

Piperacillin and amikacin were selected as the best drug candidates for this study, as piperacillin has three available pop-PK models, all providing a dose advice for critically ill children (Nichols et al., 2015; De Cock et al., 2017; Béranger et al., 2018) and one published amikacin pop-PK model was available, but this study did not provide a dose advice for critically ill children (Sherwin et al., 2014).

Pop-PK models were available for *piperacillin* from studies by Béranger et al., De Cock et al. and Nichols et al., which included 67, 47, and 12 PICU patients, respectively (Nichols et al., 2015; De Cock et al., 2017; Béranger et al., 2018). Age of patients ranged from 1 m to 18 y, and patients with renal dysfunction were either excluded beforehand or not included in the final study. Béranger and Nichols identified piperacillin PK was best fitted by a one compartment model, De Cock developed a 2-compartmental model.

The 2-compartment amikacin model by Sherwin et al. included 232 amikacin concentrations from 70 critically ill, pediatric burn patients, with ages ranging from 6 m up to 17 y (17). An overview of model and patient characteristics is shown in **Table 1**.

TABLE 1 | Overview of study characteristics, populations, PK parameters and dose advice in the used pop-PK models.

Author	Drug	Dose regimen used in study	Population	Median age + weight (range)	Covariates final model	PK parameters	Dose advice
Béranger	PIP	300 mg/kg/d, 4 daily doses, 30 min infusion	67 critically ill children	2.3–2.6 y (1–18 y) 11.9–13.7 kg (2.7–53 kg)	Cl: weight, eGFR Vd: PELOD-2	PIP Cl 0.18 L/kg/h PIP Vd 0.351 l/kg	400 mg/kg/d CON or EXT
De Cock	PIP	300 mg/kg/d, 4 daily doses, 5–30 min infusion	47 critically ill children	2.83 y (2 m–15 y) 14 kg (3.4–45 kg)	Cl: weight, PMA Vd: weight	PIP Cl 0.25 L/kg/h PIP central Vd 0.13 L/kg, peripheral Vd 0.11 L/kg	75 mg/kg loading dose +400 mg/kg/d CON
Nichols	PIP	300 mg/kg/d, 3 daily doses, 3 h infusion	12 critically ill children	5 y (1–9 y) 18.3 kg (9.5–30.1 kg)	Cl: weight Vd: -	PIP Cl 0.199 L/kg/h PIP Vd 0.366 L/kg	100 mg/kg every 6–8 h as EXT
Sherwin	AMI	10–20 mg/kg/d, 2–4 daily doses, 30 min infusion	70 critically ill pediatric burn patients	4.5 y (0.5–17 y) 20 kg (8–90 kg)	Cl: weight Vd: weight	AMI Cl 0.085 L/h/kg AMI central Vd 0.239 L/kg, peripheral Vd 0.573 L/kg	No dose advice

AMI, amikacin; Cl, clearance; CON, continuous infusion; eGFR, estimated glomerular filtration rate; EXT, extended infusion; PELOD-2, Pediatric Logistic Organ Dysfunction two score; PIP, piperacillin; PMA, postmenstrual age; Vd, volume of distribution.

Simulation Patient Population

After exclusion of duplicate entries and patients with missing demographic data, the patient dataset included 307 patients in total, with a median age of 4.9 y (**Table 2**). Creatinine concentrations were available for 77 patients, with a median eGFR of 115.2 ml/min/1.73 m^2. Disease severity scores (Pediatric Logistic Organ Dysfunction (PELOD)-2 scores), which were a covariate in the Béranger piperacillin model, could not be obtained from our hospital records, so the mean population value from the Béranger study (PELOD-2 = 4) was used (Béranger et al., 2018).

Concentration (PK) Targets for Selected Drugs

The PK target associated with piperacillin efficacy is the percentage of time the unbound plasma concentration exceeded the minimal inhibitory concentration (%fT/MIC), which should be 100% based on latest consensus (Nichols et al., 2015; De Cock et al., 2017; Béranger et al., 2018). For our simulations we used a target concentration of 16 mg/L, which is the clinical breakpoint of *Pseudomonas aeruginosa*, as a worst-case scenario [European Committee on Antimicrobial Susceptibility Testing (EUCAST)]. The fraction of unbound piperacillin was assumed to be 70% (Piperacillin - Summary of Product Characteristics), similar to the assumed level of protein binding in the models (Nichols et al., 2015; De Cock et al., 2017; Béranger et al., 2018). The PTA for reaching the piperacillin PK-target (unbound Cmin > 16 mg/L) was assessed for the advised dosing regimens by Béranger, de Cock, Nichols and the DPF dose across the three models. Overall PTA was defined as the mean PTA across all models.

For amikacin a Cmax/MIC-ratio of 8–10 is the most commonly defined PK target for efficacy and associated with optimal bacterial killing (Tsai et al., 2015). Additionally, the safety target for amikacin is a Cmin < 5 mg/L, which is associated with a reduced risk of ototoxicity and nephrotoxicity (Zorginstituut Nederland. Amikacine. Farmacotherapeutisch Kompas, Roberts et al., 2012). Sherwin et al. used target Cmax and Cmin of 25–30 mg/L and 4–8 mg/L, respectively (Sherwin et al., 2014). As the epidemiological cut-off value obtained from EUCAST for most bacteria is 8 mg/L [European Committee on Antimicrobial Susceptibility Testing (EUCAST)] we used a target Cmax of 60–80 mg/L to ensure the target Cmax/MIC ratio to be at least 8, a target also used in critically ill adults with severe infections (de Montmollin et al., 2014). Unbound amikacin concentrations were not taken into account, as amikacin protein binding is negligible (Amikacin Summary of Product Characteristics SmPC, 2020).

TABLE 2 | Demographic and clinical characteristics of the Radboudumc PICU-dataset from 2018 (n = 307).

Demographic variables	Median (IQR) [range] or n (%)
Gender	
Male	164 (53.4%)
Female	143 (46.6%)
Postnatal age	4.9 y (1.2–11.5) [0.1–17.9]
Age categories	
1 m–1 y	66 (21.5%)
1–2 y	40 (13.0%)
2–4 y	30 (9.8%)
4–8 y	59 (19.2%)
8–12 y	39 (12.7%)
12–18 y	73 (23.8%)
Weight	18.0 kg (10.0–38.0) [2.1–98.0]
eGFR (n = 77)	115.2 ml/min/1.73 m^2 (93.5–143.1) [20.9–196.2]

PICU, pediatric intensive care unit; eGFR, estimated glomerular filtration rate.

Dose Simulations - Piperacillin

As input for the simulations we used the dosing advice provided in the articles: Béranger et al. (Béranger et al., 2018) advised 400 mg/kg/d as a continuous infusion, De Cock et al. (De Cock et al., 2017) advised a loading dose of 75 mg/kg followed by a 400 mg/kg/d continuous infusion, and Nichols et al. (Nichols et al., 2015) advised 400 mg/kg/d as extended 3-h intermittent infusions every 6 h.

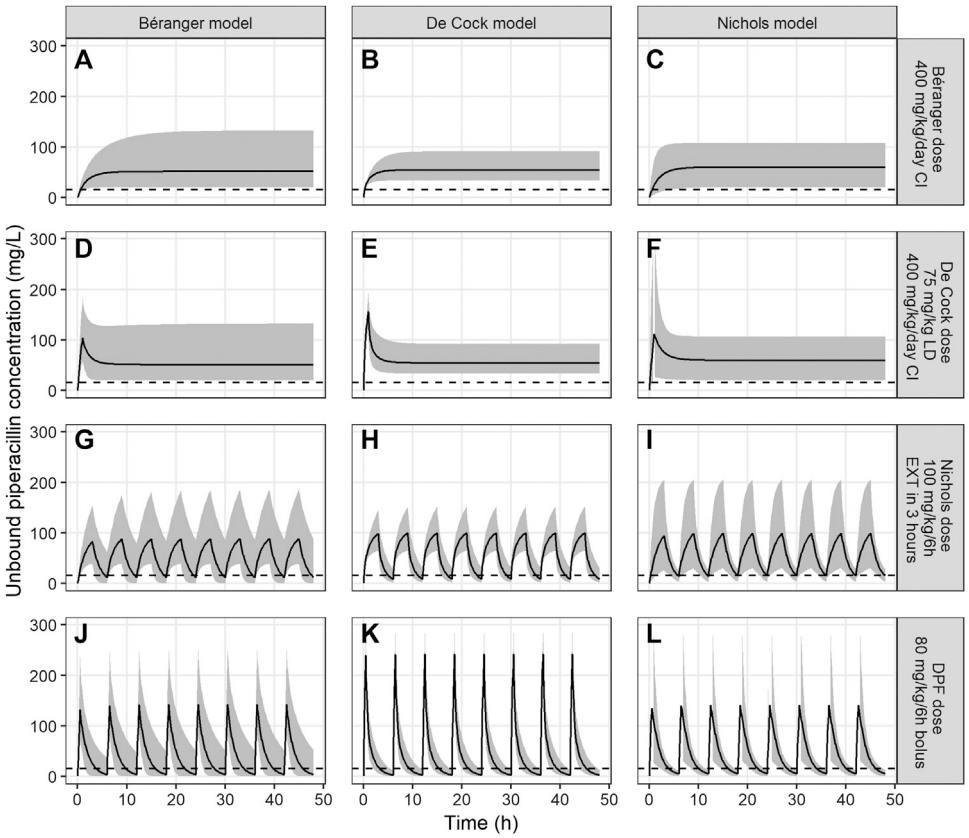

FIGURE 1 | Unbound piperacillin concentrations over 48 h for models of Béranger, De Cock and Nichols. The black line represents the median piperacillin concentration, the shaded grey area the 95% prediction interval, and the dotted line the target Cmin of >16 mg/L. Columns represent the simulations of a single model (panel **(A)**, **(D)**, **(G)** and **(J)** for the Béranger model, panel **(B)**, **(E)**, **(H)** and **(K)** for the De Cock model and panel **(C)**, **(F)**, **(I)** and **(L)** for Nichols model). The rows represent different dosing recommendations from the different models (panel **(A)**, **(B)** and **(C)** for the dose proposed by Béranger (400 mg/kg/d as continuous infusion), panel **(D)**, **(E)** and **(F)** for the dose proposed by De Cock (75 mg/kg loading dose +400 mg/kg/d as continuous infusion), panels **(G)**, **(H)** and **(I)** for the dose proposed by Nichols (100 mg/kg/6 h as extended infusion during 3 h) and panels **(J)**, **(K)** and **(L)** for the current DPF dose (80 mg/kg/6 h as bolus infusion)).

Simulated concentration-time profiles for piperacillin were compared to concentration-time plots in the original publications. Our simulations showed reasonable representation of median Cmax, Cmin and interindividual variability in the original studies. Concentration-time profiles of these simulations and cross-checks between different models and piperacillin dosing regimens, are presented in **Figure 1**.

Both continuous dosing recommendations, by Béranger and De Cock, resulted in the highest Cmin concentrations. For the dosing regimen of Béranger steady-state median (95% prediction interval) piperacillin concentrations were 51.2 mg/L (20.0–134.0), 54.8 mg/L (33.8–91.1) and 59.8 mg/L (20.3–107.2) in the models of Béranger, De Cock and Nichols, respectively (**Figure 1**, first row). The dose regimen proposed by De Cock et al. (400 mg/kg/d as continuous infusion with a 75 mg/kg loading dose) yielded similar median concentrations 51.4 mg/L (19.7–132.6), 54.8 mg/L (33.5–90.5) and 59.8 mg/L (20.2–107.8) (**Figure 1**, second row), but reached therapeutic concentrations faster. Contrarily, regimens using intermittent doses, as advised by Nichols et al. and the DPF dose, did not reach median Cmin > 16 mg/L (**Figure 1**, third and fourth row).

PTA of piperacillin at a MIC of 16 mg/L was > 90% in for both continuous dosing regimens by Béranger and de Cock (**Figure 2**) across all three models. The intermittent dosing regimen of Nichols (400 mg/kg/d, 6 h dosing interval, extended infusion of 3 h) showed an overall PTA of 36.7%, ranging from 19.2% in the de Cock model to 47.7% in the Nichols model. However, this is still markedly higher than what is reached with the current DPF dosing regimen, with an overall PTA of 9.6%, ranging from 0.6–25.8% in the Nichols and Béranger model respectively.

Dose Simulations - Amikacin

There was no dosing advice presented in the Sherwin article, so the starting point for the simulations was the dosing advice in the DPF (15 mg/kg every 24 h) and the highest registered dose (20 mg/kg/d) in the summary of product characteristics (SmPC) (Amikacin Summary of Product Characteristics SmPC). Subsequently, a trial and error-method resulted in a concentration course over time, for which the predetermined PK-targets for effectivity and toxicity were reached (**Figure 3**).

Dosing regimens of 10 mg/kg/24 h, 15 mg/kg/24 h, 10 mg/kg/12 h, 20 mg/kg/24 h and 25 mg/kg/24 h were tested. The dosing

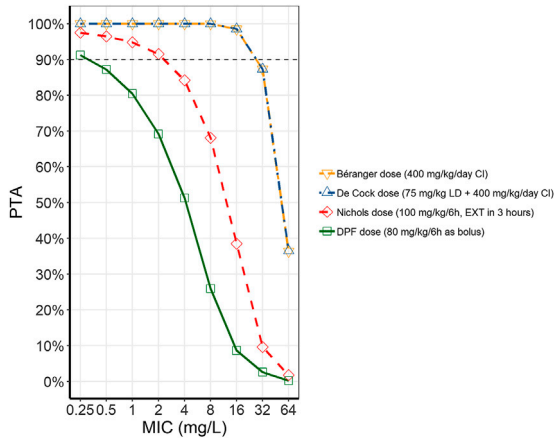

FIGURE 2 | Probability of target attainment (PTA) for piperacillin with different dosing regimens. The different lines represent the average PTA across the three models at different MICs for the different dosing regimens (Béranger dose = yellow, dashed line, downward facing triangle; De Cock dose = blue, dash-dotted line, upward facing triangle; Nichols dose = red, dashed line, diamonds; DPF dose = green, solid line, squares). (CI, continuous infusion; DPF, Dutch Pediatric Formulary; EXT, extended infusion; LD, loading dose; MIC, minimum inhibitory concentrations).

regimen of 20 mg/kg every 24 h, administered over 30 min, reached predetermined PK-target in most patients, with a simulated Cmax of 70.2 mg/L (95% prediction interval 51.7–97.5) and for Cmin 1.1 mg/L (95% prediction interval 0.3–2.3). Other dosing regimens demonstrated suboptimal results: all dosing regimens under 20 mg/kg/dose failed to reach appropriate Cmax concentrations (33.9 mg/L (24.6–45.0) for 10 mg/kg/dose and 50.6 mg/L (35.5–68.3) for 15 mg/kg/dose). On the other hand, a regimen of 25 mg/kg/24 h resulted in supratherapeutic Cmax concentrations (82.3 mg/L (55.9–107.5)). PTA of the safety target (Cmin < 5 mg/L) was 100% for all simulated dosing regimens.

Probability of target attainment (PTA) was simulated for the currently proposed dosing regimen from the DPF (15 mg/kg/24 h) and our proposed dose of 20 mg/kg/24 h (**Figure 4**). For an MIC of 8 mg/L, the current dose reaches a PTA of 63.5%, while a dosing regimen of 20 mg/kg/24 h reaches a PTA of 96.2%. Differences in PTA between these two dosing regimens for other MICs was minimal.

Decision Framework for Best Evidence Dosing Guidelines

Piperacillin

(1) What is the level of certainty on the target concentrations?

Moderate to high, based on EUCAST MIC concentrations and widely accepted definition of target attainment %fT/MIC >100. The percentage unbound drug is estimated, in line with other studies of this drug in this population.

(2) What is the clinical risk of over- or underdosing?

In general penicillins show a relatively mild safety profile. The additional risk of overdosing of tazobactam, the accompanying drug in all piperacillin formulations, should be taken into account. However,

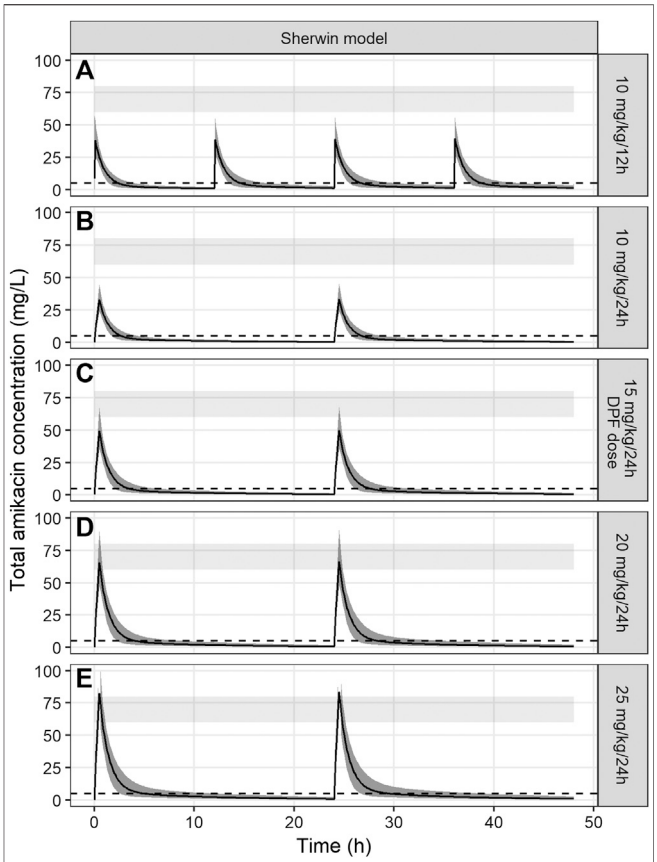

FIGURE 3 | Amikacin concentration-time curves simulated over 48 h using the PK model of Sherwin et al. The black line represents the median amikacin concentration, the dark grey area around the line the 95% prediction interval. The light grey band represents the target Cmax (60–80 mg/L) and the dotted line represents the target Cmin (<5 mg/L). Panels **(A)**–**(E)** represent different tested dosing regimens, including the currently advised DPF dose (panel **(C)**).

this also appears to be relatively safe in higher than licensed doses (McDonald et al., 2016). Underdosing may result in ineffective bacterial clearance, which weighs heavier than the relatively mild side-effects, especially in critically ill patients.

(3) What is the level of certainty of the model output?

Simulation of concentrations using all three models resulted in similar exposures as in the publications. Moreover, all studies used state of the art internal validation methods. However, interindividual and residual variability was relatively large in all three models, which widens the prediction intervals of our simulations.

(4) Does the currently advised DPF dose result in adequate target exposure?

No, only 9.6% reaches the target Cmin concentration of >16 mg/L with the current intermittent dosing regimen of 320 mg/kg/d as intermittent dose.

(5) Which dose results in better target exposure, is this a significant improvement?

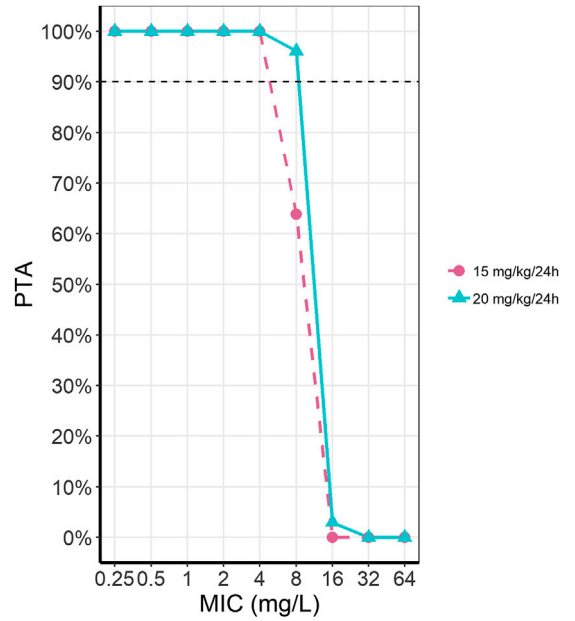

FIGURE 4 | Probability of target attainment (PTA) for amikacin for two dosing regimens at different MICs. The two presented dosing regimens are the current DPF recommendation of 15 mg/kg/24 h (pink, dashed line, circles) and our optimally simulated dose of 20 mg/kg/24 h (light blue, solid line, triangles).

400 mg/kg/d performed significantly better than the DPF daily dose of 320 mg/kg/d. Continuous infusion performed best (PTA > 90%), and when combined with a loading dose of 75 mg/kg this is the most optimal dosing regimen to reach fast and steady therapeutic concentrations.

(6) Is the proposed dose practical?

Continuous infusions may not be practical in critically ill children where venous access is always challenging and limited. Intermittent doses using an extended dosing interval may be more practical in clinical practice.

(7) Is the population in the published PK model comparable to the simulated population (e.g., with respect to demographics, severity of illness, underlying disease)? If not, will this impact the dosing requirements?

The models all included critically ill children with mixed underlying reasons for ICU admission which did cover most of the pediatric age range, but with a slightly lower median age compared to our simulation cohort. Therefore, these results might be applicable to critically ill children, but less applicable for non-critically ill children, although piperacillin-tazobactam will likely only be prescribed to severely ill children. Additionally, we used a worst-case scenario for MIC, whereas actual MIC targets may differ for other bacteria or other areas where microbial resistance may be different (Woksepp et al., 2016).

(8) Overall conclusion for piperacillin:

According to our simulations, the proposed optimal dosing regimen for critically ill children is a loading dose followed continuous infusion to reliably reach target concentrations shortly after diagnosis (De Cock et al., 2017). In situations where continuous infusion is not possible, the alternative option would be the Nichols dosing regimen of 400 mg/kg/d as an extended 3-h infusion (Nichols et al., 2015). For non-critically ill children, the current dosing advice could be continued, although a similar simulation study for non-critically ill children also suggested a slightly higher dose of 360 mg/kg/d and extended infusion in 2 h to reach adequate targets (Thibault et al., 2017). Additionally, as dose-related toxicity is limited, harmonizing the dose across the pediatric populations would be more practical.

Amikacin

(1) What is the level of certainty on the target concentrations?

Moderate, based on EUCAST MIC concentrations and a common definition of target attainment: Cmax/MIC ratio to be at least 8, a target also used in critically ill adults with severe infections. However, others use less aggressive target Cmax, possible in a setting with less microbial resistance. Additionally, although Cmax/MIC is the most commonly used target, a recent publication also proposes AUC/MIC to be the optimal target for aminoglycoside efficacy (Bland et al., 2018).

(2) What is the clinical risk of over- or underdosing?

Amikacin's dose-related toxicity is kidney failure and ototoxicity related to the Cmin. A meta-analysis of amikacin side-effects in adults shows a prevalence of nephrotoxicity and irreversible ototoxicity of 5.3% and 8.6%, respectively (Jenkins et al., 2016), which may cause a major burden on healthcare and patient lives. Underdosing may result in ineffective bacterial clearance, and potentially life-threatening infections and/or sepsis. Therefore, therapeutic drug monitoring (TDM) is routinely advised for aminoglycosides, so the dosing regimens of an individual patient can be adjusted to ensure therapeutic, non-toxic amikacin exposure.

(3) What is the level of certainty of the model output?

Moderate. Simulations of concentrations using the model parameters resulted in similar exposures as published. Moreover, the study used state of the art internal validation methods, but external validation is missing.

(4) Does the currently advised DPF dose result in adequate target exposure?

No, the DPF dose results in a PTA of 63.5% at MICs of 8 mg/L.

(5) Which dose results in better target exposure, is this a significant improvement?

20 mg/kg/d results in better PTA at the same MIC (96.2%), with similar (non-toxic) Cmin. For patients infected with a micro-organism of this MIC this would be a significant improvement. However, target attainment for different MICs is comparable between 15 and 20 mg/kg/d.

(6) Is the proposed dose practical?

Yes.

(7) Is the population in the published PK model comparable to the simulated population (e.g., with respect to demographics, severity of illness, underlying disease)? If not, will this impact the dosing requirements?

The model population consisted of a highly specific subgroup of critically ill children, pediatric burn patients (Sherwin et al., 2014). It is known that due to e.g., fluid retention, pharmacokinetics may differ in patients with extensive burn injury, resulting in lower exposures. Hence, the data cannot be automatically extrapolated to non-burned critically ill children. The study does cover the full pediatric age range within their cohort.

(8) Overall conclusion for amikacin:

Although the simulated dosing regimens suggested a higher daily dose (20 mg/kg/d) than the current DPF, the difference in patient population, potentially explaining the difference with the current DPF dose, the risk of dose-related toxicity in another (critically ill) population, and the relatively small benefit limited to MICs of 8 mg/L does not support an overall change in DPF dose. In critically ill pediatric burn patients, this higher dose could be considered, but only in the absence of renal failure and with strict TDM.

DISCUSSION

In this proof of concept study we explored the feasibility to develop a framework to aid the implementation of model-based dosing guidelines using published pop-PK models in critically ill children, with piperacillin and amikacin as examples. We found that this model-based strategy is feasible to use in practice and we were able to compare dosing advices from three different models of piperacillin, which showed marked differences in PTA between doses advised in the studies. Additionally, we generated a simulated dose for amikacin, an antibiotic for which the dosing advice was not provided in the paper describing the model (Sherwin et al., 2014). Lastly, we used a standardized framework of questions to explore whether these findings warrant a change in the dosing regimen advised by the DPF or other pediatric drug handbooks.

Simulations for both antibiotics suggest that the current DPF dosing regimen results in a suboptimal target attainment in critically ill children. For piperacillin, the evidence is more apparent, as all three articles propose at least 400 mg/kg/d for adequate exposure specifically for critically ill children (Nichols et al., 2015; De Cock et al., 2017; Béranger et al., 2018). These results might warrant an alteration in the DPF dosing recommendation, as supported by our decision framework, which also takes study quality and clinical benefit and risks into account.

For amikacin, while the simulation suggests a higher daily dose, our decision framework does not support a change in dosing regimen. Our simulation results may be only applicable for critically ill children with severe burn injury, a highly specific subgroup with unique pharmacokinetic challenges (Sherwin et al., 2014). Severe burn injury induces several pathophysiological alterations, including capillary leak, extreme interstitial edema, hypovolemia and reduced organ perfusion in the early phase (Udy et al., 2018). Furthermore, treatment of severe burn patients revolves around large volumes of IV fluid resuscitation to increase intravascular pressure and organ perfusion, but also leading to additional extracellular fluid accumulation (Udy et al., 2018). Both pathophysiological alterations and therapies contribute to markedly higher Vd of hydrophilic drugs, like amikacin (Tsai et al., 2015). Additionally, the second phase of burn injury typically involves organ hyperperfusion, which may cause augmented renal clearance making critically ill, burn patients a highly challenging subgroup to dose correctly (Udy et al., 2014; Udy et al., 2018).

In the Sherwin cohort these pharmacokinetic changes are evident, as total amikacin Vd was markedly higher (0.81 L/kg) compared to non-burned infants (0.337 L/kg) (Treluyer et al., 2002). The most commonly used PK-target for amikacin efficacy (Cmax/MIC), is largely influenced by this larger Vd resulting in a higher dose to reach similar Cmax. Additionally, aminoglycosides concentrations are subject to routine TDM, so potential reduced exposure with the current regimen can corrected when necessary. While simultaneously, a higher dose may result in irreversible toxicity in non-burn patients. Therefore, a nationwide dose alteration might not be warranted at the moment.

Pharmacokinetic studies of other antibiotic agents in critically ill children, also suggest similar reduced (simulated) target attainment (Jenkins et al., 2016; McDonald et al., 2016; Bland et al., 2018). Unfortunately, a direct and practical translation to clinical practice is lacking. Not only are model-informed doses frequently not proposed in these manuscripts, even if they are, authors are very reluctant to support clinical implementation as they consider further validation unnecessary. We do support high quality data to establish with large certainty the correctness of model-informed doses (Ince et al., 2009). At the same time, in the absence of more data and the practice of off-label prescribing, not using existing pharmacokinetic data to add to the current evidence-base that supports doses used in real-life clinical care is a missed opportunity. Our decision framework helps to interpret study results with the aim to translate findings to the clinical setting, in a similar risk-benefit analysis that is currently applied by the DPF (van der Zanden et al., 2017). This allows for a thorough evaluation of study results not only for pharmacological efficacy, but also for toxicity, practicality and assessment of external validity of research findings to another clinical setting.

Although our model-based approach to generate evidence-based dosing recommendations seems feasible, it comes with some limitations. The quality of the model-based results is largely influenced by the quality and population of the data provided in literature. We used only pop-PK model data to ensure the highest possible quality of PK parameter estimates, but the models were not externally validated and for amikacin the only available PICU study was performed in burn patients which limits the external validity of our findings. Ideally, future research towards this approach should also include lower-quality data, for example non-compartmental estimates of Vd and Cl, but accurate simulations of drug exposure might prove difficult with suboptimal data. Secondly, this method benefits from established target concentrations that correlate with either effect, drug toxicity or both, which is not available for all drug classes. Thirdly, we have generated a dosing advice using a trial-and-error approach and with a relatively small virtual PICU

cohort, which might be further optimized by more advanced modelling techniques and a larger database of virtual patients including more covariate data. Lastly, although we aimed to close the knowledge gap for evidence-based dosing in children with limited resources, it is of the essence to not abandon the drug dosing quality improvement cycle and evaluate the updated dosing regimens (Ince et al., 2009).

Ideally all dosing recommendations would be based on the most robust form of pharmacokinetic evidence, e.g., from large clinical PK trials or robust pop-PK studies. Additionally, routine TDM strategies could be applied in clinical practice to ensure therapeutic and non-toxic drug exposure after the starting dose has been given. Given the large inter-individual variability in critically ill children, the relatively well-known PK targets associated with efficacy and/or safety, and the inability to judge therapeutic effect by other parameters, routine TDM for antibiotics could be beneficial in this patient population (Wallenburg et al., 2020). Ultimately, model-informed precision dosing applications that are currently under development can translate these robust PK data into tailored dosing regimens for an individual patient, using TDM samples and Bayesian feedback to further improve and individualize dosing of antibiotics in special populations (Darwich et al., 2017; Keizer et al., 2018).

However, reality shows overall dosing recommendations for children regularly need to be made using suboptimal, best-evidence data. In this dilemma between costly, high-grade, patient-specific evidence and pragmatic, best-evidence dosing guidelines, our method could be used as an additional tool to improve current dosing guideline practices. This method is relatively easy to apply by professionals involved in pediatric dosing guidelines, even without prior modelling experience, as it only requires basic knowledge on model structures and R. Within current practice, it can serve to compare multiple models and can be used to simulate dosing regimens using real PK data. Future studies regarding this method should focus on the applicability in a clinical setting, like the DPF. If not implemented properly, this might harm reproducibility and ease of use in practice.

CONCLUSION

Our framework using existing PK data to established model-informed doses can be used as a relatively affordable, easy and efficient simulation tool in special populations, and can be used in conjunction with current strategies for developing evidence-based dosing recommendations. We have shown for piperacillin in critically ill children a higher dose might be warranted. In contrast, for amikacin population differences, uncertainty on target exposure, increased risk of toxicity and small benefits, do not support a change in the clinical dosing guidelines. Although this method cannot replace well-designed clinical trials, it can prove to be valuable, especially for the pediatric population, where off-label prescribing remains very prevalent.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

SH and SW published systematic review that served as a basis for current work. JS, SH, BG, and SB carried out practical work of current study (data cleaning, building simulation script and performing simulations). RH, BG, TZ, MH, and SW provided supervision support over the course of the current study. JS and SH wrote the first version of the manuscript. Final version of the manuscript written by SH, JS, SB, BG, TZ, MH, RH, and SW. Overall, SH and JS have contributed equally.

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Conflict of Interest: SW is Medical Director of the Dutch Pediatric Knowledge Center Pharmacotherapy for Children and as such responsible for the Dutch Pediatric Formularies and its international editions. TZ is managing director of the Dutch Paediatric Pharmacotherapy Expertise Network and as such responsible for the Dutch Pediatric Formularies and its international editions. MH is pharmacist for the Dutch Pediatric Formulary.

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Population Pharmacokinetics and Dose Optimization of Ganciclovir in Critically Ill Children

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Objective: The present study aims to establish a population pharmacokinetic model of ganciclovir and optimize the dosing regimen in critically ill children suffering from cytomegalovirus related disease.

Methods: A total of 104 children were included in the study. The population pharmacokinetic model was developed using the Phoenix NLME program. The final model was validated by diagnostic plots, nonparametric bootstrap, visual predictive check, and normalized prediction distribution errors. To further evaluate and optimize the dosing regimens, Monte Carlo simulations were performed. Moreover, the possible association between systemic exposure and hematological toxicity were also monitored in the assessment of adverse events.

Results: The ganciclovir pharmacokinetics could be adequately described by a one-compartment model with first-order elimination along with body weight and estimated glomerular filtration rate as significant covariates. As showed in this study, the typical population parameter estimates of apparent volume of distribution and apparent clearance were 11.35 L and 5.23 L/h, respectively. Simulations indicated that the current regimen at a dosage of 10 mg/kg/d would result in subtherapeutic exposure, and elevated doses might be required to reach the target ganciclovir level. No significant association between neutropenia, the most frequent toxicity reported in our study (19.23%), and ganciclovir exposure was observed.

Conclusion: A population pharmacokinetic model of intravenous ganciclovir for critically ill children with cytomegalovirus infection was successfully developed. Results showed that underdosing of ganciclovir was relatively common in critically ill pediatric patients, and model-based approaches should be applied in the optimizing of empiric dosing regimens.

Keywords: ganciclovir, population pharmacokinetics, children, dosing, critically ill

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INTRODUCTION

Ganciclovir (GCV) is a pro-drug nucleoside guanosine analogue that exhibits potent activity against herpesviruses, including cytomegalovirus (CMV) (Villarreal, 2001). After phosphorylation in CMV infected cells, GCV is transformed into its triphosphate derivative, which is the active product that inhibits viral replication. Currently, GCV is not only approved for the treatment and prevention of

CMV infections in immunocompromized patients (Sia and Patel, 2000), but also the treatment of congenital CMV infection and other CMV related diseases as an off-label drug.

As previous study showed that the oral bioavailability of GCV was less than 10% (Boeckh et al., 1998), despite the fact that the co-administration of food would increase its absorption. Hence, intravenous infusion was the main method to deliver GCV. However, following intravenous infusion, GCV was weakly bounded to plasma proteins (1–2%) over a concentration of 0.5–51 mg/L (McGavin and Goa, 2001), and it could easily penetrate the cerebrospinal fluid. Several studies showed that a large portion of the administered dose was eliminated from the body by glomerular filtration and renal tubular secretion as unchanged drug, which exhibited a good correlation between the clearance of GCV and creatinine clearance in adult patients (Roberts et al., 2014b; Al-Badr and Ajarim, 2018). As previous pharmacokinetic/pharmacodynamic studies confirmed, the desirable antiviral outcomes would require an area under drug plasma concentration-time curve over 24 h ($AUC_{0\text{-}24}$) of 40–50 μg h/ml in both pediatric and adult patients following solid organ transplant (Wiltshire et al., 2005; Dong et al., 2018). However, it was estimated that nearly 80% patients may fail to achieve the target AUC level using the current pediatric GCV dosing regimen, thus increasing the risk of therapeutic failure in pediatric patients (Stockmann et al., 2015).

In addition, the pharmacokinetic profiles of GCV were highly variable among pediatric patients, especially among hospitalized children with critical illness. A growing evidence showed that altered pharmacokinetic characteristics in critically ill children caused by pathophysiological changes might reduce the likelihood of attaining pharmacodynamic target in this population (Roberts and Lipman, 2009; Roberts et al., 2014a). Furthermore, more studies found that CMV reactivation was prevalent in immunocompetent critically ill patients with a high incidence of 15–20%. Worse still, CMV reactivation was also considered to be correlated with clinical adverse outcomes and the increase of inpatient mortality (Limaye et al., 2008; Papazian et al., 2016; Alyazidi et al., 2018).

Therefore, the aims of the present study were to develop a population pharmacokinetic (PopPK) model for critically ill children receiving intravenous GCV and to further evaluate and optimize the current dosing regimen in this vulnerable population based on modeling and simulating approaches.

METHODS

Study Design and Patient Population

This trial was an open-labeled, retrospective pharmacokinetic study of GCV, conducted in Wuhan Children's hospital from Dec 2017 to Jan 2020. Critically ill patients aged one month to 18 years with confirmed CMV infection who had received intravenous GCV were included in our study. While for patients who are allergic to GCV, lessing than 24 h of GCV therapy, missing data for key variables, or patients simultaneously enrolled in another clinical trial were excluded.

This study was designed in accordance with legal requirements and the Declaration of Helsinki and was approved by the Ethics Committee of Wuhan Children's hospital with waiving of the need for informed consent (approval number: 2020R075-E01).

Dosing Regimen, Pharmacokinetic Sampling and Data Collection

GCV was administered by intravenous infusion over 1 h at a dose of 5 mg/kg twice a day. An opportunistic sampling strategy was adopted (Leroux et al., 2015). The residual serum samples were drawn from routine biochemical specimens and stored at −20°C until assay. Serum concentrations were tested within 48 h after sampling. The actual administration time and sampling time of each sample were precisely recorded and used in PopPK analysis.

Demographic and physiological characteristics of all patients were obtained from the electronic medical records system, including gender, age, body weight (WT), height, blood urea nitrogen (BUN), serum creatinine concentration (SCR), uric acid (UA), total bilirubin concentration (TBIL), alanine aminotransferase concentration (ALT), and aspartate aminotransferase concentration (AST). The estimated glomerular filtration rate (eGFR) and body surface area (BSA) were calculated based on the Gao formula (Gao et al., 2013) and the Mosteller formula (Mosteller, 1987), respectively. And based on the calculated data, the renal function status were classified into (1) elevated renal function (eGFR ≥120 mL/min/1.73m^2), (2) normal renal function (90 mL/min/1.73m^2 ≤ eGFR <120 mL/min/1.73m^2), (3) mild renal insufficiency (60 mL/min/1.73m^2 ≤ eGFR <90mL/min/1.73m^2), (4) moderate renal insufficiency (30 mL/min/1.73m^2 ≤ eGFR <60mL/min/1.73m^2), (5) severe renal insufficiency (eGFR <30 mL/min/1.73 m^2).

Analytical Method of Ganciclovir

GCV concentrations were quantified using a validated high-performance liquid chromatography (HPLC Agilent Technologies Inc., 1260 infinity II) with ultraviolet (UV) detection. Sample preparation was carried out using C18 solid-phase extraction columns (Agela Technologies, Cleanert ODS C18, 500 mg/3 mL). A 0.5-ml volume of serum sample was pipetted into a column preconditioned with methanol and water, then the analytes were eluted with 1 mL of 20% methanol. The chromatographic separation was performed using methanol (4%) and water (96%) as the mobile phase in a DIKMA Luster C18 column (5 μm, 4.6 × 250 mm) at 30°C. The flow rate was 0.8 ml/min. Samples were then detected at 254 nm. The calibration curve was linear over a concentration range of 0.1–20.0 μg/mL, and the lower limit of quantification (LLOQ) was 0.1 μg/mL. The intra- and inter-day coefficients of variation were less than 8%.

PopPK Modeling

Pharmacokinetic data of GCV was analyzed using the Phoenix® NLME software (Version 8.1, Pharsight Corporation, USA). For statistical analysis and output visualization, RStudio (version 1.3, http://www.rstudio.com/) was employed. Lindstrom-Bates

TABLE 1 | Model description of the seven candidate models for clearance.

Candidate models	Model description		
		k_1	MF
Model I: the 3/4 allometric model	$CL/F = \theta_{CL} \times \left(\frac{WT}{WT_{median}}\right)^{k1} \times MF$	0.75	1
Model II: the simplest WT-based exponent model		Estimated	1
Model III: the simplest BSA-based exponent model		Estimated	1
Model IV: the maturation model		0.75	$MF = \frac{1}{1+\left(\frac{Age}{TM_{50}}\right)^{-\gamma}}$
Model V: the WT-dependent exponent model		$k_1 = k_0 - \frac{k_{max} \times WT^{\gamma}}{k_{50}^{\gamma} + WT^{\gamma}}$	1
Model VI: the age-dependent exponent model		$k_1 = k_0 - \frac{k_{max} \times Age^{\gamma}}{k_{50}^{\gamma} + Age^{\gamma}}$	1
Model VII: the BSA-dependent exponent model		$k_1 = k_0 - \frac{k_{max} \times BSA^{\gamma}}{k_{50}^{\gamma} + BSA^{\gamma}}$	1

θ_{CL}, typical value of clearance; θ_{Vd}, typical value of volume of distribution; MF, factor for maturation; TM_{50}, maturation half-time; γ, Hill coefficient defining the steepness of the sigmoidal curve; k^1, allometric exponent; k_0, the exponent at a theoretical weight of 0 kg , BSA of 0 m^2, or age at 0 years; k_{max}, a maximum decrease of the exponent; k_{50}, the weight, BSA or age when a 50% drop in the maximum decrease of the exponent is achieved.

First-Order Conditional Estimation (FOCE-LB) algorithm was applied in all model runs.

Base Model

Both one- and two-compartment models with first-order elimination were tested to fit the GCV concentration data. The initial structural model was selected on the basis of visual inspection of the data and the values of Akaike information criterion (AIC) and Bayesian information criterion (BIC).

The interindividual variability was modeled for each pharmacokinetic parameter using an exponential model (**Eq. 1**).

$$P_i = \theta \times \exp(\eta_i) \tag{1}$$

where P_i denotes the estimated pharmacokinetic parameter for individual i, θ is the population typical value of the parameter, and η_i denotes the random variable for individual i, which is defined as normally distributed with a mean of 0 and a variance of ω^2.

Additionally, proportional and combined-error models were explored to estimate the residual error variability. The equations were as follows (**Eqs 2–4**).

$$Y = \text{IPRED} + \varepsilon \tag{2}$$

$$Y = \text{IPRED} \times (1 + \varepsilon) \tag{3}$$

$$Y = \text{IPRED} \times (1 + \varepsilon_1) + \varepsilon_2 \tag{4}$$

where Y and IPRED denote the measured concentration and individual prediction, respectively. And ε devotes the residual random error, which is assumed to be Gaussian distributed with a mean of 0 and a variance of σ^2.

Covariate Analysis

Demographic data (gender, age, WT, height, BSA), renal function (BUN, SCR, UA), and hepatic function (TBIL, ALT, AST) were investigated as potential covariates for their influences on the pharmacokinetics of GCV. Besides, kidney function (KF) was also taken into account as a dimensionless parameter, and the value of which was calculated as dividing individual eGFR by the normal renal function (120 mL/min/1.73 m^2). Prior to performing covariate screening, correlation coefficients were calculated for all pair-wize variables, meanwhile highly intercorrelated covariates (correlation coefficient >0.5) were not simultaneously introduced into the model.

Covariates analysis was carried out by means of a stepwise forward inclusion and backward elimination method. And covariates were screened by implementing a likelihood ratio test on the changes in the objective function value (OFV). During the forward selection, a significant reduction in OFV of 3.84 or more ($p < 0.05$) was considered sufficient for inclusion in the base model. This process was repeated until the full model has been constructed. Then, backward elimination was performed to remove covariates from the full model. And an increase in OFV of at least 6.63 ($p < 0.01$) was required to retain the covariate in the final model. Meanwhile, the biological plausibility and clinical significance of the potential covariates were also considered.

Relationships between potential variables and pharmacokinetic parameters were assessed. Power model and exponential model were used to evaluate the continuous covariates and categorical covariates, respectively. Furthermore, to describe differences in body size and the processes of clearance maturation, both WT and BSA were tested using theory-based allometric models. The description of seven candidate models (Model I-VII) were summarized in **Table 1**.

Model Validation

The final model was validated both graphically and statistically by goodness-of-fit plots, nonparametric bootstrap analysis, visual predictive check (VPC), and normalized prediction distribution errors (NPDEs). The goodness-of-fit was evaluated using diagnostic plots, including observed concentrations (DV) vs. population predictions (PRED), DV vs. individual predictions (IPRED), conditional weighted residuals (CWRES) vs.. PRED, and CWRES vs. time. The nonparametric bootstrap approach was utilized to generate 1,000 re-sampled datasets, among which the median

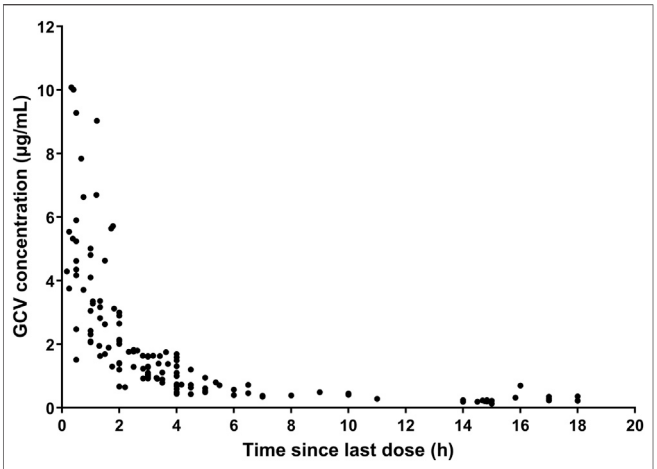

FIGURE 1 | GCV concentrations vs. time.

estimates with 95% confidence intervals (CIs) were further calculated and compared with the final parameter estimates, to assess the precision of the final model. The VPC was performed using 1,000 simulations to assess the predictive performance of the final model. The observations and simulations were then compared by computing the 25th, 50th, and 97.5th percentiles for each. The model was further evaluated using statistical tests and visual inspection of NPDE plots, including quantile-quantile plot, histogram of the NPDE distribution, scatterplots of NPDE vs. PRED and NPDE vs. time after the last dose.

Dosing Simulations

A Monte Carlo simulation with 10,000 iterations was performed to evaluate and optimize the dosing regimens using the pharmacokinetic parameter estimates obtained from the final model. Concentration vs. time profiles of various dosage regimens in patients with different levels of renal function and WT were simulated. Meanwhile, the $AUC_{0\text{-}24}$ values of each simulated patient were also computed. The probability of target attainment (PTA) of an $AUC_{0\text{-}24}$ of ≥40 μg h/ml was subsequently determined. As to the dosage regimen, it was considered acceptable if the PTA is higher than 80%.

Assessment of Adverse Events

Potential adverse effects were closely monitored in the study. Hematological toxicities were evaluated by a comparison of hematological parameters, including neutrophil count, platelet count, lymphocyte count, and hemoglobin concentration, obtained before and after the administration of GCV. Neutropenia, thrombocytopenia, lymphopenia, and anemia were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (National Cancer Institute, 2017). Statistical analyses were carried out using SPSS software Version 19.0 (SPSS Inc.,Chicago, IL, USA).

TABLE 2 | Demographic and physiological characteristics of patients in this study (n = 104).

	Number	Mean ± SD	Median (range)
Patients	104		
Gender (M:F)	54:50		
Age (years)		3.06 ± 2.99	2.46 (0.10–12.83)
WT (kg)		13.7 ± 8.3	12.0 (2.5–55.0)
Height (cm)		90.8 ± 25.3	90.0 (44.0–161.0)
BSA (m^2)		0.58 ± 0.25	0.55 (0.17–1.57)
GCV dose ($mg{\cdot}kg^{-1}{\cdot}d^{-1}$)		9.7 ± 0.7	10.0 (5.6–12.2)
GCV concentration ($\mu g{\bullet}mL^{-1}$)		2.11 ± 2.16	1.39 (0.13–10.08)
Laboratory parameter			
BUN (mmol/L)		3.11 ± 1.18	2.93 (0.77–6.60)
UA (μmol/L)		252.4 ± 89.7	244.3 (86.0–522.0)
SCR (μmol L^{-1})		26.9 ± 8.3	26.0 (12.7–68.4)
eGFR (mL/min/1.73 m^2)		106.96 ± 15.39	110.85 (14.61–129.13)
TBIL (μmol L^{-1})		13.9 ± 21.5	7.5 (2.2–169.7)
ALT (U L^{-1})		62.5 ± 81.1	25.0 (6.0–440.0)
AST (U L^{-1})		68.9 ± 60.6	50.5 (9.0–442.0)

WT, body weight; BSA, body surface area; GCV, ganciclovir; BUN, blood urea nitrogen; UA, uric acid; SCR, serum creatinine concentration; eGFR, estimated glomerular filtration rate; TBIL, total bilirubin concentration; ALT, alanine aminotransferase concentration; AST, aspartate aminotransferase concentration.

RESULT

Patient Characteristics

A total of 104 patients were enrolled in the present study, and 138 measured GCV concentrations (range 0.13–10.08 μg/mL) were obtained from 1–3 samples per patient. No patient was excluded according to the exclusion criteria. The GCV concentration-versus-time profile was showed in **Figure 1**. The study population consisted of 54 male and 50 female patients between 0.10 and 12.83 years old. And the body weights were recorded from 2.5 to 55.0 kg. Among all subjects, 64 (61.5%) of these patients were infants aged 0–3 years, 28 (26.9%) were young children aged 3–6 years, and twelve (11.5%) were old children aged >6 years. According to the criteria described previously, 12 patients were classified as the elevated renal function group, 80 patients as the normal renal function group, and 11 patients as the mild renal insufficiency group, while one patient with severe renal insufficiency was excluded from grouping and subgroup comparison. The demographic and physiological characteristics of patients were summarized in **Table 2**.

PopPK Model Development

In the present study, the two-compartment model yielded a similar OFV as compared to the one-compartment model. In consideration of the results gathered from published papers and the clinical practicality of the model, a one-compartment model with first-order elimination was deemed as an appropriate structural model. And the apparent clearance (CL) and apparent volume of distribution (V_d) was then derived from the PopPK model. The inter-individual variability was optimally described by an exponential model, while the residual variability could be best expressed using a proportional model.

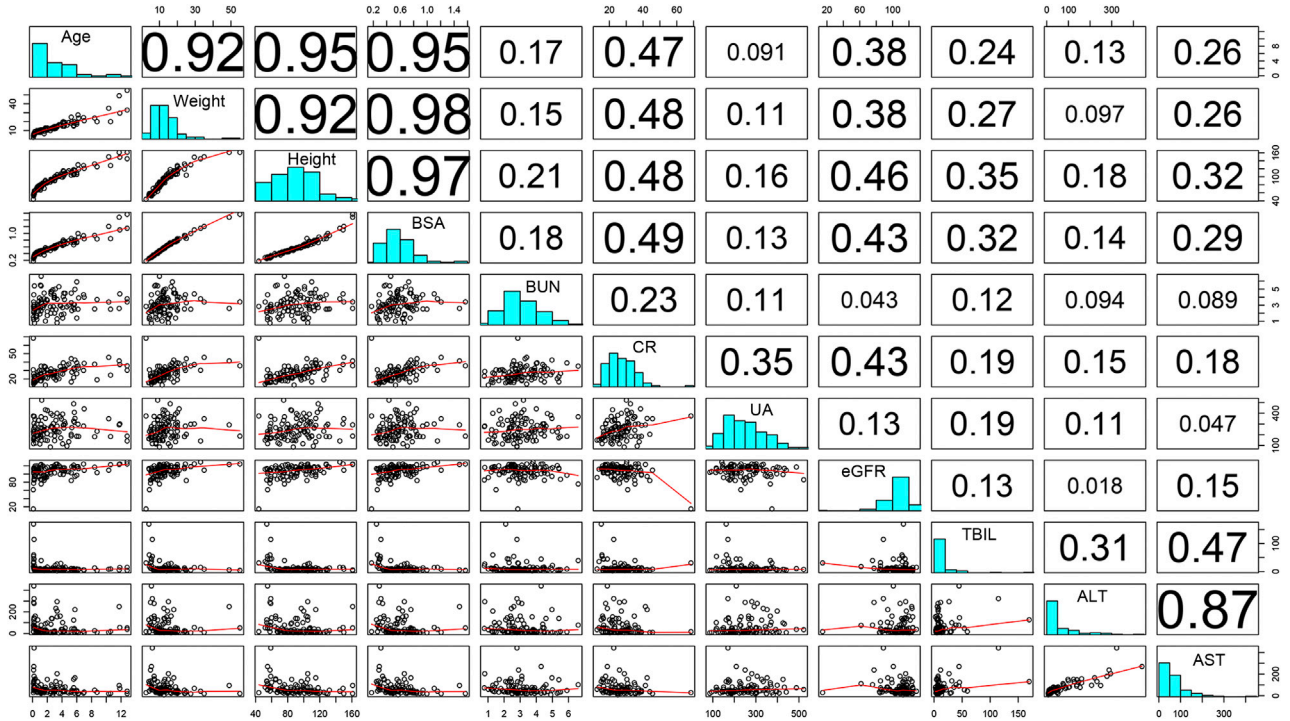

FIGURE 2 | Scatterplot matrix of covariate analysis.

TABLE 3 | Parameter estimates of the seven candidate models for clearance.

Parameters	Model I: the 3/4 allometric model	Model II: the simplest WT-based exponent model	Model III: the simplest BSA-based exponent model	Model IV: the maturation model	Model V: the WT-dependent exponent model	Model VI: the age-dependent exponent model	Model VII: the BSA-dependent exponent model
OFV	**311.74**	**298.25**	**312.02**	**306.98**	**332.86**	**298.85**	**309.25**
AIC	**323.74**	**308.25**	**324.02**	**320.98**	**350.86**	**316.85**	**327.25**
BIC	341.31	322.89	341.58	341.47	377.2	343.19	353.59
θ_{CL} (SE%)	4.68 (5.77)	4.57 (6.21)	4.68 (6.21)	10.05 (7.73)	4.35 (8.62)	5.62 (7.38)	6.53 (10.29)
θ_{Vd} (SE%)	11.18 (8.90)	10.97 (9.11)	10.99 (9.14)	14.05 (9.56)	16.50 (10.15)	13.79 (9.63)	17.79 (10.74)
$MF = 1/[1+(Age/TM_{50})^{-\gamma}]$							
TM_{50} (SE%)	–	–	–	0.90 (26.43)	–	–	–
γ (SE%)	–	–	–	0.08 (31.64)	–	–	–
k_1	0.75	0.79 (11.64)	1.03 (11.39)	–	–	–	–
$k_1 = k_0 - k_{max} \times WT^{\gamma}/(k_{50}^{\gamma} + WT^{\gamma})$ or $k_1 = k_0 - k_{max} \times Age^{\gamma}/(k_{50}^{\gamma} + Age^{\gamma})$ or $k_1 = k_0 - k_{max} \times BSA^{\gamma}/(k_{50}^{\gamma} + BSA^{\gamma})$							
k_0 (SE%)	–	–	–	–	2.18 (25.46)	1.42 (14.62)	1.60 (27.51)
k_{max} (SE%)	–	–	–	–	1.52 (21.27)	0.95 (29.45)	0.38 (30.23)
k_{50} (SE%)	–	–	–	–	4.15 (20.61)	0.35 (39.51)	0.56 (36.61)
γ (SE%)	–	–	–	–	16.97 (44.52)	0.44 (33.09)	1.08 (37.58)

WT, body weight; BSA, body surface area; OFV, objective function value; AIC, Akaike information criterion; BIC, Bayesian information criterion; θ_{CL}, typical value of clearance; θ_{Vd}, typical value of volume of distribution; SE, standard error; MF, factor for maturation; TM_{50}, maturation half-time; γ, Hill coefficient defining the steepness of the sigmoidal curve; k^1, allometric exponent; k_0, the exponent at a theoretical weight of 0 kg , BSA of 0 m^2, or age at 0 years; k_{max}, a maximum decrease of the exponent; k_{50}, the weight, BSA or age when a 50% drop in the maximum decrease of the exponent is achieved.

In **Figure 2**, the resulting matrix of correlation coefficients among the potential covariates is visualized. Under the premise that simultaneous introduction of collinear variables was avoided, the covariates were added to the base model to construct a full model. To account for the influence of developmental changes, WT- or BSA-based allometric models (Model I-VII) for CL were tested, as presented in **Table 3**. Among the candidate models, the simplest WT-

TABLE 4 | Covariate screening and final model development process

Steps	Covariates screening	OFV	ΔOFV	*p* value	Comments
1	None forward inclusion	359.92			Base model
2	CL-WT	301.70	−58.22	<0.01	
3	CL-WT/V_d-WT	293.65	−8.05	<0.01	
4	CL-WT-KF/V_d-WT	285.73	−7.92	<0.01	
5	CL-WT-KF-*ALT*/V_d-WT backward elimination	280.89	−4.84	<0.05	Full model
6	CL-WT-KF/V_d-WT	285.73	4.84	>0.01	Final model

OFV, objective function value; ΔOFV, change of objective function value; CL, apparent oral clearance; V_d, apparent volume of distribution; WT, body weight; KF, kidney function; ALT, alanine aminotransferase concentration.

TABLE 5 | Pharmacokinetic parameter estimates from the final model and bootstrap results.

Parameter	Final model		Bootstrap analysis			Bias[a] (%)
	Estimate	SE (%)	Median estimate	2.5th Percentile	97.5th Percentile	
θ_{Vd} (L)	11.35	9.77	11.26	8.43	14.00	−0.79
θ_{CL} (L·h^{-1})	5.23	6.60	5.17	4.12	5.95	−1.15
θ_1	0.80	19.52	0.79	0.44	1.14	−1.25
θ_2	0.92	21.77	0.97	0.48	1.46	5.43
θ_3	1.02	11.63	0.98	0.58	1.32	−3.92
Inter-individual						
ω_{Vd} (%)	65.78	19.20	63.79	38.31	89.27	−3.03
ω_{CL} (%)	12.90	38.06	13.11	3.30	22.91	1.63
Residual variability						
σ (%)	8.23	23.61	8.37	4.12	13.37	1.70

SE, standard error; θ_{Vd}, typical value of apparent volume of distribution; θ_{CL}, typical value of apparent clearance; θ_1, exponent for WT as covariate for V_d; θ_2, exponent for KF as covariate for CL; θ_3, exponent for WT as covariate for CL; ω_{Vd}, square root of interindividual variance for V_d; ω_{CL}, square root of interindividual variance for CL; σ, residual variability.
[a]Bias = (median estimate from bootstrap analysis—estimate from the final model)/estimate from the final model.

based exponent model (Model II) corresponding to the lowest OFV, AIC, and BIC, respectively, was chosen for further analysis. After the covariate screening procedure, WT and KF were identified as determinant variables for CL, and were also related to significant drops in the OFV of 58.22 points and 7.92 points, respectively. Besides, WT had a notable effect on V_d, which significantly reduced the OFV by 8.05 units. The covariate screening procedure according to the descending order of OFV was detailed in **Table 4**.

The final model for parameter estimation is presented as follows:

$$V_d\,(L) = \theta_{V_d} \times \left(\frac{WT}{12.0}\right)^{\theta_1} \quad (5)$$

$$CL\left(L \cdot h^{-1}\right) = \theta_{CL} \times KF^{\theta_2} \times \left(\frac{WT}{12.0}\right)^{\theta_3} \quad (6)$$

where V_d is the apparent volume of distribution, CL is the apparent oral clearance, WT is body weight, and KF is kidney function.

The pharmacokinetic parameter estimates of the final model are presented in **Table 5**. The typical value of V_d and CL were 11.35 and 5.23 L/h, respectively. The individual Bayesian estimates of CL was 0.40 ± 0.10 L/h/kg. The relationships between significant variables and CL were depicted by the locally weighted scatterplot smoothing (LOWESS) curves (**Figure 3**). Noteworthy, the result of the one-way ANOVA test showed significant differences in CLs among the three groups (p = 0.010, F = 4.804).

Model Evaluation

The Goodness-of-fit plots for the final model showed that the predictions were found to be in acceptable agreement with the observations. The majority of the conditional weighted residuals were between −3 to +3 (**Figure 4**). Furthermore, the values of model estimates were similar to that of bootstrap median estimates with a slight bias of lessing than ±8%. All parameter estimates from the final model were included in 95% CI computed from bootstrap analysis (**Table 5**). The VPC plots showed that most observations were positioned within the 95% CI of the simulations (**Figure 5**), indicating the good prediction performance of the final model. No obvious trend was observed in the scatterplots for NPDE analysis (**Figure 6**). Besides, the p values were 0.122, 0.623, 0.289, and 0.367 obtained from the Wilcoxon signed rank test, the Fisher test for variance, the Shapiro-Wilks test, and the global test, respectively. The results confirmed that the NPDE exhibited homogeneity of variance and also conformed to a normal distribution.

Dosing Simulations

Table 6 and **Figure 7** showed the PTA values of different dosing regimens for patients with various renal function status and WT

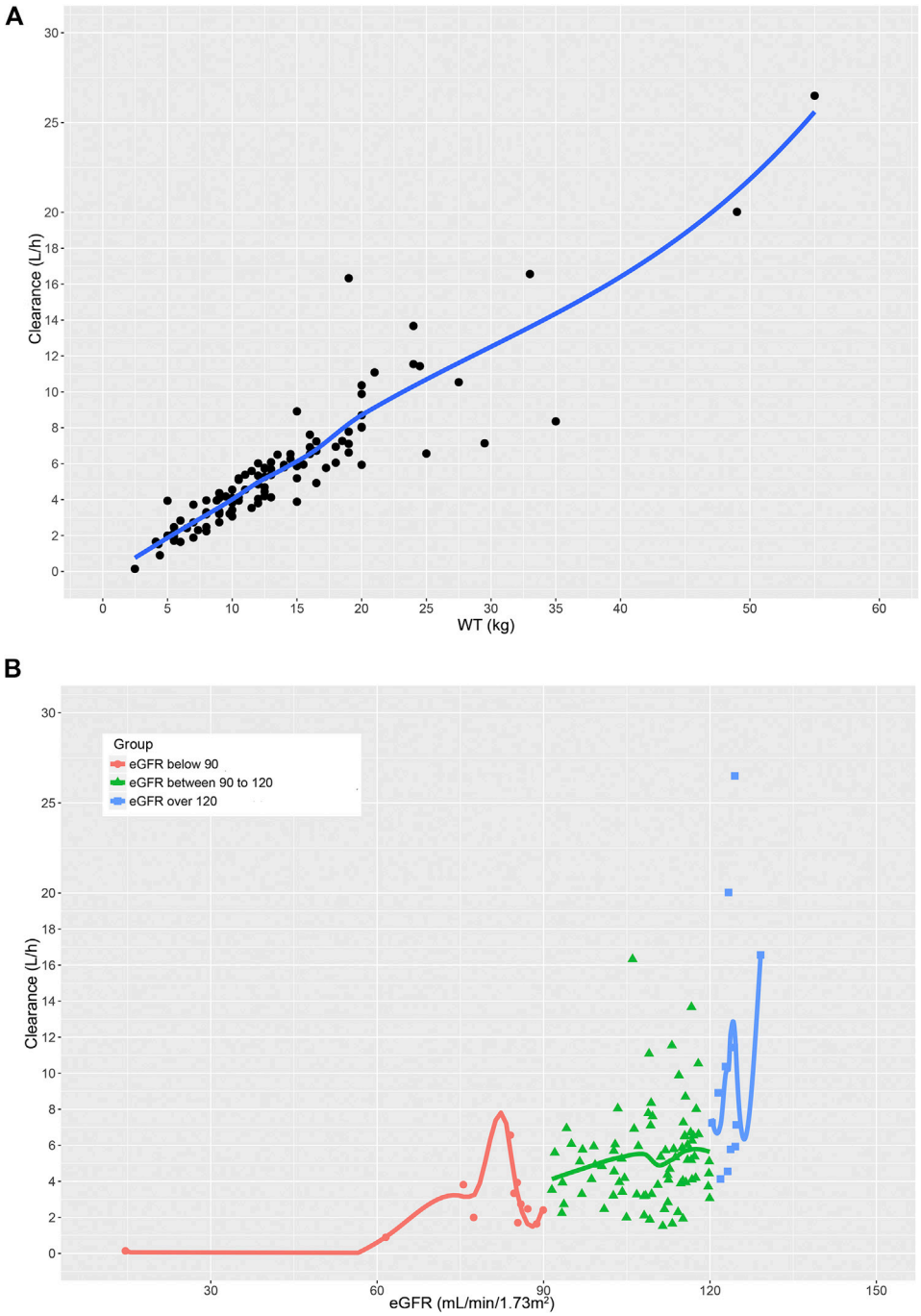

FIGURE 3 | The relationship between **(A)** GCV clearance and WT. **(B)** GCV clearance and eGFR in children with different renal function.

levels. The results of Monte Carlo simulations demonstrated that the current clinical dosage (10 mg/kg/d) was associated with insufficient drug exposure and resulted in pretty low PTA values for patients who weighed more than 5 kg in all renal function groups. When GCV was dosed on a linear WT adjusted basis (mg/kg), dosing regimens of 15.0, 20.0, and 21.0 mg/kg/d provided acceptable PTAs in patients with mild renal insufficiency (83.37%), normal renal function (85.68%), and elevated renal function (82.15%), respectively. On the other hand, when KF was fixed at 0.5, 0.75, 1.0, and 1.25, adequate PTA could be achieved in dosage regimens of 10–10.5, 14.5–15.5, 19.0–20.0, and 23.0–24.5 mg/kg/d, respectively (**Table 7**).

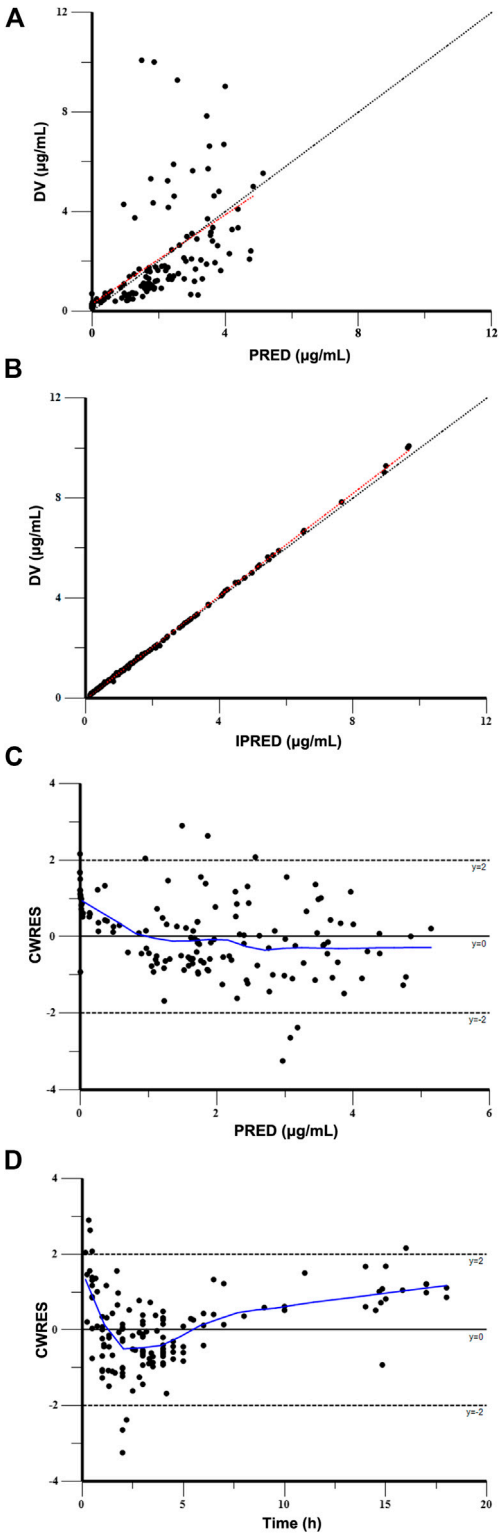

FIGURE 4 | Goodness-of-fit plot for the final model. **(A)** Observed concentrations (DV) vs. population predictions (PRED), **(B)** DV vs. individual predictions (IPRED), **(C)** conditional weighted residuals (CWRES) vs. PRED, and **(D)** CWRES vs. time.

Assessment of Adverse Events

Hematological parameters obtained before and after GCV treatment were summarized in **Table 8**. The mean values of hemoglobin, platelet, and leukocyte did not change after therapy in comparison with the baseline, while only a significant decrease in neutrophil counts was found during GCV treatment ($p < 0.001$). In the current study, 8 cases of grade 2 anemia (7.69%), 2 cases of grade 2–3 lymphopenia (1.92%), and 20 cases of grade 2–4 neutropenia (19.23%) were observed, while no thrombocytopenia was found. Individual values for $AUC_{0\text{-}24}$, trough concentration (C_{min}), peak concentration (C_{max}), and the time above GCV concentration of 0.025–1.5 μg/mL (Tc > 0.025–1.5 μg/mL) were derived using Bayesian method. The relationship between systemic exposure and incidence of neutropenia was analyzed using multivariate logistic regression. Both unadjusted odds ratio (OR) and adjusted OR were estimated. Furthermore, all patients were stratified by different trough concentration levels, and the incidence of neutropenia between groups were compared by Pearson Chi-square tests. The results were shown in **Supplementary Material Tables S1** and **S2**. The *p*-values obtained through statistical analyses implied that the GCV exposure (C_{min}, C_{max}, $AUC_{0\text{-}24}$, Tc > 0.025–1.5 μg/mL) had no significant influence on the occurrence of neutropenia under current dosage regimen (10 mg/kg/d).

DISCUSSION

The majority of the current PopPK studies for GCV was focused on neonates with congenital CMV infection, pediatric and adult solid organ transplant patients. The detailed data on GCV pharmacokinetics in critically ill children was almost blank. Therefore, our study attempted to fill the research gaps concerning the pharmacokinetic profiles and dose individualization of GCV in this population.

In the present study, the disposition kinetics of GCV in critically ill children was adequately described using a one-compartment model with first-order elimination. WT and eGFR were found to have significant effects on GCV clearance. When normalized for WT, the Bayesian estimates of CL (0.40 ± 0.10 L/h/kg) was in line with the one reported in pediatric renal transplant recipients (0.39 ± 0.14 L/h/kg) (Facchin et al., 2019), while slightly higher than the CL reported in neonates with congenital CMV disease (0.287 L/h/kg) (Acosta et al., 2007). This discrepancy may be attributed to physiologic changes in clearance processes that occurred during childhood development.

As shown in the covariate analysis results, both WT and KF were identified as the most influential parameters on CL. It is well recognized that the most obvious difference between children and adults is the body size (Holford et al., 2013), which is generally parameterized by WT or BSA. Our study demonstrated that WT as a primary covariate was superior to

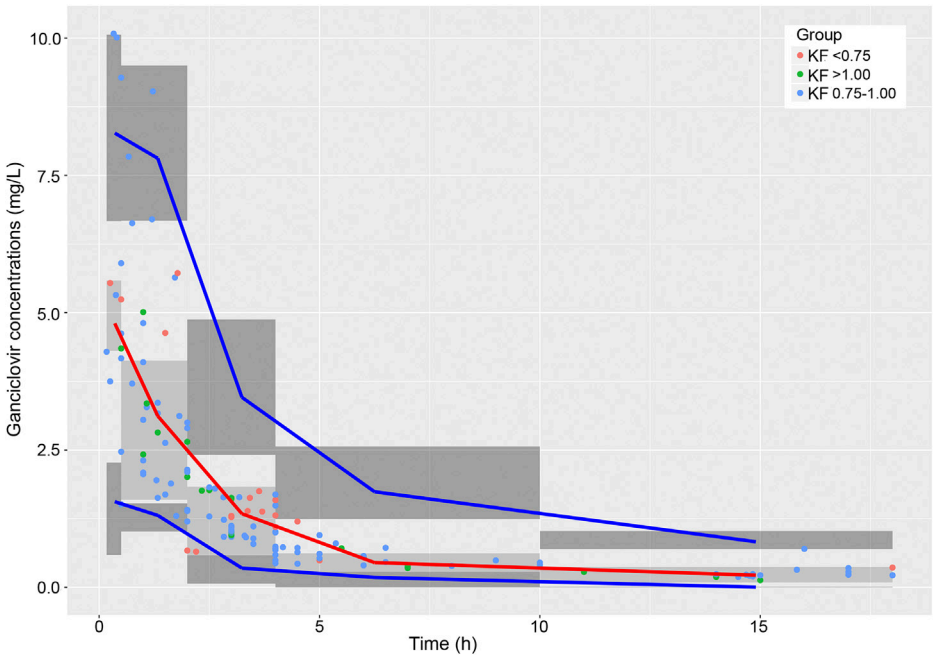

FIGURE 5 | Visual predictive check of the final model. The observed concentrations in patients with different renal functions are shown as red, blue, and green circles. The red line is the 50th percentile of the simulated data, and lower and upper blue lines represent the 2.5th and 97.5th percentiles of the simulated data, respectively. The three shaded areas represent the 95% intervals of the 2.5th, 50th and 97.5th percentiles of the simulated concentrations, respectively.

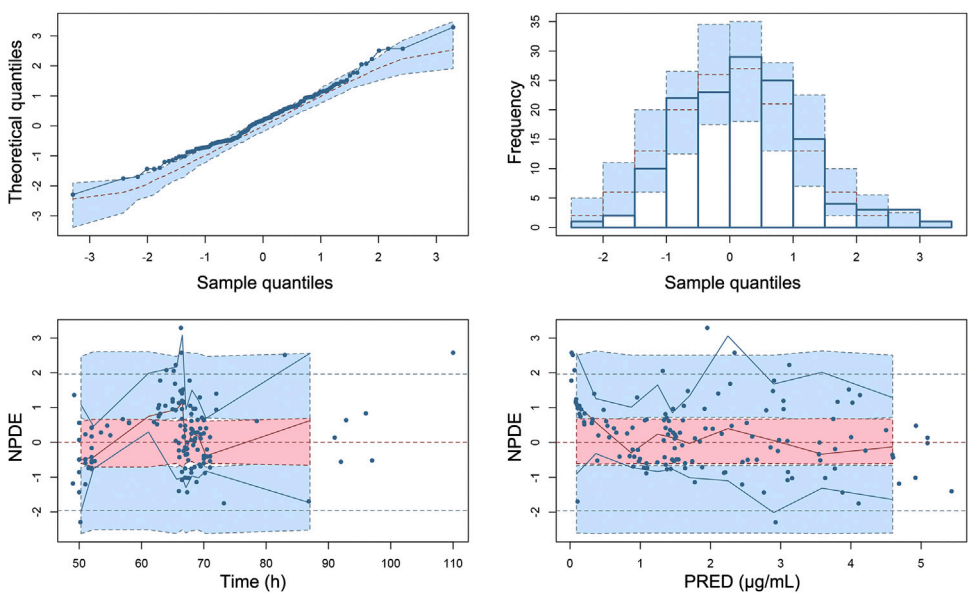

FIGURE 6 | Normalized prediction distribution errors (NPDE) of the final population pharmacokinetic model. **(A)** Quantile–quantile plot of NPDE vs. the expected standard normal distribution, **(B)** histogram of NPDE with the density of the standard normal distribution overlaid, **(C)** Scatterplot of NPDE vs. time, and **(D)** scatterplot of NPDE vs. PRED. Blue dots represent observed concentrations. Red lines show the medians of observed data and blue lines show the 5th and 95th percentiles of observed concentrations. Red or blue shaded areas represent the 95% prediction interval for the respective metric.

BSA when allometric exponent model was used, which was inconsistent with the Jorga et al. (2019). In addition, considering that GCV is a renally excreted antiviral drug with high hydrophilicity, the renal function would significantly alter the clearance capacity of GCV (Tsai et al., 2015). KF and eGFR were determined to reflect the

TABLE 6 | The PTAs of different dosing regimens for patients with varying renal function

Classes of renal function	Dose (mg/kg/d)	AUC_{0-24}		
		Mean (μg·h/ml)	Range	PTA (%)
60–90 mL/min/1.73 m^2 (KF 0.5–0.75)	10.0	32.55	15.11–69.79	11.36
	12.5	40.79	19.91–74.21	50.25
	15.0	48.81	22.76–99.30	83.37
	17.5	56.96	26.91–111.60	96.19
90–120 mL/min/1.73 m^2 (KF 0.75–1.0)	10.0	25.54	10.56–49.18	0.92
	15.0	38.24	16.17–80.18	37.48
	20.0	51.03	24.25–104.71	85.68
	25.0	63.54	26.73–136.86	98.39
> 120 mL/min/1.73 m^2 (KF>1.0)	10.0	22.98	11.62–43.30	0.40
	15.0	34.62	15.96–69.57	19.45
	20.0	46.10	22.27–87.61	74.63
	21.0	48.41	23.36–97.15	82.15
	25.0	57.76	27.98–108.64	96.80

AUC_{0-24}, the area under drug plasma concentration-time curve over 24 h; PTA, the probability of target attainment; KF, kidney function.

renal function and also had an important influence on the prediction of CL. It was evident from the LOWESS curves that WT showed a significant positive correlation with CL, while only a weak positive relationship between eGFR and CL was observed. Intriguingly, although there existed significant differences in CL among the three renal function groups, this statistical significance disappeared after WT-normalization of CL. This could be elucidated by the fact that the number of cases in mild renal insufficiency group and elevated renal function group was small.

Currently, various dosing algorithms for intravenous ganciclovir have been proposed in published researches. And WT, BSA, eGFR or creatinine clearance values were used to compute individual GCV doses (Jorga et al., 2019). According to the result of the covariate analysis, the WT-based algorithm was considered more appropriate than the BSA-based algorithm for dosage regimen design for critically ill pediatric patients. For renally excreted drugs, the recommended standard dose may be inadequate for patients with elevated renal function, which ultimately resulted in therapy failure or drug resistance in this population. After comprehensive consideration, patients in our study were stratified according to different renal function status and WT levels for simulation-based dosage evaluation and optimization. The simulation results suggested that the commonly used dosing regimen (10 mg/kg/d) would lead to underexposure for nearly all patients in three renal function groups. Therefore elevated doses might be required to achieve therapeutic pharmacodynamic targets. Furthermore, WT and renal function based approach could be used to individualize GCV dosing and to promote clinical efficacy.

It was reported that the main adverse effect related to GCV treatment was hematologic toxicity, including which the incidence of neutropenia was the most common (Kimberlin, 2002). Similarily, neutropenia was also demonstrated to be the most common adverse effects in the present study (18.27%). However, we couldn't find definite association between GCV exposure and the incidence of neutropenia when a conventional dose of GCV (10 mg/kg/d) was given. However, the link between exposure to GCV and the occurrence of neutropenia is still controversial (Paya et al., 2004; Wiltshire et al., 2005; Billat et al., 2016). Wiltshire et al. (2005) proposed that higher GCV exposure might result in a tendency to increased neutropenia. In contrast, Billat et al. (2016) found that the decrease in the neutrophil count was associated with intracellular GCV triphosphate exposure rather than plasma GCV level during treatment. In this regard, further studies were needed to obtain more compelling evidence.

There are several limitations in this study. Firstly, external validation could not be implemented due to the small population size. Secondly, a low proportion of patients with renal insufficiency making it difficult to establish a clear link between renal function and pharmacokinetic parameters of GCV. Finally, pharmacokinetic-pharmacodynamic relationship cannot be investigated owing to the lack of clinical data.

CONCLUSION

In summary, a PopPK model for intravenous GCV in children suffered from critical illness had been successfully established and validated. Results showed that only WT and KF were considered to be major determinants of GCV pharmacokinetic parameters. For critically ill pediatric patients, the recommended clinical dosage (10 mg/kg/d) could lead to a high risk of underexposure. And elevated doses might be required to reach target GCV exposure and improve therapeutic effect in this vulnerable population. Futhermore, the model-based simulations also demonstrated that GCV dosing based on WT and renal function was rational. It's worth noting that the association between high-doses GCV and risk of adverse events is still unclear, therefore high doses of GCV should be used with extra attention.

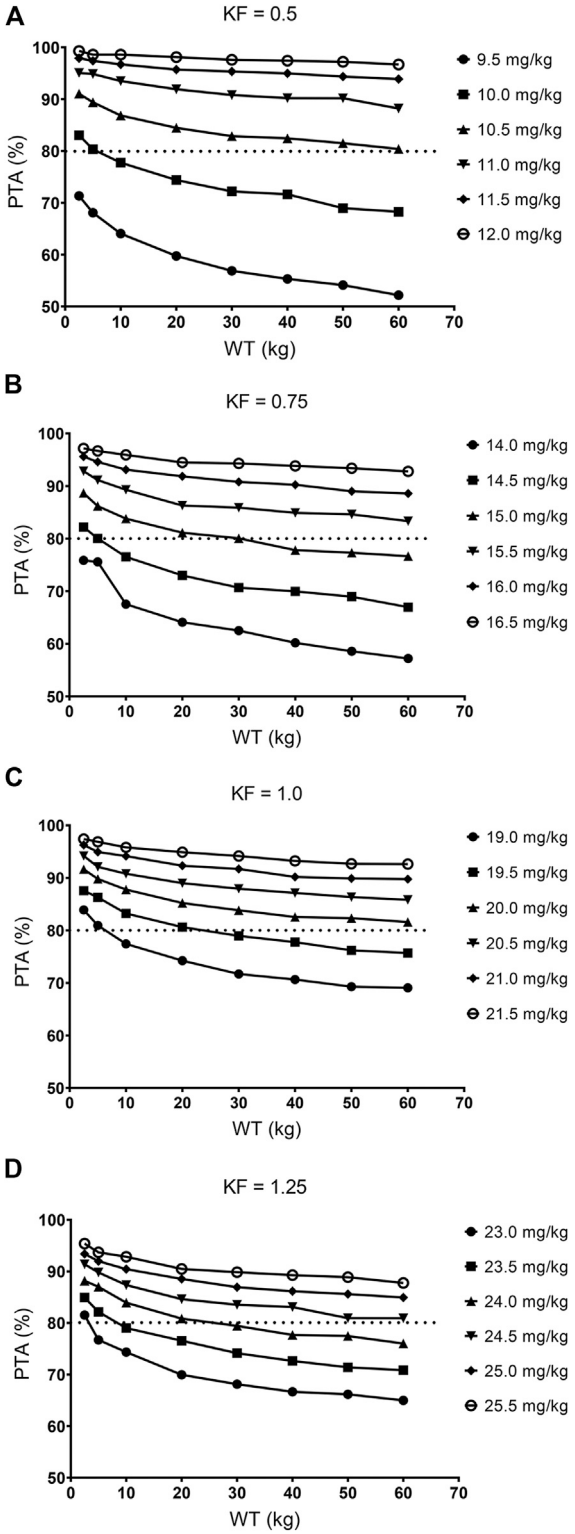

FIGURE 7 | The PTAs of various dosing regimens for patients with different WT levels.

TABLE 7 | Optimal dosage regimens based on simulation.

eGFR or KF	WT (kg)	Dosage regimen (mg/kg/d)
eGFR = 60 mL/min/1.73m^2 or KF = 0.5	2.5	10.0
	5	10.0
	10	10.5
	20	10.5
	30	10.5
	40	10.5
	50	10.5
	60	10.5
eGFR = 90 mL/min/1.73m^2 or KF = 0.75	2.5	14.5
	5	14.5
	10	15.0
	20	15.0
	30	15.0
	40	15.5
	50	15.5
	60	15.5
eGFR = 120 mL/min/1.73m^2 or KF = 1.0	2.5	19.0
	5	19.0
	10	19.5
	20	19.5
	30	20.0
	40	20.0
	50	20.0
	60	20.0
eGFR = 150 mL/min/1.73m^2 or KF = 1.25	2.5	23.0
	5	23.5
	10	24.0
	20	24.0
	30	24.5
	40	24.5
	50	24.5
	60	24.5

eGFR, estimated glomerular filtration rate; KF, kidney function; WT, body weight.

TABLE 8 | Hematological parameters before and after GCV treatment.

	Before GCV treatment	After GCV treatment	*p* value
Hemoglobin (g L^{-1})	109.7 ± 17.0	110.1 ± 14.9	0.815
Platelets (10^9/L)	264.6 ± 132.4	268.1 ± 121.6	0.699
Lymphocytes (10^9/L)	5.00 ± 2.90	4.77 ± 2.74	0.193
Neutrophils (10^9/L)	5.01 ± 4.44	3.13 ± 2.18	<0.001

GCV, ganciclovir.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Wuhan Children's hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SL drafted the manuscript. YW, SW, and HX concepted and supervised the study. SL and YW contributed to the analysis and interpretation of the data. SL and CS contributed to study conduction, data acquisition, and critical revision of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.614164/full#supplementary-material.

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REVIEW
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Model-Informed Precision Dosing of Antibiotics in Pediatric Patients: A Narrative Review

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Optimal pharmacotherapy in pediatric patients with suspected infections requires understanding and integration of relevant data on the antibiotic, bacterial pathogen, and patient characteristics. Because of age-related physiological maturation and non-maturational covariates (e.g., disease state, inflammation, organ failure, co-morbidity, co-medication and extracorporeal systems), antibiotic pharmacokinetics is highly variable in pediatric patients and difficult to predict without using population pharmacokinetics models. The intra- and inter-individual variability can result in under- or overexposure in a significant proportion of patients. Therapeutic drug monitoring typically covers assessment of pharmacokinetics and pharmacodynamics, and concurrent dose adaptation after initial standard dosing and drug concentration analysis. Model-informed precision dosing (MIPD) captures drug, disease, and patient characteristics in modeling approaches and can be used to perform Bayesian forecasting and dose optimization. Incorporating MIPD in the electronic patient record system brings pharmacometrics to the bedside of the patient, with the aim of a consisted and optimal drug exposure. In this narrative review, we evaluated studies assessing optimization of antibiotic pharmacotherapy using MIPD in pediatric populations. Four eligible studies involving amikacin and vancomycin were identified from 418 records. Key articles, independent of year of publication, were also selected to highlight important attributes of MIPD. Although very little research has been conducted until this moment, the available data on vancomycin indicate that MIPD is superior compared to conventional dosing strategies with respect to target attainment. The utility of MIPD in pediatrics needs to be further confirmed in frequently used antibiotic classes, particularly aminoglycosides and beta-lactams.

Keywords: pediatric, neonates, antibiotics, model-informed precision dosing, Bayesian, therapeutic drug monitoring, population PK models

INTRODUCTION

Antibiotics are the most commonly prescribed drugs in children and are potentially life-saving for patients with severe bacterial infections (1–3). Based on a cross-sectional one-day point prevalence survey, more than 35% and 40% of hospitalized children in European and non-European countries, respectively, received antibiotics (4). However, antibiotic dosing in pediatric patients is challenging and often more complex than in adult patients.

Children have different and changing body composition, body size, physiology and body chemistry. Furthermore, there is developmental growth and maturation of organs which may contribute to the variability in the pharmacokinetics/pharmacodynamics (PK/PD) of drugs and treatment outcomes (5, 6). Consequently, age-related differences in absorption, distribution, metabolism and elimination of drugs have been demonstrated in children. For example, the expression and activity of drug-metabolizing iso-enzymes in the liver is yet immature at birth and the rate of maturation has high inter-individual variability (7, 8). This can result in a significant risk of toxicity with some drugs in neonates and infants (9). Additionally, neonates are more vulnerable to life-threatening infectious diseases, due to their immature immune system, diminished humoral response, reduced skin barrier, and low microbial variation in gut microbiota composition (10–12).

In certain pediatric populations with significant intra- and inter-patient variability, such as children with obesity, inflammation, organ failure, critical illness, or other significant co-morbidities and co-medication affecting drug exposure, conventional age or weight-based dosing regimens does not seem to be optimal (13–15). These populations can greatly benefit from individualized dosing. Dosing in pediatric patients, especially antibiotic and anticancer drug treatment, is challenging and can result in supratherapeutic exposure that potentiates undesirable side effects or toxicity (16–18), while subtherapeutic exposure can contribute to treatment failure (19, 20). Moreover, under-exposure of antibiotics may result in further emergence of drug resistance, although this relationship has not been studied in detail. These factors imply that antibiotic dosing in pediatric patients demands a thorough assessment.

In general, conventional dosing regimens of antibiotics are usually based on current body weight, age or nomograms and adjusted for renal function as needed. However, this approach is often not optimal and in some cases even not sufficient to achieve predetermined PK/PD target values (21–23). Besides, dosing recommendation from developed PK models can only address the patient population and characteristics of the cohort that was used for PK model development, thus the extrapolation to different patient characteristics is not possible. For some antibiotics, therapeutic drug monitoring (TDM) is used to optimize pharmacological target attainment and therefore decrease therapeutic failure and toxicity (24). Dose adjustments should be made in an early phase of treatment, since quick and accurate intervention with antibiotics is essential for patients with severe infections. However, a first TDM sample for antibiotics is generally requested if a steady state concentration is reached (meaning after four to five half-lives of the drug), which cannot be considered 'early'. In order to predict those concentrations, population PK (popPK) modeling combined with early TDM sampling, before steady state, is a valuable dosing strategy to optimize antibiotic therapy. This approach includes interpreting drug concentrations along with patient information, such as age, body weight, kidney function, and dose history (25, 26). PopPK modeling combined with TDM typically covers an assessment of PK and concurrent dose adaptation alone. The concept of Model-informed precision dosing (MIPD) involves the use of popPK models and prospective Bayesian forecasting to reduce variability in response. A Bayesian approach delivers a population estimated value for each PK parameter including the variability components, that is, noise (residual error) and variability due to real biological differences between individuals (inter-individual variability), simultaneously.

Workflow of Model-Informed Precision Dosing Implementation

A workflow involving several steps has been proposed to achieve optimal dosing in children employing an MIPD approach (**Figure 1**) (27, 28). Firstly, an appropriate population model, including compartmental PK model, PK/PD model, or physiological-based PK (PB/PK) model, needs to be selected or developed if not available. Model development can be performed using PK/PD modeling software (e.g., NONMEM, WinNonLin, Pmetrics, or MatLab). The selected PK model should fit the population characteristics, such as age group, body composition, disease and comorbidities. Even biomarkers, for instance serum creatinine concentration to predict vancomycin concentrations, may be relevant (29). For several antibiotics, extensive modeling performances have resulted in numerous popPK models over the full pediatric age ranges (30). In contrast, some classes of antibiotics have limited models, or models that only describe a narrow age range (28). Therefore, popPK modeling is a powerful method to study PK in children due to its ability to deal with sparse and time flexible blood sampling, identification of PK variability, and dosing simulations (31). Secondly, model validation is an essential step to be conducted. Internal validation should be performed to diagnose any model misspecifications, and external validation is needed to evaluate model performance in a different cohort of patients with similar characteristics to the one used to develop the model. Although the popPK approach has been around for decades, the benefits are not always obvious to clinicians and therefore translation into clinical practice has been very limited (31). Nevertheless, there are early examples of applying MIPD in the clinical practice for carboplatin and busulfan with significant advantage over dosing strategies to achieve target exposure (32, 33). MIPD software tools are used to optimize dosing in both initial and subsequent treatment regimens combined with TDM (34). The aim is to achieve drug exposure targets in each individual patient as soon as possible, that is, to achieve drug concentration related to minimal inhibitory concentration (MIC) and at the same time avoiding toxicity and side effects. Finally,

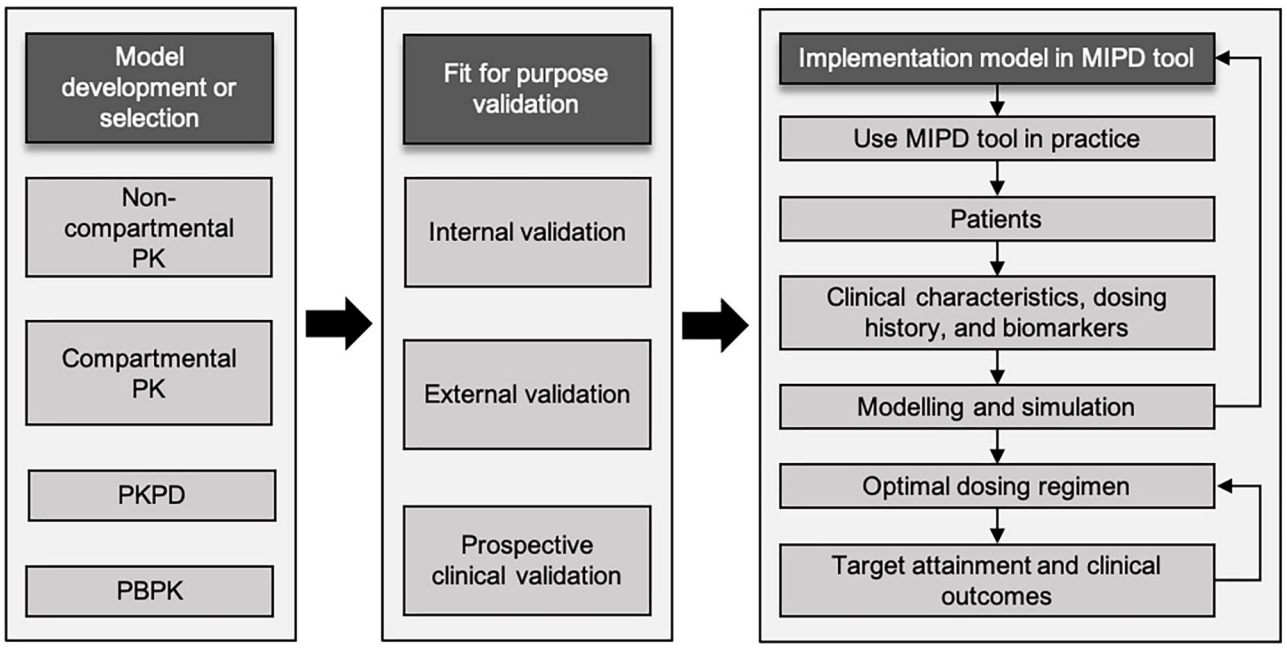

FIGURE 1 | Schematic workflow of model-informed precision dosing implementation. Adapted from Darwich et al. and Keizer et al. (27, 28). MIPD, model-informed precision dosing; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; PK/PD, pharmacokinetic/pharmacodynamics.

all these steps need to be followed to embed a validated popPK model in an MIPD software tool (35). To evaluate the benefits of MIPD approach in clinical practice, prospective clinical validation in the population of interest should be conducted (27).

Model-Informed Precision Dosing Implementation in Clinical Practice

Although numerous MIPD software tools have been developed over the past decades, they have still not been widely integrated into clinical practice (34). MIPD implementation of modeling strategies can be divided into three categories: (1) real-time implementation of MIPD models aligned in healthcare; (2) mechanistic modeling and extrapolation based on prior information on patient characteristics; (3) and model-derived dose banding from covariate analysis of large population studies (27). An overview and description of available MIPD software tools is detailed in **Table 1**. These software tools performed well with respect to all evaluated categories (34). To bring MIPD in the clinical practice, the integration of Electronic Health Record (EHR) and Clinical Decision Support (CDS) is considered as the best approach for clinical adaptation (36). The MIPD approach has been used to optimize dosing in the adult population with significant improvements (37). Likely, MIPD is a promising option to enhance drug efficacy and safety using integration of real-time patient data and it may play an important role in the wider context of precision medicine. In this narrative review, we evaluate studies assessing the clinical utility of antibiotic pharmacotherapy using MIPD in pediatric populations.

METHODS

A literature search was conducted in September 2020 without a restriction of the publication date. Three databases (Medline All Ovid, Embase and Web of Science Core Collection) were searched to assess literature on the clinical utility of MIPD for antibiotics among the pediatric population. Detailed research terms can be found in **Supplementary Table 1**. Only original research articles reporting the clinical utility of MIPD for antibiotics in pediatric patients were eligible for inclusion. **Table 2** shows the inclusion and exclusion criteria.

The references from the database were imported into a reference manager (Endnote X9®) and a published inclusion strategy was used (38). Titles and abstracts were screened independently by two reviewers (AA and AE). Disagreements were resolved by means of consensus. Relevant studies identified from references of our included articles. Even though review and expert opinion articles were excluded, the reference lists of these records were also checked. We extracted the following data: author, year of publication, study antibiotic, number of participants, age category, PK model reference, and outcome measurements, from each study included in the narrative review.

RESULTS

Search Results and Selection of Articles

Figure 2 shows the flowchart of the selection process of this review. The initial search through databases resulted in 418 records. After removing duplicates, followed by screening titles and abstracts, 23 articles were eligible as full text assessment.

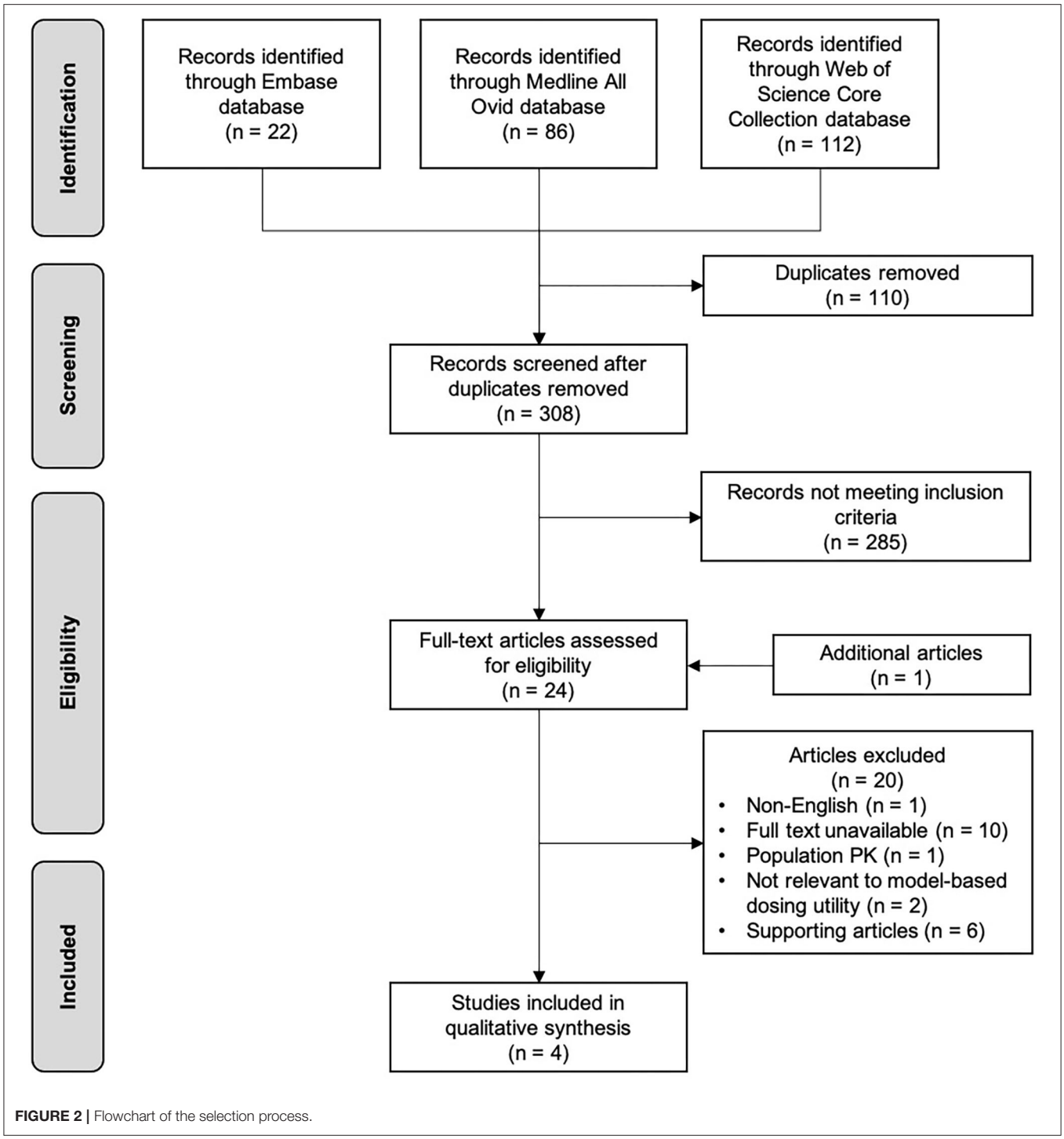

FIGURE 2 | Flowchart of the selection process.

One additional study was identified from reference list checking. A total of four studies were included in this narrative review (39–42), and six studies on this topic that did not meet the inclusion criteria were used to support the concept of MIPD (43–48). **Table 3** shows the characteristics of the four included studies. Studies were reviewed in chronological order of the year of publication concerning evolving knowledge of MIPD.

Utility Studies of Model-Informed Precision Dosing in Pediatric Patients

Smits et al. (39) is the only study included in this review which investigated MIPD of amikacin, the other included studies all evaluated vancomycin. They conducted a prospective evaluation of a model-based amikacin dosing regimen in 579 neonates with postnatal age of 1–30 days. This dosing regimen was based on

TABLE 1 | Descriptive characteristics of the model-informed precision dosing software tools.

MIPD software tools	Company/Institution	User platform	Purpose of use	Mathematical software	EHR-integrated	Overall performance (%)*
Autokinetics	Departments of intensive care medicine of Amsterdam UMC	Desktop, web-based	Research and clinical	NONMEM®, R®	Yes	68
Bestdose	Laboratory of Applied Pharmacokinetics and Bioinformatics, Children's Hospital Los Angeles	Desktop, Web-based	Research	-	No	54
DoseMeRx	DoseMe (Tabula Rasa HealthCare Company)	Web-based, android and iOS	Research and clinical	GNU Scientific Library	Yes	78
ID-ODS	Optimum Dosing Strategies	Web-based, android and iOS	Clinical	Matlab®	No	74
InsightRX Nova	Insight Rx Inc.	Web-based	Research and clinical	NONMEM®	Yes	83
MwPharm++	Mediware a.s.	Desktop, Web-based, Android, iOS	Research and clinical	-	Yes	82
NextDose	University of Auckland	Web-based	Research and clinical	-	No	66
PrecisePK	Healthware Inc.	Desktop, Web-based	Research and clinical	-	Yes	77
TDMx	Institute of Pharmacy, University of Hamburg	Web-based	Research and clinical	NONMEM®	No	56
Tucuxi	School of Engineering and Management Vaud	Desktop	Clinical	NONMEM®	Yes	57

Data adapted from Kantasiripitak et al. (34).

**These software tools were evaluated based on eight considered criteria, including user-friendliness and utilization, user support, computational aspects, population models, quality and validation, output generation, privacy, data security, and costs.*

HER, electronic health record; MIPD, model-informed precision dosing; NONMEM, non-linear mixed effects model.

several covariates, including current body weight and postnatal age. Based on a popPK model (46), a simplified version of the model-based dosing regimen was applied. To evaluate the simplified age groups and dosing intervals, the percentage of desired early trough concentration (before second dose) and peak concentrations (after second dose) was considered as the main outcome measurement. The predefined targets for neonatal population were trough concentrations of 1.5–3 mg/L and peak concentrations of >24 mg/L. The simplified model-based dosing regimen resulted in better amikacin exposure, 90.5% of the observed early peak levels reached the predefined of target of >24 mg/L. Moreover, 60.2% of the trough levels were <3 mg/L. Only 6.6% of first trough concentrations were >5 mg/L. Target concentration attainment at steady state was demonstrated using Monte Carlo simulation. In almost all patients without ibuprofen co-administration the simulations resulted in adequate trough concentrations. The prospective evaluation of the model-based neonatal amikacin dosing regimen resulted in better peak and trough concentrations in almost all patients than the previously developed population PK model. Furthermore, adapted dosing was proposed for patient subgroups with suboptimal trough levels. Moreover, since about half of the neonates with a postnatal age <14 days and body weight of >2,000 g had the first trough levels already within 3–5 mg/L, the authors suggested an interval prolongation of 6 h. This result also indicated that MIPD enables further improvement of drug dosing regimens in neonates.

Similarly, Leroux et al. (40) conducted a prospective clinical trial to evaluate the clinical utility and safety of MIPD of vancomycin dosing in 190 neonates. They developed an Excel® dosing calculator using a previously published population PK model (49). Covariates that were inserted to calculate tailored dosing included birth weight, current body weight, postnatal age (PNA), and serum creatinine concentration measured within 48 h after vancomycin treatment. The percentage of patients who attained the target trough concentrations (15–25 mg/L) was defined as the outcome measurement. Early TDM samples taken 6 to 24 h following the initiation of the vancomycin treatment were used. Furthermore, the authors compared the target attainment using MIPD to a standard dosing regimen based on their previous work (49). The target attainment to the trough range of 15–25 mg/L was 41% when the standard regimen was used, while the target attainment rate when using MIPD increased to 72%. In addition, the safety outcome during vancomycin therapy was nephrotoxicity, defined as either a two-fold increase or an increase by at least 0.6 mg/dL of serum creatinine concentrations from the start and any time until the end of therapy. Of the 190 neonates receiving the MIPD of vancomycin, only 2 (1.1 %) patients developed nephrotoxicity

TABLE 2 | In- and exclusion criteria used to select relevant articles.

Inclusion criteria	Exclusion criteria
• The study was performed in neonates, children, or adolescents aged up to 18 years or included both children and adults • The study included the clinical use of model-based/informed precision dosing (MBPD/MIPD) for antibiotics • Outcome measures are reported, that is, target attainment	• Pre-clinical or non-human studies • Modeling and simulation-only studies • Non-English articles • Conference papers and abstracts

compared to 8.7% (6 of 69) of neonates receiving standard dose in the previous study (53). The elevated serum creatinine in these two patients was considered not related to vancomycin therapy. This study clearly demonstrated the potential of MIPD to increase the efficacy and safety of vancomycin dosing in neonatal routine care.

A retrospective evaluation of vancomycin MIPD was performed by Frymoyer et al. (41). They investigated the Neo-Vanco, which was designed to personalize empiric vancomycin dosing in neonates based on post menstrual age (PMA), weight and serum creatinine levels as covariates, and externally validated (50, 51). Neo-Vanco was compared to commonly used dosing guidelines, including Neofax, Red Book, and Lexicomp. The outcome measurements in their study were the probability of attaining a 24-h area under the curve/minimum inhibitory concentration ratio (AUC_{24h}/MIC) of >400, and trough concentrations of 5–20 mg/L at steady state. The percentage of neonates predicted to achieve an AUC_{24h}/MIC of >400 target was 94% with Neo-Vanco, 18% with Neofax, 23% with Red Book, and 55% with Lexicomp (all P <0.0001 vs. Neo-Vanco). Furthermore, a trough concentration of <5 mg/L was observed infrequently in neonates for whom Neo-Vanco was used, whereas a trough concentration of <5 mg/L was predicted to occur more often with the other dosing strategies (all $P < 0.0001$ vs. Neo-Vanco). Extremely high trough concentrations of >20 mg/L occurred only in 2.8% of neonates with Neo-Vanco this was similar across the dosing approaches (Neofax 1.0% ($P = 0.030$), Red Book 2.6% ($P = 0.99$), and Lexicomp 4.1% ($P = 0.27$). Overall, results indicate that target exposure levels were attained more consistently with Neo-Vanco. Additionally, this model-based dosing approach allows the incorporation of drug-concentration data and can be used to support AUC_{24h}/MIC predictions and dose adjustments.

The third MIPD of vancomycin study was performed by Hughes et al. who conducted retrospective evaluation based on simulations (42). In this study, in 144 children aged 1–18 years a clinical decision support (CDS) dose-optimizing software program was compared with clinician judgement in individualizing vancomycin dosing regimens. InsightRX, a website platform and CDS tool, was used in this study. The aims were to integrate PK/PD models with Bayesian forecasting of drug concentrations, and to evaluate personalized dosing. A previously published population PK model was used for model fitting and simulations of concentration-time profiles (52). Depending on serum creatinine, age and current body weight, the model-based dosing was determined. Similar to the study of Frymoyer et al. (41), the primary outcome measurement was the number of steady-state trough concentrations within the target range. Target trough concentration range at steady state was defined 10–15 mg/L. The secondary outcome was predicted attainment of AUC_{24h} ≥400 mg*h/L. Their findings showed that 70.8% (102/144) of children with CDS-guided vancomycin attained the trough concentration target ranges, whereas only 37.5% (54/144) of children in the clinician-guided arm attained target ranges. Additionally, targeted AUC_{24h} was achieved in 93% (112/121) of occasions in the CDS-guided arm compared to 72% in the clinician-guided arm. Hughes et al. concluded that Bayesian software in a CDS tool improves the accuracy of PK attainment in individual pediatric patients. They argued that lower target attainment in the clinician-guided arm might be due to the hesitation of clinicians to recommend an adjusted dose above a certain amount, even when data would indicate that these changes are warranted.

Supporting Studies With Simulations Studies to Optimize Dosing Regimens in Pediatric Patients

Several studies developed popPK models of aminoglycosides (amikacin, gentamicin and tobramycin) and vancomycin for a pediatric population, and performed model-based simulations to evaluate and compare dosing guidelines with respect to target concentration attainment (43–45). After applying a PK model in their population, Dao et al. suggested that vancomycin dosing strategy should be based on the combination of gestational age, postnatal/-menstrual age and serum creatinine concentration, since these covariates are associate with body composition, volume of distribution and renal function (43). A study by Mehrotra et al. reported that Monte Carlo vancomycin dosing simulations based on serum creatinine concentration have a greater likelihood of achieving trough target concentrations compared to four common dosing regimens n preterm and term neonates (44). External validation of model-based dosing for vancomycin, gentamicin and tobramycin resulted in a significant number (14.7–66.1%) of patients that attained sub- and supratherapeutic drug levels in critically ill children and neonates. This high interindividual variability might be associated with the incapability of the PK model to identify the source of variability (45). Based on these findings, the authors highlighted the necessity of external and real-world validation of guideline changes. Explaining the large intra- and inter-individual variability should be the main focus in future research to enhance drug exposure in critically ill children.

A popPK model of amikacin was developed by de Cock et al., and was used to evaluate current amikacin dosing regimens as suggested in textbooks at that time (2012) (46). This analysis illustrated that these dosing regimens commonly resulted in too high trough levels, associated with risk of toxicity. Consequently, a new model-based dosing regimen was evolved based on current body weight and PNA, and simulated in three

TABLE 3 | Characteristics of included studies investigating the utility of model-based precision dosing for antibiotics in children.

First author, year	Study Antibiotic	Number of patients	PK model reference	Covariates	Comparison	MIPD category*	Main outcome measurement	Other outcome measurements	Most superior dosing strategy
Smits et al. (39)	Amikacin	579 neonates (1–30 days)	(46)	Current body weight, PNA	MIPD vs. population PK model	3	Early trough and peak level attainment	Toxic trough level attainment	MIPD
Leroux et al. (40)	Vancomycin	190 neonates	(49)	Current body weight, birthweight, PNA, sCr	MIPD vs. standard regimen	1	Early trough and peak level attainment	Nephrotoxicity	MIPD
Frymoyer et al. (41)	Vancomycin	492 term and preterm neonates	(50, 51)	PMA, current body weight, sCr	MIPD (Neo-Vanco) vs. Neofax, Red Book and Lexicomp	1	AUC_{24h}/MIC and trough level attainment at steady state	Toxic trough level attainment	MIPD
Hughes et al. (42)	Vancomycin	144 children (1–18 years)	(52)	Age, sCr, body weight	MIPD vs. clinician judgement-guided dosing	1	Trough level attainment at steady state	AUC_{24h} attainment	MIPD

**These categories refer MIPD implementation strategies: 1 = real-time implementation of MIPD models aligned in healthcare; 2 = mechanistic modeling and extrapolation based on prior information on patient characteristics; 3 = and model-derived dose banding from covariate analysis of large population studies.*
AUC_{24h}, the area under the concentration-time curve from 0 to 24 h; MIC, minimum inhibitory concentration; MIPD, model-informed precision dosing; PK, pharmacokinetic; PNA, post-natal age; PMA, post-menstrual age; sCr, serum creatinine.

typical patients. Findings showed that the model-based approach using birthweight and PNA was superior compared to guideline dosing regimens because it well-predicted amikacin clearance in neonates. Gonzalez et al. developed a population PK model in children to optimize clindamycin dosing in children (48). The relationship between PMA and clearance indicated that clindamycin dosing in neonates should be PMA based. Savic et al. used a modeling approach and simulations to evaluate rifampicin and levofloxacin dosing in order to attain target exposures (47). This study showed that higher rifampicin and levofloxacin dosages were required to reach target drug exposure.

Model-Based Precision Dosing Implementation for Other Drugs in Pediatrics

Besides antibiotics, the improved outcomes as a result of MIPD implementation in pediatric populations had also been reported for other drugs, for example, sirolimus, fludarabine, doxapram, busulfan, morphine, carboplatin, or methotrexate (54–61). Mizuno et al. suggested that developed model-based dosing strategy could be utilized to explain the sirolimus exposure-response and clinical outcome relationships among pediatric population from neonates to adolescents (54). In a study of fludarabine, individualized MIPD most likely resulted in reduced morbidity-mortality and minimized toxicity in children (55). Additionally, model-based exposure which was integrated with the effect monitoring of drug therapy could improve doxapram treatment in pre-term infants (57). Furthermore, MIPD of busulfan combined with TDM utilizing a Bayesian prediction provides a considerable benefit compared to conventional guidelines for the attainment of target exposure in children receiving hematopoietic cell transplantation (HCT) (58). Morphine doses based on popPK model prevent over-dosing in infants with a PNA $\geq$10 days (60). Furthermore, model-informed Bayesian estimation was also compared to PK models alone and led to better morphine exposure in critically ill neonates and infants (61). In addition, population PK model of methotrexate was integrated into CDS tool which can be utilized to evaluate high exposure of methotrexate. Subsequently, this tool is able to inform the use of glucarpidase to reduce methotrexate plasma concentration (62).

In addition to pediatric populations, few studies also investigated MIPD in adults. Andersson et al. showed a significant benefit of busulfan TDM with MIPD over standard adult dosing in patients undergoing allogeneic HCT (56). Patients in the group with MIPD-guided dosing had a progression-free survival of 69.9%, compared to 11.2% in their fixed-dose counterparts (56). According to van Beek et al. TDM combined with MIPD of rifampicin is preferable to improve tuberculosis treatment compared to the linear regression strategy (37). Similarly, MIPD of warfarin in patients with heart valve enhanced the predictive performance of the maintenance dose of warfarin (63). Keutzer and Simonsson proposed that MIPD with PK information from minimally two drug concentrations can be applied to predict the optimal individual dose considering inter-occasion variability (64). In breast cancer patients treated with tamoxifen, MIPD was also considered as the more favorable strategy for attaining target concentrations than standard tamoxifen dosing (65).

DISCUSSION

While MIPD has the potential to improve the precision of antibiotic dosing in pediatric patients, the wide integration of

MIPD for antibiotics in children into clinical practice is still scarce. The studies that we found are limited to vancomycin and amikacin. Based on the included studies, MIPD resulted in a better antibiotic exposure in children than the conventionally used dosing regimens. The improved target attainment might lead to enhanced efficacy and minimized toxicity. However, in none of the studies clinical outcomes and cost effectiveness were investigated.

MIPD is mainly used for drugs where adequate exposure at the start of therapy is critical and cannot be controlled by easy-to-measure clinical parameters (e.g., blood pressure or heart rate). Personalized dosing at the start of the treatment is crucial for effective antibiotic therapy. Therefore, MIPD in combination with TDM is desirable, so that optimal exposure is obtained both from the start and during treatment.

Three of the four eligible studies involved MIPD of vancomycin and one study amikacin. Several reasons may explain why research has been done mainly on vancomycin and less or not at all with other antibiotics. Firstly, vancomycin is well-studied because it is a first-line antibiotic to treat methicillin-resistant Staphylococcus aureus (MRSA) (66). Secondly, vancomycin has a narrow therapeutic index (67–69). Hence, guiding vancomycin dose with TDM is recommended in order to minimize the risk of nephrotoxicity and to guarantee successful therapeutic outcomes (70). Furthermore, vancomycin exposure is well-correlated with its response and toxicity, and these correlations are best predicted by the AUC_{24h}/MIC ratio (71, 72). AUC_{24h} can be calculated using Bayesian estimations and cannot directly be translated from drug concentrations. Hughes et al. (42) and Leroux et al. (40) used trough concentration as the main outcome measurement, because it was the institutional target at the time of the study. Although current consensus guidelines recommend measuring trough vancomycin concentrations as a surrogate for the AUC_{24h}, an AUC_{24h} estimation or Bayesian methods is superior, and therefore should be preferred in the MIPD approach.

For other commonly used antibiotic classes, such as aminoglycoside and beta-lactams, also can benefit from the utility of MIPD in children. Especially with aminoglycoside adequate dosing is necessary, given the toxic effects such as reversible nephrotoxicity and permanent ototoxicity (73, 74). A study by van Lent-Evers et al. suggested that model-based and TDM guided aminoglycosides dosing compared to non-guided TDM patients led to higher efficacy, shorter hospitalization and reduced nephrotoxicity (75). Accurate dosing of beta-lactams is also crucial for which MIPD could improve outcome, as these antibiotics are the cornerstone of anti-infective therapy in the critically ill patients. However, the majority of PK/PD and popPK model studies focus on agents where TDM is applied (30). Therefore, as expected, no MIPD studies of beta-lactams were performed as there is limited access to beta-lactam TDM services. Moreover, commonly used chromatographic methods are potential barriers to broad implementation in comparison with drugs easily quantifiable using immunoassay. Furthermore, PK and PD of these antibiotics in critically ill neonates and pediatric patients are poorly explored and sparse studies suggest that current dosing is frequently inadequate (30). There is a need to characterize population PK of commonly used beta-lactams in children, and patient characteristics associated with target attainment, in order to develop evidence-based dosing regimens. Additionally, the correlation between metabolism enzymes (genetic polymorphisms, drug-enzyme interaction) and other organ function parameters (e.g., CRP, IL6, biomarkers of renal clearance) should be explored as these parameters give the best description/reflection of the physical condition of critically ill children (15). This knowledge is essential for implementing MIPD to optimize exposure and improve clinical outcome in pediatric patients.

In the past decade, notable efforts have been put into the development of user-friendly, high-quality and highly-secured MIPD software tools (34). Another interesting development is the significant increase in the number of MIPD software tools with EHR integration capability to minimize data-entry burden (34). Frymoyer et al. (41) used a web-based dosing tool and Hughes et al. (42) integrated model-based dosing with a CDS tool and additional software to individualize dosing. Additionally, gentamicin model-based dosing in neonates and infants (neoGent) utilized a freely available MIPD tool which aids gentamicin TDM (76). The integration of a MIPD tool within the EHR can facilitate the adoption of precision dosing in routine clinical care (77). Kantasiripitak et al. evaluated 10 MIPD software tools and they concluded that improvements should still be made concerning EHR integration, standardization of software and model validation strategies, and prospective evidence for the software tools' clinical and cost benefits (34). AutoKinetics is one example of these tools and its functionality has been successfully expanded and adjusted for real time model informed precision antibiotic dosing at the bedside of critically ill patients (78).

The implementation of MIPD in routine practice can be challenging because it is involving patient's information, such as current characteristics, clinical data, and prior information on physiology to inform systems parameters. If data on one or several important parameters are missing for an individual patient, this will impair the translation by the model and deliver an adequate personalized dosing recommendation. In addition, routine genotypic testing and metabolic markers are rarely utilized to add information supporting individualized dosing (27). Yet, pharmacogenetics information can be incorporated with PK/PD model and TDM to bring MIPD at the bedside (79). To fully exploit the potential benefits of MIPD, the tools must be implemented in an easy-to-use framework for the team of healthcare providers. Importantly, the role of clinical pharmacists is considered as a success factor to implement MIPD (77). As suggested by Keizer et al., the struggles of MIPD from bench-to-bedside involves the many workflow steps as described in **Figure 1** (28). In order to fully deploy MIPD in clinical practice, engaged clinicians as partners in implementing MIPD is essential for the development of intuitive tools for non-modelers (27). Furthermore, education and training for healthcare professionals are greatly needed to improve the comprehension about MIPD. Specifically, clinical pharmacists or pharmacologists have responsibilities to associate the link

between PK/PD, pharmacometrics, system pharmacology, and clinical practice.

The MIPD approach is not an end in itself, but rather a tool or guide toward individualized medicine. It is associated with certain criteria that should be fulfilled, such as the existence of a well-defined concentration target and adequate allometric scaling methods, as the allometric approach explains only part of the variability in clearance (27). Furthermore, the sources of variability (e.g., age, organ failure, body weight, co-morbidity, or co-medication) in both the PK/PD target and MIC should be considered when using MIPD to assess target exposure. The use of a measured MIC obtained by a single MIC determination is debatable, since routine clinical laboratories cannot determine MICs with sufficient accuracy due to the inherent assay variation in the MIC test and the variation in any MIC determination (80). The epidemiological cut-off (ECOFF) of the presumed pathogens, can be used since the MIC is often unknown at the start of therapy. Although the ECOFF is in many situations similar to the clinical breakpoint, it is still important to closely evaluate the PK/PD target against the local drug resistance epidemiology.

Ultimately, the goal for MIPD is a bedside dashboard tool to determine adequate dosing at the start and during the treatment. This also includes real-time monitoring of disease progression and generating alerts for collecting PD data or covariates that are relevant. This can be of great additional value for treatment of vulnerable pediatric populations, where the clinical stakes are high for the treatment outcome and safety. Beside the need for widely developing and implementing MIPD tools at the point-of-care, it is also important to evaluate its clinical feasibility, efficacy and cost effectiveness. To do this, we still have to wait for results from randomized controlled trials investigating whether early MIPD in combination with TDM is superior to standard drug dosing strategies (81).

CONCLUSION

This narrative review presents the current reported evidence for the clinical utility of MIPD of antibiotics in pediatric patients. The MIPD-approach poses a valid tool to predict future individual antibiotic exposure by means of Bayesian forecasting. We found only three studies of vancomycin and one study of amikacin concerning MIPD in children. Even though, those studies demonstrated that MIPD was superior compared to conventional dosing strategies with respect to the target attainment, the clinical utility of MIPD needs to be further confirmed for antibiotics, particularly aminoglycosides and beta-lactams.

AUTHOR CONTRIBUTIONS

AA and BK: conception and design. AA and AE: analysis, interpretation of the data, and wrote the first draft of the manuscript. All authors contributed to subsequent drafts and gave final approval of the version to be published.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Simplified Dosing Regimens for Gentamicin in Neonatal Sepsis

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Background: The effectiveness of antibiotics for the treatment of severe bacterial infections in newborns in resource-limited settings has been determined by empirical evidence. However, such an approach does not warrant optimal exposure to antibiotic agents, which are known to show different disposition characteristics in this population. Here we evaluate the rationale for a simplified regimen of gentamicin taking into account the effect of body size and organ maturation on pharmacokinetics. The analysis is supported by efficacy data from a series of clinical trials in this population.

Methods: A previously published pharmacokinetic model was used to simulate gentamicin concentration vs. time profiles in a virtual cohort of neonates. Model predictive performance was assessed by supplementary external validation procedures using therapeutic drug monitoring data collected in neonates and young infants with or without sepsis. Subsequently, clinical trial simulations were performed to characterize the exposure to intra-muscular gentamicin after a q.d. regimen. The selection of a simplified regimen was based on peak and trough drug levels during the course of treatment.

Results: In contrast to current World Health Organization guidelines, which recommend gentamicin doses between 5 and 7.5 mg/kg, our analysis shows that gentamicin can be used as a fixed dose regimen according to three weight-bands: 10 mg for patients with body weight <2.5 kg, 16 mg for patients with body weight between 2.5 and 4 kg, and 30 mg for those with body weight >4 kg.

Conclusion: The choice of the dose of an antibiotic must be supported by a strong scientific rationale, taking into account the differences in drug disposition in the target patient population. Our analysis reveals that a simplified regimen is feasible and could be used in resource-limited settings for the treatment of sepsis in neonates and young infants with sepsis aged 0–59 days.

Keywords: gentamicin, neonatal sepsis, pharmacokinetics, modeling and simulation, dosing optimization, bacterial infection, resource-limited and remote setting

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INTRODUCTION

Bacterial infections persist as a global health problem (UNICEF, 2018). Children mortality remains exceptionally high during the first month of life, with more than 99% of neonatal deaths occurring in developing countries. Moreover, a quarter of these deaths are attributed to neonatal sepsis (Liu et al., 2012; Chan et al., 2013; Lawn et al., 2014). The recommended initial empirical therapy for a neonate with suspected bacterial sepsis and/or meningitis includes ampicillin and an aminoglycoside (Zaidi et al., 2011; Polin et al., 2012; World Health Organization, 2015; Seale et al., 2015). This combination expands the antimicrobial spectrum and can be prescribed at a considerably low cost (Lee et al., 2014). However, despite the availability of clinical guidelines and recommendations for the treatment of serious bacterial infections in resource-limited settings, where the recommended inpatient treatment may not be feasible, challenges still exist in the effective delivery of life-saving drugs to this vulnerable population (Lassi et al., 2010; Esamai et al., 2013; African Neonatal Sepsis Trial et al., 2015; Simen-Kapeu et al., 2015). In addition to accessibility, acceptability or affordability issues, this is also due to the complexity of the recommended dosing regimens, which have been introduced into clinical practice in a rather empirical manner. Such an approach does not warrant optimal exposure of newborns to antibiotic agents, which show a different disposition profile in this population (Cella et al., 2010a; Medellin-Garibay et al., 2015; Samardzic et al., 2016).

In fact, a few historical antibiotic efficacy trials were performed in neonates >20 years ago and these have been conducted without careful evaluation of the implications that differences in drug disposition represent for the dose rationale (Evans et al., 1986; Buring et al., 1988; Wiese, 1988; Fisk, 1993). By contrast, a vast body of evidence is currently available that allows one to assess the role of age and disease-related changes in drug disposition and overall differences in the pharmacokinetic properties of antibiotics (Manolis and Pons, 2009; Pandolfini et al., 2013; Roberts et al., 2014; Stockmann et al., 2014; Pineda and Watt, 2015). Here we assess the feasibility of a simplified regimen of gentamicin taking into account the effect of body size and organ maturation on pharmacokinetics. Using quantitative clinical pharmacology methods, and more specifically clinical trial simulations, we characterize the impact of covariate factors on the disposition of gentamicin in preterm and term infants aged 0–59 days. The aim of this analysis was to evaluate the performance of it is possible to evaluate current World Health Organisation (WHO) guidelines, which recommend gentamicin doses between 5 and 7.5 mg/kg and identify a simplified regimen for the use of intramuscular gentamicin in resource-limited settings.

Making use of clinical trial simulations, it is possible to evaluate clinically relevant scenarios including the effect of intrinsic (e.g., disease) and extrinsic (e.g., co-medication) factors known to alter the pharmacokinetic properties of a drug (Anderson, 2010; Bellanti and Della Pasqua, 2011). These considerations are especially important in very young pediatric patients, who are not simply small in terms of total body size or surface area. They differ in terms of organ function capacity, ontogeny and maturation, all of which can affect pharmacokinetic processes in a nonlinear manner, and consequently lead to differences in systemic and target tissue exposure (Cella et al., 2010b; Rodieux et al., 2015). Such a nonlinearity implies that the use of dosing recommendations on a milligram per kilogram basis (mg/kg) does not necessarily correct for the underlying differences in pharmacokinetics.

Yet, efficacy findings supporting dose recommendations have often overlooked the importance of exposure and pharmacokinetic-pharmacodynamic data (Zaidi et al., 2013a; Baqui et al., 2015). In this regard, it is important to underline that the antibacterial activity of gentamicin is concentration-dependent, as expressed by the ratio of peak plasma concentration over the minimum inhibitory concentration (C_{max}: MIC), which should exceed 8–10 for optimal efficacy (Moore et al., 1987; Levison and Levison, 2009). Nevertheless, attainment and maintenance of target levels may be challenging in preterm and term newborn infants, as changes in organ function occur relatively fast. Gentamicin is essentially eliminated by renal excretion through glomerular filtration and as such its elimination is determined by nephrogenesis, which reaches completion between 32 and 36 weeks of gestation (Rodriguez et al., 2004; Schreuder et al., 2011). In addition, gentamicin disposition is affected by distributional differences, such as extracellular body water and changes in renal blood flow. During the first weeks of life, there is a progressive rise in glomerular filtration rate (GFR) resulting from an acute increase in cardiac output induced by a decrease in renal vascular resistance (Vanpee et al., 1992; Andersen et al., 2012). Consequently, renal elimination of gentamicin in neonates is largely linked to both gestational age and post-natal (PNA) age.

The selection of a dose and dosing regimen for the neonatal population should therefore account for the effect of maturation (increase in age and function) and growth (increase in size). Ultimately, we envisage the possibility of deriving simplified fixed dose regimens for intramuscular gentamicin, which will facilitate prescription and dispensation practice in a resource-limited setting whilst minimizing the risk of under and overexposure of preterm and term neonates to antibiotics.

MATERIALS AND METHODS

Clinical Data

Demographic and clinical response data from patients who were enrolled into the AFRINEST and SATT trials were used as reference for the purpose of the current investigation. The availability of these data allows for resampling of relevant covariates taking into account actual distributions and correlations between demographic and clinical baseline characteristics. As shown in **Supplementary Figure S1**, data for post-natal age presents a skewed distribution, which adequately reflects the epidemiologic characteristics of sepsis after birth. An overview of the demographic variables included in the analysis is presented in **Table 1**. Further details of the trial

TABLE 1 | Demographic characteristics of the pediatric patients enrolled in the AFRINEST and SATT trials (Zaidi et al., 2013b; African Neonatal Sepsis Trial et al., 2015; Baqui et al., 2015), which were used in subsequent simulation scenarios.

Patient characteristics	Value
Number of patients	10,840
Post-natal age (days), median (range)	16 (1–59)
Weight (kg), median (range)	3.3 (1.5–8)
Male, %	51

protocols are available elsewhere (Zaidi et al., 2013b; African Neonatal Sepsis Trial et al., 2015; Baqui et al., 2015). The studies have been conducted in full conformance with the principles of the Declaration of Helsinki and with the local laws and regulations concerning clinical trials.

Virtual Population Cohort

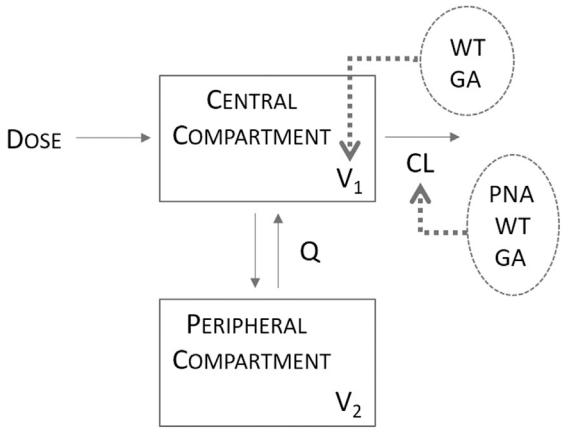
The baseline data were used to create a virtual cohort with similar characteristics of the pediatric patients enrolled in the AFRINEST and SATT trials. Of interest were the demographic characteristics which have been identified as influential covariates on disposition parameters. As information on gestational age (GA) was not available for individual patients in the clinical trials, GA was imputed from post-menstrual age (PMA), body weight (BW) and gender using the approach described by Sumpter and Holford (Sumpter and Holford, 2011). The method relies on the assumption of a correlation between actual body weight, weight at birth and gestational/post-natal age. To prevent spurious variability in subsequent simulation steps and avoid combinations of individual BW and GA which might not be biologically plausible, each individual patient was assigned a GA value that corresponded to the median of the predicted GA distribution for the patient's body weight. Subsequently, the proportion of preterm infants with imputed GA between 24 and 36 weeks was compared with epidemiological data describing the prevalence of preterm births (Tucker and McGuire, 2004; Chawanpaiboon et al., 2019), which occur on average in 12% of the population. In addition, predicted values were further compared against data describing the incidence of sepsis between birth and 59 days (Waters et al., 2011; Blencowe et al., 2013; Downie et al., 2013). An overview of the correlations between body weight, GA and PNA for preterm and term newborns and infants is shown in **Supplementary Figure S2**.

Pharmacokinetic Model Selection

The search strategy for model selection included the following keywords and MESH terms in PubMed: "gentamicin," "pharmacokinetics," "model," "sepsis," "neonates" and/or "infants." Three important criteria were used for inclusion of publications, namely, 1) Comparable demographics to the population in our analysis, 2) No confounding comorbidity or comedications and 3) Internal and external validation procedures. An additional exclusion criteria regarded the choice of parameterization used to describe the disposition properties of gentamicin. Models based on empirical parameterization were deemed unsuitable for prospective simulations. Initially, five candidate models were identified that seemed relevant for the purposes of the current investigation (**Supplementary Table S1**). However, after careful review of the publications only the model proposed by Fuchs and colleagues appeared to satisfy all the predefined inclusion and exclusion criteria (Fuchs et al., 2014). Moreover, the model was developed using a very large population including newborns and infants from 24 to 42 weeks gestational age (namely, 994 preterm and 455 term newborns). Such a large population ensured parameter estimates with higher precision, as well as accurate characterisation of the interindividual variability in disposition characteristics in this group of patients.

In brief, Fuchs and colleagues have identified a two-compartment pharmacokinetic model to describe the disposition of gentamicin in preterm and term neonatal patients following intravenous administration over a 30 min infusion, most of the time in association with amoxicillin. Model evaluation was based on standard graphical and statistical criteria and included external validation procedures. The average parameter estimates and corresponding between-subject variability (BSV%) for a median body weight of 2.17 kg were 0.089 L/h (28%) for clearance (CL) and 0.908 L (18%) for the central volume of distribution (Vc). Body weight, gestational age and post-natal age positively influenced CL, whereas body weight and gestational age positively influenced the volume of distribution of the central compartment (**Figure 1**; **Supplementary Table S2** for details on the pharmacokinetic parameter estimates). To ensure that model parameters and covariate-parameter correlations were coded correctly, an initial evaluation was performed to assess model performance. The model by Fuchs et al. was used to simulate gentamicin plasma concentrations in sepsis patients described in Thomson et al. (Thomson et al., 2003).

Subsequently, the generalisability of the pharmacokinetic model for the simulation of gentamicin concentration vs. time profiles was assessed in a population that reflects real-world conditions. An additional evaluation, from now on referred to as secondary external validation was performed using therapeutic drug monitoring data collected in subjects with or without sepsis at the Robert Debré Children's Hospital, Paris, as part of therapeutic drug monitoring. Initially, 37 plasma samples from 29 subjects with comparable demographic baseline characteristics, who were treated with standard gentamicin intravenous doses were retrieved for the secondary external validation. Of these, one subject was excluded from the data set because of inaccurate details on the reported dosing regimen. An overview of the demographic variables of the subjects used for model building in Fuchs et al. and for the secondary external validation is presented in **Table 2**. For the evaluation of model performance, *post-hoc* parameter estimates were obtained for each subject in the secondary external validation data set by using the MAXEVAL = 0 option. Then, goodness-of-fit (GOF), visual predictive checks (VPC) and model prediction error (MPE) were assessed. The VPC was generated using 1,000 simulations. Median and 90%



Deterministic model parameters

V_1 – Volume of distribution (central compartment)
V_2 – Volume of distribution (peripheral compartment)
Q – Inter-compartmental clearance
CL – Clearance

Covariate factors

GA – Gestational age
PNA – Postnatal age
WT – Body weight

FIGURE 1 | Population pharmacokinetics of gentamicin in a large cohort of preterm and term neonates, as described by Fuchs et al. (2014) Absorption was assumed to be instantaneous and suitable for the description of gentamicin profiles following intramuscular administration.

TABLE 2 | Demographic characteristics of patients used for model building and secondary external validation.

Patient characteristics	Model building *	Secondary external validation
Number of patients	1,449	28
Gestational age (weeks), median (range)	34 (24–42)	37 (24.7–41)
Post-natal age (days), median (range)	1 (0–94)	4.5 (1–145)
Post-menstrual age (weeks), median (range)	34.4 (24.2–42.4)	37 (25.9–60)
Weight (kg), median (range)	2.2 (0.4–5.5)	2.9 (0.6–4.5)
Male, %	57.5	54

** Values from model building are adapted from Fuchs et al. (2014) with permission.*

confidence intervals of the simulated values were calculated for each subject and plotted together with the observed data. The mean percentage error (MPE) was calculated according to the following formula:

$$MPE\ (\%) = \frac{IPRED - DV}{DV} \cdot 100$$

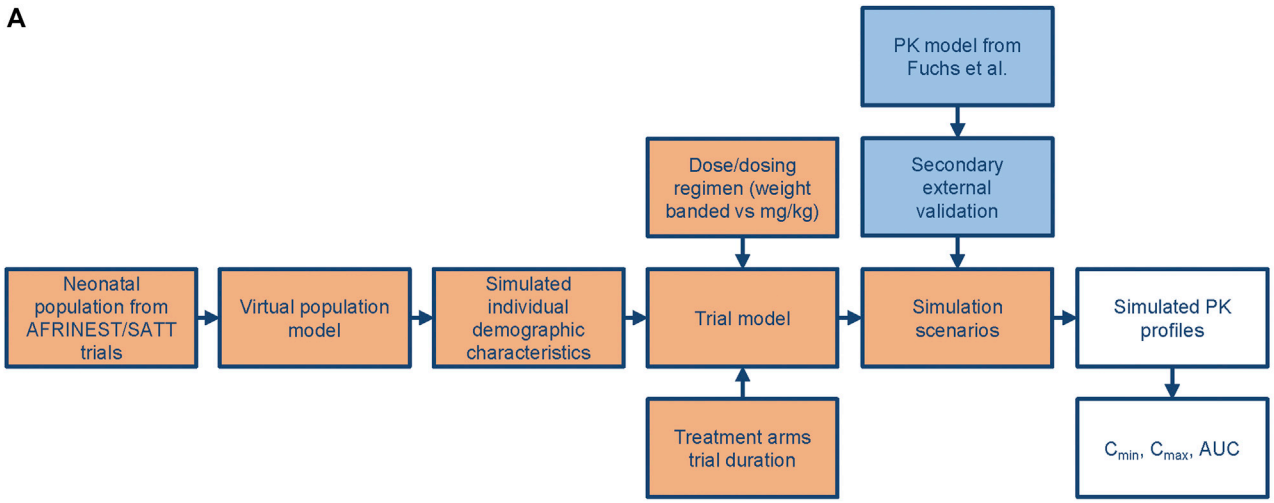
where IPRED is the individual predicted concentration and DV is the observed concentration.

In addition, the positive predicted value (PPV) and the negative predicted value (NPV) were calculated to evaluate the ability of the model to correctly predict trough concentrations below the safety threshold (2 mg/L). Finally, the secondary parameters of interest (AUC, C_{max} and C_{min}) were derived from the predicted pharmacokinetic profiles using noncompartmental methods.

Simulation Assumptions

As the current evaluation is part of a broader investigation aimed to identify the feasibility of simplified regimens for first line antibiotics for the treatment of severe bacterial infections when referral is not possible, a common set of assumptions has been used for each of the drugs in scope. As presented previously by D'Agate and colleagues for amoxicillin (D'Agate et al., 2020), six key assumptions were required for the assessment and interpretation of the results, namely:

(1) Treatment failure was assumed to be linked to pharmacokinetic variability (i.e., underexposure), rather than resistance (Roberts and Lipman, 2006).
(2) Correlations between patient demographic characteristics and physiological processes that determine interindividual differences in drug disposition were considered to be constant across the course of disease, unless stated otherwise.
(3) The absorption rate of gentamicin after intramuscular administration was deemed to be very fast and as such for modeling purposes, dose was assumed to be delivered directly into the central compartment, as per parenteral administration. This assumption is supported by previous investigations, which have shown comparable disposition profiles of gentamicin after intramuscular and intravenous administration (Hayani et al., 1997; Gemer et al., 2001). In addition, Seaton et al. and Thomson et al. both showed that a first order absorption



B

Design characteristics	Protocol details
Dose/weight bands	In addition to the weight bands and doses used in AFRINEST/SATT trials, sets of varying number of weight bands and regimens were evaluated
Dosing regimen	Once daily
Sampling scheme	0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours after dose
Duration	7 days
Number of subjects	9944
Patient demographics	Same population demographics from the AFRINEST/SATT trials
Secondary PK parameters of interest	Cmax, Cmin, AUC
Inclusion criteria	Same as those applied to the AFRINEST/SATT trials

C

Scenario	Weight bands (kg)	Total daily dose (mg)
1	<2.0	8
	2.0 – 2.5	10
	2.5 – 3.0	12
	3.0 – 4.0	18
	4.0 – 5.0	26
	5.0 – 6.0	32
	≥6.0	32-44
2	<2.0	3-4 mg/kg
	≥2.0	5-7.5 mg/kg
3	<2.5	8
	2.5 – 4.0	16
	≥4.0	5 mg/kg
4	<2.5	8
	2.5 – 5.0	16
	≥5.0	30
5	<2.5	10
	2.5 – 4.0	16
	≥4.0	30

FIGURE 2 | (A) Workflow for the implementation of clinical trial simulations aimed at the evaluation of simplified dosing regimens for gentamicin in neonatal sepsis. **(B)** Design characteristics for the study protocol used in the clinical trial simulations. **(C)** Simulation scenarios evaluated for the identification of a simplified dosing regimen based on weight bands and fixed doses.

model does not describe intramuscular pharmacokinetic data in infants and children (Thomson et al., 2003; Seaton et al., 2007).

(4) Dose proportionality (i.e., pharmacokinetic linearity) was assumed beyond the observed range of doses and concentrations if higher doses (i.e., up to two-fold) were used in simulation scenarios.

(5) Differences of up to 10% in median secondary pharmacokinetic parameter estimates (AUC, C_{max}, and C_{min}) were not deemed clinically relevant. Such a variation allows for the effect of model uncertainty whilst taking into account the impact of changes in dosage forms, as defined by current regulatory guidelines, which permit even larger variation when evaluating whether different formulations are bioequivalent.

(6) Treatment adherence was assumed to vary randomly and to be dose-independent for the purposes of simulations.

Simulation Scenarios—*In Silico* Clinical Trial Protocol

Gentamicin exposure following once daily intramuscular administration was simulated in a virtual cohort (n = 9,994) of

preterm and term newborns and infants with post-natal age varying from 0 to 59 days. In addition to the effect of demographic covariates simulation scenarios have also accounted for the skewed distributions in age and body weight, which reflects the incidence and prevalence of sepsis in this population. An outline of the simulation steps and selected scenarios for the identification of a simplified regimen are summarized in **Figure 2**. The currently recommended dosing regimen by WHO was used as reference scenario for the purpose of comparisons between regimens (World Health Organization, 2015).

The parameters of interest included the peak concentration (C_{max}) and the trough concentration (C_{min}) associated with once daily gentamicin administration. In addition, the area under the curve (AUC) was calculated to compare exposure across weight and age groups in the population as this parameter correlates with the total dose delivered, which is currently given in mg/kg. Given that gentamicin is delivered intramuscularly and absorption is rapid, formulation was not considered a significant source of variability in the simulation scenarios (Thomson et al., 2003).

All simulation scenarios were based on the use of once daily doses of gentamicin for a period of 7 days. Pharmacokinetic sampling was implemented according to a typical sampling scheme with one pre-dose and 11 post-dose samples (**Figure 2**). Even though optimization techniques have not been applied, the selected sampling intervals were assumed to allow accurate estimation of AUC over the dosing interval as well as identification of peak and through levels of gentamicin. C_{max} and C_{min} were calculated, respectively, by taking the maximum predicted concentration and the predicted pre-dose concentration after the first dose and at steady state conditions at the end of treatment. For the sake of comparison, integration of the concentration vs. time data according to the trapezoidal rule was applied for the calculation of the AUC. All simulations were performed using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, United States). R version 3.1.2 (R Core Team, 2013) was used to graphically summarize the results.

Threshold values for target peak and trough concentrations were selected for comparison of the performance of the different dosing regimens taking into account pharmacokinetic-pharmacodynamic indices as well as microbiological susceptibility data, safety and efficacy results from available clinical studies. A cut-off value of 10 mg/L was used for peak concentrations and 2 mg/L for trough concentrations. These thresholds were used as a proxy for efficacy and safety, respectively. Consequently, the selected regimens aimed at maximizing the proportion (in percentage, %) of sepsis patients aged 0–59 days with peak concentrations above the reference threshold level of 10 mg/L, whilst minimizing those below the 2 mg/L threshold for trough concentrations. The reference thresholds were based on recommendations from the British National Formulary (https://bnf.nice.org.uk/drug/gentamicin.html) and a comprehensive review on the use of gentamicin for the treatment of suspected or proven sepsis (Rao et al., 2015; Ibrahim et al., 2016). Given the aforementioned criteria, no formal hypothesis test was used to compare scenarios. Each scenario was summarized taking into account the weight bands associated with the corresponding scenario. Median estimates were calculated along with the 90% confidence intervals for the parameters of interest.

RESULTS

Our analysis shows how doses and dosing regimens can be evaluated in a systematic manner, considering the contribution of factors known to affect drug disposition in the neonatal patient population. In addition to the selected simplified regimen, two scenarios are discussed: 1) the performance of the dosing regimens used in AFRINEST and SATT studies and 2) the 2015 WHO recommendations for management of possible serious bacterial infections in young infants 0–59 days old when referral is not feasible (World Health Organization, 2015). Predicted concentration vs. time profiles, peak and through concentrations in the AFRINEST and SATT studies were used as basis for further assessment and interpretation of the role of interindividual variability in drug disposition in the neonatal population.

Model Performance and Secondary External Validation

The secondary external validation procedures showed that model predictions for trough concentrations are associated with a median MPE of −7.7%. This was slightly higher than the median MPE reported for the external validation in Fuchs et al. (i.e., −3%). Clearly, the higher variability observed for the MPE in this group of patients reflects the heterogeneity of the pediatric population. Yet, the model showed adequate performance, predicting correctly whether a trough concentration is below the threshold for safety (2 mg/L) with a PPV of 0.94 and an NPV of 0.87.

The goodness-of-fit plots for the secondary external validation data set are shown in **Supplementary Figure S3**, together with the data from the external validation performed by Fuchs et al. These plots indicate comparable model performance for the different data sets, but with a higher unexplained variability. An overview of the concentration vs. time profiles is depicted in **Supplementary Figure S4**, where the individual VPCs show the predictive performance of the model, especially for lower concentrations. The predicted median AUC was 110 mg h/L (90% CI 49–129 mg h/L), C_{max} was 14.4 mg/L (90% CI 10.6–20.9 mg/L) and C_{min} was 0.66 (90% CI 0.07–2.58 mg/L).

Predicted Gentamicin Exposure in the AFRINEST and SATT Studies

Despite the use of six weight bands to account for the effect of body weight, the median exposure to gentamicin, expressed as the area under concentration vs. time curve, was found to vary by more than 50% across the different groups (**Figure 3**). Whilst

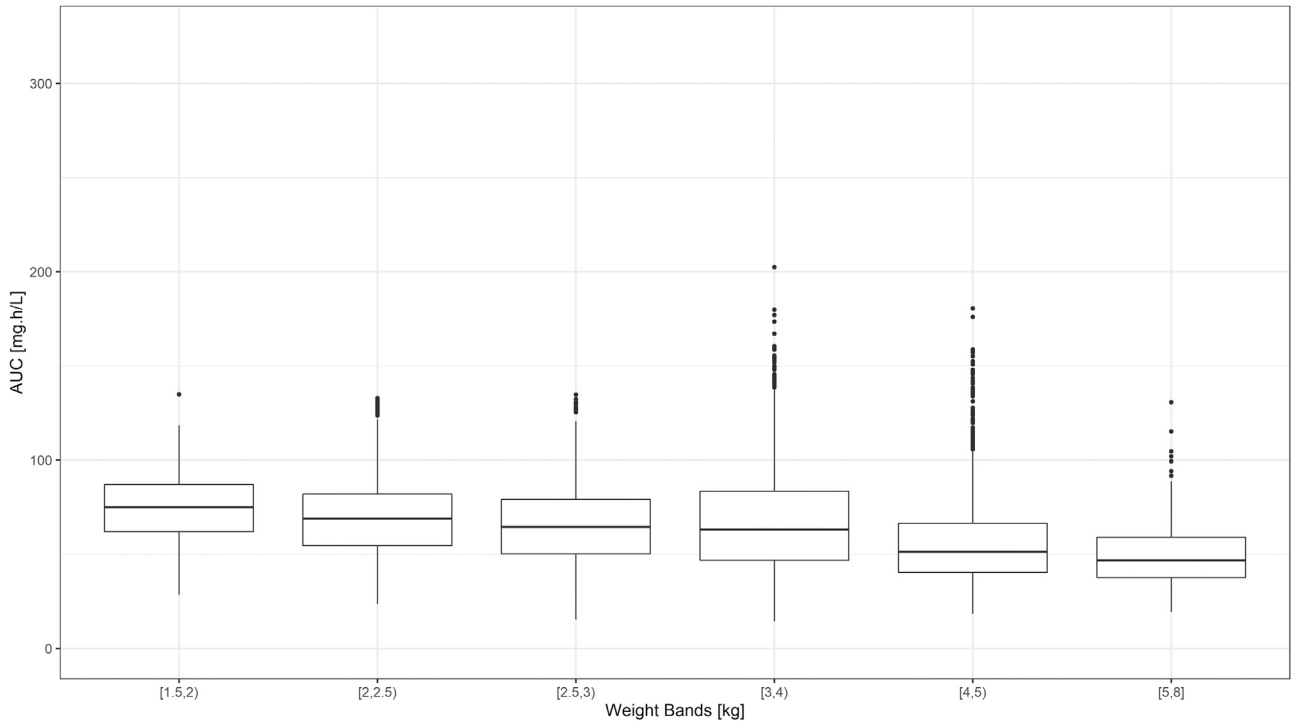


FIGURE 3 | Predicted gentamicin AUC in sepsis patients aged between 0–59 days. Estimates are summarized according to the weight bands used in the original AFRINEST/SATT trials. Hinges represent 25th and 75th percentiles (respectively, Q1 and Q3), whiskers represent Q1 – 1.5IQR and Q3 + 1.5IQR, respectively, where IQR is the interquartile range. All the subjects outside this range are represented by the dots (*N* = 9,994).

most subjects appear to achieve target peak and trough concentrations of gentamicin, considerable fluctuation in drug levels was observed across the different weight bands. Target concentrations are not achieved in a small proportion of subjects in the lower weight bands.

An overview of the variability in the predicted peak and trough concentrations of gentamicin is shown in **Figure 4**, where C_{max} and C_{min} values are summarized after the first dose of a once daily dosing regimen over a period of 7 days. Data were stratified by weight bands, as per protocol. In addition, the predicted percentage (%) of sepsis patients with peak concentrations below the reference threshold level of 10 mg/L and trough concentrations above 2 mg/L is summarized in **Table 3**.

Comparison Between the Proposed Simplified Regimen and the WHO Recommendations

In contrast to current guidelines, which recommend the use of gentamicin in mg/kg, our analysis demonstrates the feasibility of implementing a fixed dose regimen based on three weight bands. **Figure 5** shows the population predicted plasma concentration vs. time profile of gentamicin for the proposed simplified regimen along with the 90% confidence intervals, as compared to the 2015 WHO recommended doses of 5.0 – 7.5 mg/kg. As it can be observed, the two regimens seem to overlap considerably with each other.

Summary statistics of the two main secondary parameters (C_{max} and C_{min}) are presented along with the 90% confidence intervals in **Table 4**. An overview of the variability in the predicted peak and trough concentrations of gentamicin is shown in **Figure 6**, where data are stratified by weight bands. It is clear from the results that despite correction for differences in body weight, considerable variation is observed between lower and upper weight ranges. Given the possibility of selecting gentamicin doses between 5.0 and 7.5 mg/kg, some children remain significantly below the target threshold for peak concentrations, whilst others exceed the threshold of 2 mg/L. As can be seen from **Table 3**, the proposed simplified regimen represents an opportunity for dose optimization not only with respect to the current WHO recommended doses, but also when considering more complex regimens, as those implemented in the AFRINEST/SATT trials.

Of note are the changes in disposition characteristics in preterm low weight newborns and infants, especially for subjects between 1.5 and 2.0 kg, as doses of 3.0 mg/kg lead to a significant proportion of subjects below the target peak concentration. The proposed regimen practically eliminates the problem, with all subjects reaching C_{max} values greater than 10 mg/L. However, an increase in the proportion of subjects with C_{max} > 2 mg/L is also observed. The 95% percentile of C_{min} in this subgroup of subjects is 2.45 mg/L.

In addition, to assess the implications of the different regimens, data were also presented using narrower weight bands (**Supplementary Figure S5**). Our results reveal that a

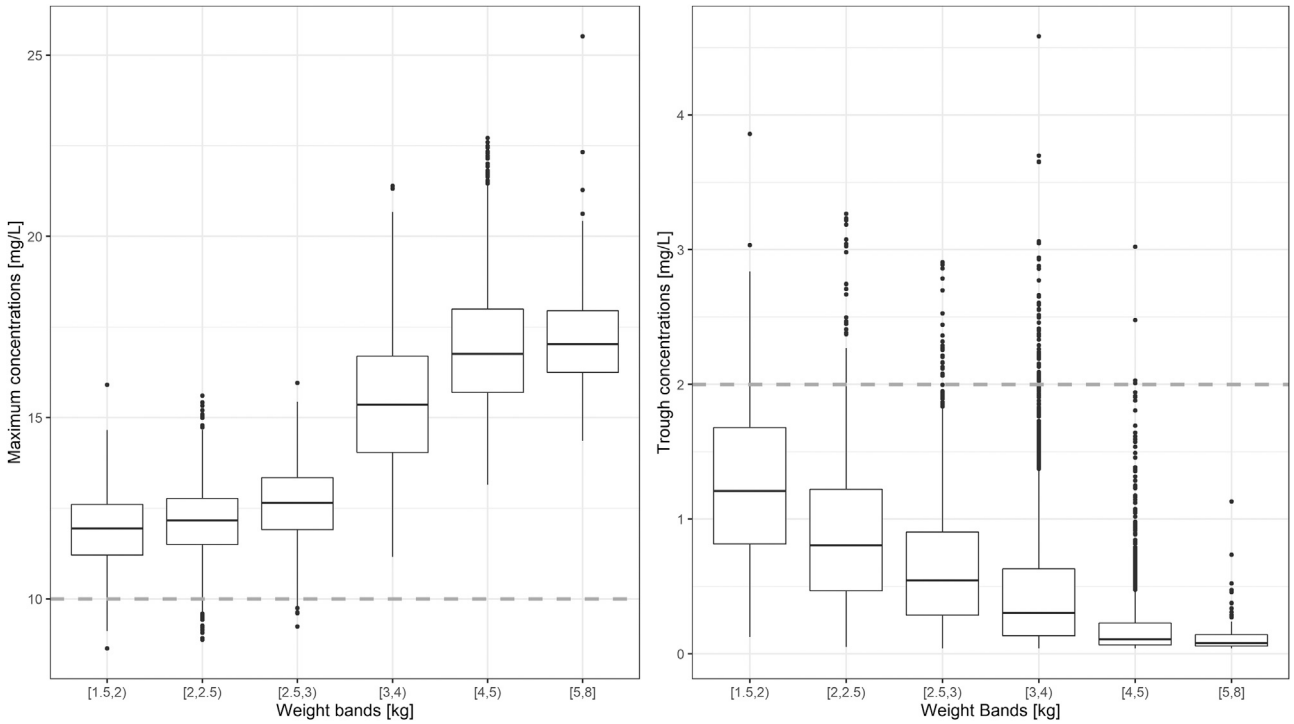


FIGURE 4 | Predicted gentamicin peak **(left)** and trough **(right)** concentrations in sepsis patients aged between 0 and 59 days. Estimates are summarized according to the weight-bands used in the original AFRINEST/SATT trials. Hinges represent 25th and 75th percentiles (respectively, Q1 and Q3), whiskers represent Q1 – 1.5IQR and Q3 + 1.5IQR, respectively, where IQR is the interquartile range. All the subjects outside this range are represented by the dots (*N* = 9,994). Dashed lines represent the threshold values for peak and trough concentrations of 10 and 2 mg/L, respectively.

TABLE 3 | Predicted percentage (%) of sepsis patients aged 0–59 days with peak concentrations below the reference threshold level of 10 mg/L and trough concentrations above 2 mg/L after a once daily dosing regimen of gentamicin.

Trial weight band (kg)	No. patients/ weight band	% of patients with C_{max} < 10 mg/L				No. of patients with C_{max} < 10 mg/L			
		AFRINEST/SATT study regimen	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])	AFRINEST/SATT study regimen	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])
1.5–2.0	294	3.7	0.0	98.3	17.7	11	11	289	52
2.0–2.5	820	4.1	4.1	12.2	0.0	34	34	100	0
2.5–3.0	1,783	1.1	0.0	0.0	0.0	20	0	0	0
3.0–4.0	4,656	0.0	0.1	0.0	0.0	0	3	0	0
4.0–5.0	2,081	0.0	0.0	0.0	0.0	0	0	0	0
5.0–8.0	360	0.0	0.0	0.0	0.0	0	0	0	0
Trial weight band (kg)	**No. patients/ weight band**	**% of patients with C_{min} > 2 mg/L**				**No. of patients with C_{min} > 2 mg/L**			
		AFRINEST/SATT study regimen	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])	AFRINEST/SATT study regimen	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])
1.5–2.0	294	12.6	27.6	0.3	6.1	37	81	1	18
2.0–2.5	820	5.1	5.1	6.0	26.2	42	42	49	215
2.5–3.0	1,783	1.4	6.6	2.5	13.6	25	117	45	242
3.0–4.0	4,656	1.3	0.7	0.7	4.0	59	34	31	185
4.0–5.0	2,081	0.2	0.4	0.0	0.6	4	9	1	12
5.0–8.0	360	0.0	0.0	0.0	0.0	0	0	0	0

[a]*Lower doses are 3 mg/kg for low birth weight (<2.0 kg) newborns and 5 mg/kg for those with body weight >2.0 kg.*

[b]*Higher doses are 4 mg/kg for low birth weight newborns and 7.5 mg/kg for those with body weight >2.0 kg.*

Data are summarized according to the weight bands used in the trials.

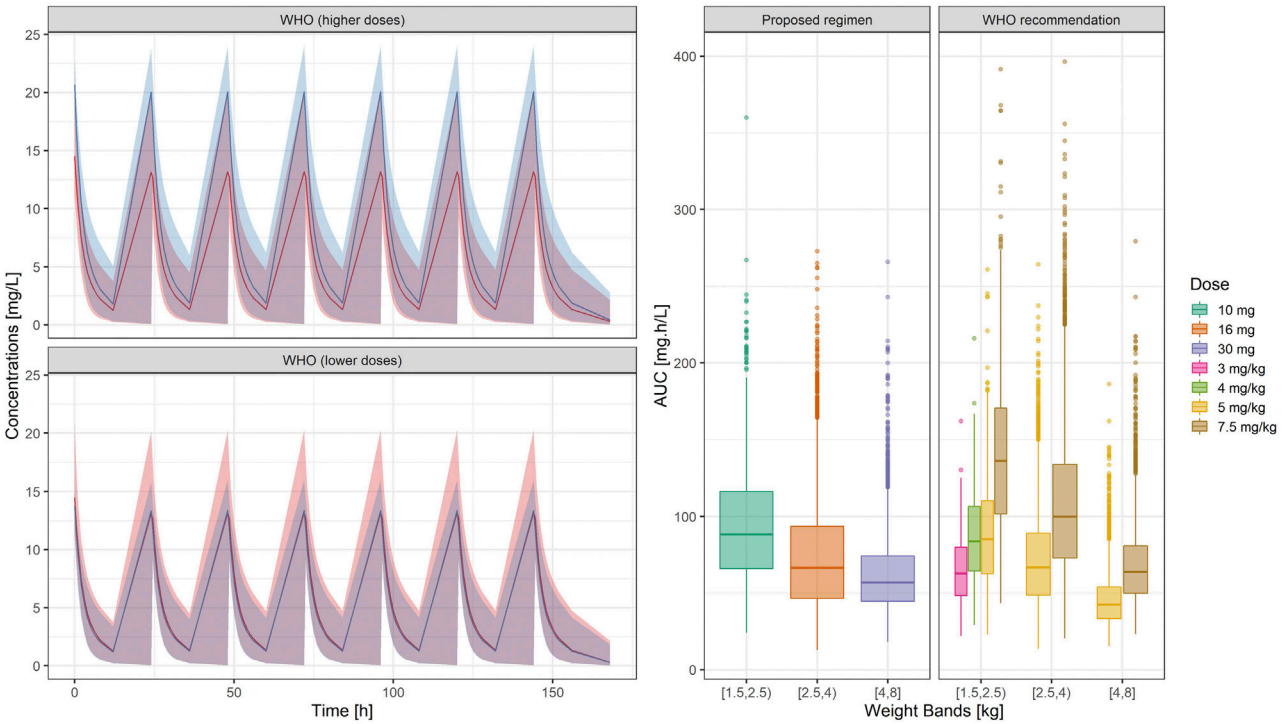


FIGURE 5 | (Left) Predicted gentamicin concentration vs. time profile in sepsis patients aged between 0 and 59 days. Each panel compares the pharmacokinetic profiles in the target population after the proposed regimen (red) with those obtained after higher (upper panel) and lower doses (lower panel) of the WHO recommended regimen (blue). Solid line depicts the median profile; shaded area represents the 90% prediction intervals. Time 0 is used as reference for the first dose **(Right)** Systemic exposure, expressed as area under the concentration vs. time curve. Hinges represent 25th and 75th percentiles (respectively, Q1 and Q3), whiskers represent Q1 – 1.5IQR and Q3 + 1.5IQR, respectively, where IQR is the interquartile range. All the subjects outside this range are represented by the dots (*N* = 9,994). Overall, the weight-banded regimens result in similar exposure ranges, with a slight trend to lower values in the highest weight band.

TABLE 4 | Predicted peak (C_{max}) and trough (C_{min}) concentrations of gentamicin after a once daily dosing regimen.

Weight band (kg)	C_{max} (mg/L)				C_{min} (mg/L)			
	AFRINEST/SATT study regimens	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])	AFRINEST/ SATT study regimens	Proposed regimen	WHO (lower doses[a])	WHO (higher doses[b])
1.5–2.5	12.37 (10.2, 14.88)	12.8 (10.46, 17.33)	12.(7.35, 15.69)	20 (10.06, 23.6)	0.9 (0.2, 2.15)	0.96 (0.2, 2.45)	0.82 (0.19, 1.93)	1.24 (0.3, 3.04)
2.5–4.0	14.55 (11.58, 18.28)	14.49 (11.27, 18.47)	14.48 (12.44, 16.34)	21.73 (18.66, 24.51)	0.37 (0.06, 1.48)	0.37 (0.06, 1.64)	0.36 (0.06, 1.47)	0.52 (0.08, 2.19)
4.0–8.0	16.82 (14.48, 20.07)	18.(15.38, 23.1)	13.79 (12.7, 16.02)	20.69 (19.05, 24.03)	0.1 (0.04, 0.67)	0.11(0.04, 0.75)	0.09 (0.04, 0.57)	0.12 (0.05, 0.79)

Values shown are the median, 5th and 95th percentiles.

[a]*Lower doses are 3 mg/kg for low birth weight (<2.0 kg) newborns and 5 mg/kg for those with body weight >2.0 kg.*

[b]*Higher doses are 4 mg/kg for low birth weight newborns and 7.5 mg/kg for those with body weight >2.0 kg.*

considerable number of patients <2 kg appear to remain below the target threshold for peak concentrations following a 3.0 mg/kg dose. This situation is corrected by the proposed simplified regimen. Whereas the difference between the proposed regimen and WHO recommendations are small, heterogeneity in renal maturation may drive the variation observed in trough levels in newborns with body weight between 2.0 and 2.5 kg. The simplified regimen presented in **Table 5** is therefore preferable and should be used as final recommendation for the treatment of neonatal sepsis.

DISCUSSION AND CONCLUSION

Currently, the WHO recommends the use of gentamicin in combination with ampicillin or amoxicillin as empirical therapy for sepsis in newborns and infants (0–59 days old) (World Health Organization, 2015). Recent clinical trials in this vulnerable population, such as AFRINEST and SATT have shown promising findings, in that high efficacy rates have been achieved with a dosing regimen that can be implemented

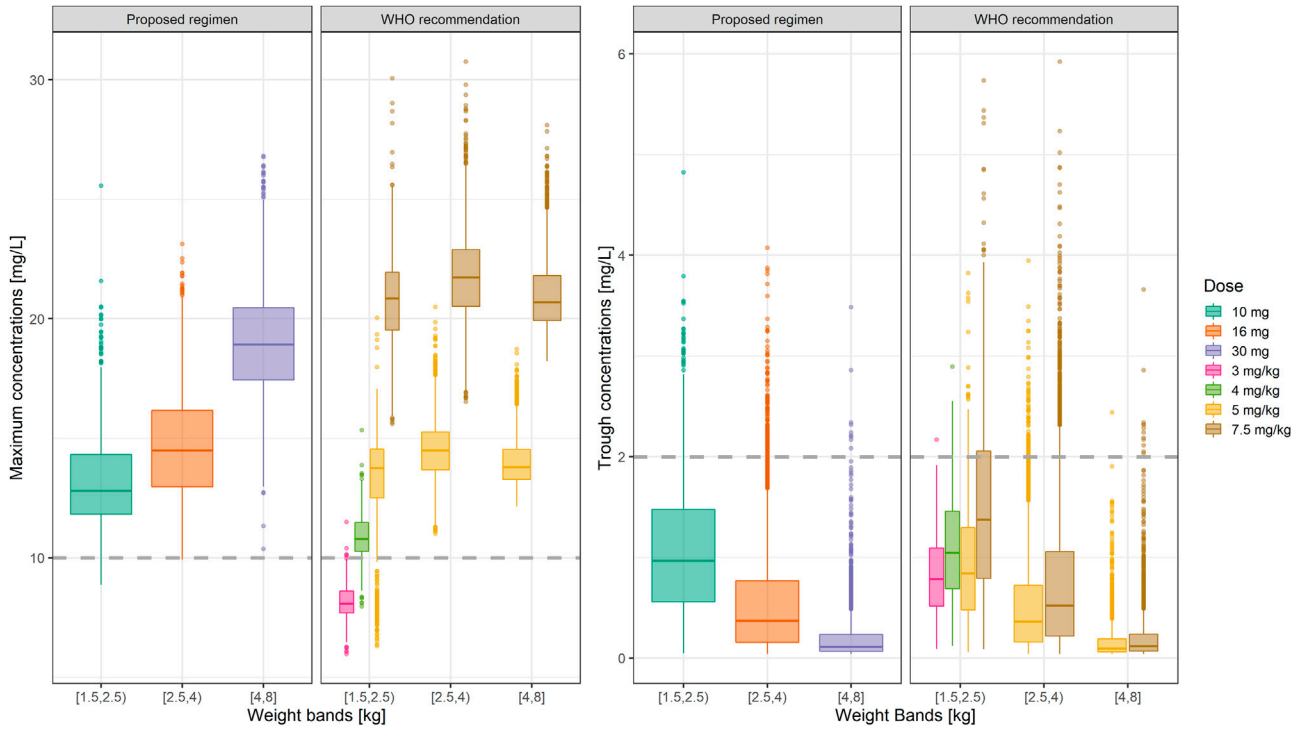


FIGURE 6 | Predicted gentamicin peak **(left)** and trough **(right)** concentrations in sepsis patients aged between 0 and 59 days stratified according to the weight bands for the proposed simplified regimen. Panels show how the simplified regimen compares to the 2015 WHO recommendations. Hinges represent 25th and 75th percentiles (respectively, Q1 and Q3), whiskers represent Q1 – 1.5IQR and Q3 + 1.5IQR, respectively, where IQR is the interquartile range. All the subjects outside this range are represented by the dots (*N* = 9,994). Dashed lines represent the threshold values for peak and trough concentrations of 10 and 2 mg/L, respectively.

TABLE 5 | Proposed simplified regimen based on fixed doses of gentamicin for the treatment of sepsis patients aged between 0 and 59 days.

Weight band	Body weight range (kg)	Simplified regimen (mg)	Volume of gentamicin 40 mg/ml administered per dose (ml)
1	1.5–2.5	10	0.25
2	>2.5–4.0	16	0.40
3	>4.0–8.0	30	0.75

in community-based settings (Zaidi et al., 2013a; Zaidi et al., 2013b; African Neonatal Sepsis Trial et al., 2015; Baqui et al., 2015). However, the dosing regimens used in these trials remain complex and as such do not warrant compliance in clinical practice (African Neonatal Sepsis Trial Group, 2013). Consequently, response to treatment may not be comparable to that observed during the trials. In fact, the use of mg/kg may represent an important hurdle for the implementation of such interventions in a community-based setting. Here we have shown how increasing understanding of the pharmacokinetics and pharmacokinetic-pharmacodynamic (PKPD) relationships of the antibiotics can be used in conjunction with quantitative clinical pharmacology principles to guide the dose rationale for gentamicin in newborns and infants with sepsis (Vinks et al., 2015; Mehrotra et al., 2016).

Any attempt to optimize dose and simplify dosing regimens will require therefore an alternative, less empirical approach than clinical evidence of efficacy (Khan and Joseph, 2012; Rao et al., 2015). Given that gentamicin exhibits concentration-dependent bactericidal activity and prolonged post-antibiotic effects, it is essential to understand how drug levels vary across different subgroups in the target patient population, such as infants and newborns. Ultimately, it appears that it is the amount of drug (e.g., C_{max} relative to the MIC) rather than the dosing frequency that determines the treatment response (van Maarseveen et al., 2016). Therefore, in our analysis, we have used a target threshold for C_{max} of 10 mg/L, rather than a range of concentrations or the C_{max}/MIC ratio. This decision allowed for direct assessment of the observed drug levels and potential implications for the overall efficacy and safety profile of gentamicin. Furthermore, the use of this criterion implies that exposure levels can be considered efficacious for susceptible pathogens with MIC values lower or equal to 1 mg/L.

Historically, the dosing regimens used for gentamicin have evolved from multiple daily dosing to extended-interval dosing both in adults and in children (Kent et al., 2014). These regimens have aimed at ensuring that peak blood concentrations are sufficiently high to elicit a therapeutic response while avoiding high trough concentrations, which could be potentially toxic after prolonged treatment (Hoff et al., 2009; Dersch-Mills et al., 2012; Radivoyevitch et al.,

2015). However, pharmacokinetic data in infants exhibits large inter- and intra-individual variability, mainly because of the developmental changes occurring from the first month of life. As a consequence, gentamicin dosing regimens based on mg/kg body weight may not fully correct for age-related changes in organ function, composition, maturation and growth (Koren et al., 1985; Salgado et al., 2010; Rodieux et al., 2015).

In contrast to most of the published pharmacokinetic and PKPD data available in the scientific literature (Lingvall et al., 2005; Nielsen et al., 2009; Sherwin et al., 2009; Roberts et al., 2010; Mohamed et al., 2012; Chin et al., 2013; De Cock et al., 2014; Sampson et al., 2014; Valitalo et al., 2015), our investigation has not been limited to a small group of patients. In fact, we have been able to evaluate pharmacokinetic variability across a large patient population, including the impact of demographic baseline covariates and other relevant disease-related factors on the disposition of gentamicin in neonates and infants. Our analysis has included a range of scenarios aimed at demonstrating the feasibility of a simplified dosing regimen with gentamicin, which accounted for relevant sources of variability in pharmacokinetics. Of note is the identification of weight bands that can be used in combination with fixed dose levels, while ensuring acceptable target peak and trough concentrations of gentamicin. Indeed, a simplified regimen that minimizes the proportion of patients below the peak concentration threshold of 10 mg/L, whilst maximizing the proportion of patients below the trough concentration threshold of 2 mg/L was identified based on the use of three weight bands, namely, <2.5, 2.5–4.0, and >4.0 kg. These cut-off values were selected taking into account the weight categories currently used for the other antibiotics indicated for the treatment of sepsis when referral is not possible (Baqui et al., 2015; World Health Organization, 2015). It should be noted that the predicted differences in exposure between the proposed simplified regimen and WHO recommendations are unlikely to be clinically relevant, with exception of patients weighting <2.5 kg. Our simulations reveal that peak concentrations will be significantly lower in this weight band after the use of gentamicin doses based on the WHO guidelines. Therefore, a dose of 10 mg should be considered for this group of patients, even if this regimen may be associated with trough levels that are slightly above 2 mg/L (95% CI: 0.2–2.45).

From a clinical perspective, in addition to demonstrating the feasibility of an alternative regimen for effective treatment of sepsis, our work also illustrates the role of comprehensive clinical trial simulations for the optimization of therapeutic interventions. We have shown how virtual patient cohorts can be created for the evaluation of interindividual differences in pharmacokinetic disposition taking into account the effect of demographic, physiological and clinical factors known to alter the distribution and elimination of gentamicin in newborns and infants (Moore et al., 1987; Roberts and Lipman, 2006; Levison and Levison, 2009; van Maarseveen et al., 2016). Nevertheless, to date none of the existing guidelines and recommendations regarding the dose rationale for gentamicin have been developed taking these factors into account in a strictly quantitative manner. Such an empiricism in the dose rationale cannot be overlooked. Clearly, in some cases, the use of linear dosing algorithms, such as doses in mg/kg body weight may result in sub-optimal or undesirable drug levels across the target population (Hansen et al., 2003; Neef et al., 2006; Rocha et al., 2007; Zakova et al., 2014).

We acknowledge that very few studies have evaluated clinical response taking into account pharmacokinetic variability and so far no data on drug levels have been collected after administration of gentamicin in a resource-limited setting (Dersch-Mills et al., 2012). However, we believe that extrapolation of the pharmacokinetic parameters from a hospital setting to out-patient protocols, as described in the current investigation can be performed with sufficient precision to assess the impact of covariates on drug disposition, irrespective of the treatment setting (Thomson et al., 2003; Roberts and Lipman, 2006; Fuchs et al., 2014). As highlighted in previous paragraphs, we also recognize that assumptions need to be made about the role of other intrinsic and extrinsic sources of variability (e.g., compliance, disease severity, age of onset), which were not included in our analysis (Garcia et al., 2006; Thingvoll et al., 2008; Marsot et al., 2012). For example, information about serum creatinine was not available in the AFRINEST and SATT trials data sets, nor was it included as a covariate on gentamicin elimination parameters in the model developed by Fuchs et al. However, changes in clearance due to renal maturation are captured by the maturation function, expressed in terms of the effect of gestational and postnatal age. Obviously, the maturation function cannot explain differences associated with organ impairment, which may exist due to the presence of co-morbidities or complications due to worsening of sepsis. In such cases, doses would need to be adjusted based on the same principles used for renal impairment. We have also had to use predefined correlations between body weight, gestational and post-menstrual age in preterm and term newborns and infants, which may not fully replicate the variation in a real-world setting, where the correlation between body weight, gestational and post-menstrual age may be further affected by other extrinsic factors, such as malnutrition and disease severity (e.g., diarrhea). We anticipate that these limitations should not alter the conclusions drawn from the current analysis. Furthermore, we should highlight that the use of single cut-off value for the selection of the doses for each weight band created a rather stringent criterion for treatment performance, as microbiological susceptibility data would not be available in a setting where referral is not possible. In reality, ranges have been used for C_{max} (e.g., 8–12 mg/ml or 6–15 mg/ml) along with varying dosing intervals to ensure both peak and trough target levels are achieved in most neonatal patients (Touw et al., 2009; Martínková et al., 2010; Yu et al., 2020). Nevertheless, we recommend the use of sparse sampling schemes in prospective clinical trials to confirm the predicted pharmacokinetic profiles and ensure the effective implementation of the proposed dosing regimen for the treatment of sepsis in newborns and infants.

The reader should be aware that the recent WHO guidelines have been developed taking into account the existing evidence, from clinical practice and randomised clinical trials in neonates (0–28 days old) and young infants (0–59 days old) with severe bacterial infection in resource-limited settings, where families do not accept or cannot access referral care (World Health Organization, 2015). Whereas the goal of such guidelines is to provide clinical guidance on the simplest antibiotic regimens that

are both safe and effective for outpatient treatment of clinically severe infections in children 0–59 days old, it appears that an opportunity has been missed to ensure that recommendations are supported by a dose rationale based on an integrated analysis of pharmacokinetics and PKPD principles.

In summary, our findings are promising in that a simpler dosing regimen can be implemented in community-based settings. Intramuscular gentamicin can be used as a fixed dose according to a weight-banded regimen. The proposed regimen for neonates and young infants with sepsis aged 0–59 days differs from current guidelines in that it takes into account the effect of body weight, gestational age and post-natal age as determinants of the variability in the pharmacokinetics of gentamicin. A dose rationale that accounts for the role of influential factors on drug disposition represents a major advancement in the treatment of possible serious bacterial infections in resource-limited settings.

DATA AVAILABILITY STATEMENT

The simulated data sets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

SD and FM contributed to the data analysis, presentation of the results and preparation of the manuscript. EJ-A provided the data for the secondary external validation and contributed to the review of the manuscript. ODP contributed to the discussion of the clinical implication and preparation and review of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.624662/full#supplementary-material.

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frontiers in Pharmacology

BRIEF RESEARCH REPORT
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Population Pharmacokinetic Study of Cefathiamidine in Infants With Augmented Renal Clearance

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Objectives: Augmented renal clearance (ARC) of primarily renally eliminated antibacterial agents may result in subtherapeutic antibiotic concentrations and, as a consequence, worse clinical outcomes. Cefathiamidine is frequently used as empirical antimicrobial therapy in children with ARC, but pharmacokinetic studies in infants are lacking. This population pharmacokinetic study in infants with ARC was conducted to determine optimal dosing regimens of cefathiamidine.

Methods: The population pharmacokinetics was conducted in 20 infants treated with cefathiamidine. Plasma samples of cefathiamidine were collected using opportunistic sampling, and the concentrations were detected by UPLC-MS/MS. Data analysis was performed to determine pharmacokinetic parameters and to characterize pharmacokinetic variability of cefathiamidine using nonlinear mixed effects modelling (NONMEM) software program.

Results: The data (n = 36) from 20 infants (age range, 0.35–1.86 years) with ARC were fitted best with a 1-compartment model. Allometrically scaled weight and age as significant covariates influenced cefathiamidine pharmacokinetics. The median (range) values of estimated clearance and the volume of distribution were 0.22 (0.09–0.29) L/h/kg and 0.34 (0.24–0.41) L/kg, respectively. Monte Carlo simulations showed that the cefathiamidine doses of 100 mg/kg/day q12 h, 50 mg/kg/day q8 h and 75 mg/kg/day q6 h were chosen for bacteria with MIC 0.25, 0.5 and 2 mg/L, respectively.

Conclusion: The population pharmacokinetic model of cefathiamidine for infants with ARC was developed. The PTA - based dosing regimens were recommended based on the final model.

Keywords: cefathiamidine, pharmacokinetics, dosing, infants, augmented renal clearance

INTRODUCTION

Cefathiamidine is a first-generation cephalosporin discovered in 1974 and is used to treat infections in pediatric patients (National pediatric multi-center cooperative group of cefathiamidine observation, 2003). According to epidemiological studies, cefathiamidine is one of the most commonly prescribed antimicrobial drugs in Chinese pediatric hospitals (Zhang et al., 2008a; Zhang et al., 2008b; Fan et al., 2019). The database from the China Medical Information Center showed that cefathiamidine was the fourth most frequently used cephalosporin in 2016. It has broad antibacterial activity against *Enterococcus*, *Streptococcus pneumoniae*, *Branhamella catarhalis*, *Streptococcus pyogenes, Methicillin-sensitive Staphylococcus epidermidis* (MSSE), *Haemophilus influenza, and Methicillin-sensitive Staphylococcus aureus* (MSSA) (Tze-ying et al., 1979; Chen and Williams, 1983). It has a protein binding capacity of 23% and is excreted primarily in unchanged form through the renal route (> 90%) within 12 h after intravenous administration (Tze-ying et al., 1979). Hence, the kidney function is a crucial factor affecting the pharmacokinetics of cefathiamidine.

Augmented renal clearance (ARC) is a phenomenon in critically ill adult and pediatric patients characterized by increased creatinine clearance and elimination of renally eliminated drugs (Heggen et al., 2019). However, there is no uniform ARC criterion for pediatric patients. ARC was defined based on estimated glomerular filtration rate (eGFR) ≥ 130 ml/min/1.73 m^2 in pediatric patients (Béranger et al., 2018; Béranger et al., 2019; Lv et al., 2020). ARC is strongly associated with subtherapeutic concentrations of antibiotics such as β-lactams and vancomycin, which leads to underexposure and, as a consequence, to increased treatment failure (Udy et al., 2012; Carlier et al., 2013; Udy et al., 2015; Lv et al., 2020). ARC is likely to influence the pharmacokinetic (PK) parameters of cefathiamidine owing to an enhanced eGFR, which results in enhanced drug clearance. In critically ill children, standard antibiotic dosing may not achieve optimal exposure due to this ARC. Nevertheless, dose optimization for pediatric patients with ARC is scarce due to a lack of PK studies; only one study has previously been reported in children with ARC, aged 2.0–11.8 years (Zhi et al., 2018). To date, the pharmacokinetics of cefathiamidine are lacking in infants with ARC.

Thus, this study intended to establish a population PK model of cefathiamidine suitable for infants with ARC and to determine optimal dosing regimens for these infants.

METHODS

Study Design

This open-label, single-center PK study of cefathiamidine was performed at Children's Hospital of Hebei Province affiliated to Hebei Medical University, China. Subjects were included: Infants (≤2 years) with ARC (eGFR ≥ 130 ml/min/1.73 m^2); these infants received intravenous cefathiamidine as a routine antimicrobial treatment (suspected or confirmed bacterial infections). Subjects were excluded if they had intolerance or allergic reactions to cefathiamidine or were enrolled in other clinical trials. This clinical study of cefathiamidine was approved by the ethics board of hospital.

Dosing Regimen and Pharmacokinetic Sampling

Cefathiamidine Injection (Xianlisu®, Guangzhou Baiyunshan Pharmaceuticals, Guangzhou, China) was administered twice daily as a 30 min intravenous infusion of 100 mg/kg/day. The scavenged sampling approach was utilized to exclusively obtain the residual blood specimens after routine biochemical examination (Zhao and Jacqz-Aigrain, 2015), without additional study-specific blood sampling. The samples were spun down for 5 min at 10,000 rpm, separated and stored frozen at −80 °C. Clinical data and sample information were accurately recorded in a database: age, sex, weight, height, serum creatinine, administration time and sampling time.

Method of Cefathiamidine Analysis

Concentrations of cefathiamidine were determined by UPLC-MS/MS. The samples were prepared using ceftiofur as internal standard and methanol as deproteination reagent. The separation was achieved using methanol-water as the mobile phase in gradient mode. The m/z in multiple reaction monitoring transitions were 473.5^+ – 201.3^+ for cefathiamidine and 524.3^+ – 241.4^+ for ceftiofur. The linearity range of cefathiamidine assay based on 50 μl plasma was 30–10,000 ng/ml. The intra- and inter-day coefficients of variation for control samples did not exceed 5% and 15%, respectively. The lower limit of quantification (LLOQ) was 30 ng/ml. The method was validated according to the US FDA guideline (US FDA, 2018) (see **Supplementary Material**).

Cefathiamidine Population Pharmacokinetic Modeling

NONMEM V 7.4 software program (Icon Development Solutions, Ellicott City, MD, Unites States) was applied to analyze cefathiamidine PK data. The first-order conditional estimation (FOCE-I) with interaction algorithm was used to assess PK parameters in the model-building.

Inter-individual variability was assessed for the PK parameters by an exponential equation:

$$\theta_i = \theta * e^{\eta i}.$$

Here, θ_i is the estimated parameter for the i^{th} subject, θ represents the typical population parameter value and ηi the interindividual variability which is assumed to be a normal distribution with a mean of zero and variance ω2.

For residual error model, we attempted to evaluate exponential, additive and combined (proportional plus additive) error forms. One- and two-compartment models were initially compared to obtain the appropriate basic PK

model. Allometric exponents were explored for weight on clearance (CL) and volume of distribution (V) by fixed (allometric exponents of 0.75 and one for CL and V, respectively) (Holford et al., 2013) and estimated analysis methods. After that, the potential covariates (weight, age, eGFR and sex) on PK parameters were investigated by a stepwise forward selection - backward deletion method (Mandema et al., 1992). The eGFR from serum creatinine was calculated using the Schwartz formula (Schwartz et al., 1987). In the stepwise fashion, the likelihood ratio test was applied to evaluate the influence of covariates on population model parameters. A covariate was considered if a statistically significant ($p < 0.05$, $\chi 2$ distribution with one degree of freedom) decreasing (reduction > 3.84) objective function value (OFV) for the forward addition step. All statistically significant covariables were incorporated into the full model and then were further evaluated in the backward deletion step. If a covariance was deleted which led to a significant ($p < 0.01$, $\chi 2$ distribution with one degree of freedom) rise (< 6.635) in OFV, the covariant was eventually excluded from the full model.

The PK model was validated by statistical and graphical approaches. Goodness-of-fit plots, comprising conditional weighted residuals (CWRES) vs time, CWRES vs population prediction (PRED), observed (DV) vs PRED, DV vs individual prediction (IPRED), were used for diagnostics (Hooker et al., 2007). The sampling importance resampling (SIR) analysis with M = 5,000, 2000, 2000, 1,000 samples and m = 1,000, 1,000, 1,000, 500 resamples (4 iterations) was conducted to evaluate the stability and accuracy of the parameter estimates by sir-package in PsN (v5.0.0) software (Dosne et al., 2016; Dosne et al., 2017). RStudio 1.4 using R 3.6.1 was used for graphical output. The convergence of SIR procedure was assessed by the dOFV distribution. The dOFV was the difference between the objective function value of the parameter vector and the OFV of the final parameter estimates. The parameter estimates (median and 95% confidence intervals) from the SIR analysis were contrasted with the parameter values from the original dataset. The normalized prediction distribution error (NPDE) was also applied to evaluate the final PK model (Comets et al., 2008). The original datasets were simulated 1,000 times using parameters from the final PK model. The NPDE results were based on the default graphical summary provided by the NPDE R package (v1.2) (Comets et al., 2008): 1) QQ-plot of the NPDE; 2) histogram of the NPDE. The NPDE was assumed to follow the N (0, 1) distribution.

PTA-Based Optimization of Dosing Regimen

The percentage of time that free drug concentration is above MIC for the dosing interval (fT_{MIC}) is important for the therapeutic efficacy of β-lactams (Hoog et al., 2005). The maximum antibacterial effect of β-lactams was assumed to be attained when the free fraction of drug exceeds the MIC for 60%–70% of dosing interval (Craig, 1998; Drusano, 2004). The 70% fT_{MIC} target was used as a conservative pharmacodynamic endpoint for infants.

Considering the balance between maximum efficacy, minimum toxicity and reduction of resistance, the following pharmacokinetic-pharmacodynamic target was chosen: 70% of patients attained the target of 70% fT_{MIC} (Cohen-Wolkowiez et al., 2012; Zhi et al., 2018; Shi et al., 2020). A fixed unbound fraction of 77% was used to calculate fT_{MIC} in this study (Tze-ying et al., 1979). Cefathiamidine is used to treat severe and often life-threatening infections in pediatric patients caused by *Streptococcus pneumoniae* (MIC_{90} 0.25 mg/L); *Streptococcus pyogenes* (MIC_{90} 0.5 mg/L); *H. influenza, Moraxella catarrhalis* and *Enterococcus* (MIC_{90} 2 mg/L); MSSA and MSSE (MIC_{90} 8 mg/L) for susceptible isolates (Guangzhou Baiyunshan Pharmaceuticals, 2015). Monte Carlo simulations (n = 1,000) were performed for various dosing regimens in infants by utilizing the original datasets to calculate the target attainment rate for the following MICs: 0.25, 0.5, 2, and 8 mg/L. The dose of cefathiamidine was simulated on an mg/kg basis. Target attainments rates were calculated for simulated doses to explore the PTA - based dosage regimen in infants with ARC.

RESULTS

Study Population

In total, 20 infants with ARC who underwent cefathiamidine treatment were recruited in this PK study. All infants received cefathiamidine as an intravenous infusion at an administered dose of 100 mg/kg/day q12 h. The median (range) eGFR of infants was 197 (132–413) ml/min/1.73 m^2. Weight and age were all normally distributed in this study (p = 0.20 and p = 0.08, respectively, Kolmogorov-Smirnov test). The mean (SD) values of age and weight in the infants were 1.20 (0.43) (range 0.35–1.86) years and 10.33 (1.57) (range 8.0–12.5) kg, respectively. The patient characteristics are presented in **Table 1**.

Model Building

For the population modeling, 36 cefathiamidine blood samples, with concentrations ranging from 0.15 to 222.00 μg/ml, were available. The concentrations of all samples were above the LLOQ. The concentration on log scale vs time profile of cefathiamidine is presented in **Supplementary Figure S1**.

The PK data of cefathiamidine were adequately illustrated by a 1-compartment model with first-order elimination. The model parameters were estimated regarding CL and V. For cefathiamidine, inter-individual variability (IIV) was exponentially modeled and then estimated for V and CL. An exponential model best described residual variability.

Covariate Analysis

The weight with allometric scaling approach was incorporated into the basic model (fixed allometric exponents of 0.75 and 1 for CL and V, respectively), with a significant decrease in the OFV of 7.37 points. Age was the most critical covariate on CL, along with a further OFV drop of 13.61 points and IIV drop of 15%. The η-shrinkages of the final PK model were 15.1 and 28.5% for CL and

TABLE 1 | Baseline characteristics in 20 infants.

Characteristics	Number	Mean (SD)	Median (Range)
Patients	20		
Male/female	10/ 10		
Race	Chinese		
Age (years)		1.20 (0.43)	1.25 (0.35–1.86)
Current weight (kg)		10.33 (1.57)	10.25 (8.00–13.00)
Scr (μmol/L)		18 (6)	20 (10–26)
eGFR (mL/min/1.73 m^2)		230 (86)	197 (132–413)
Dose (mg/dose)		533 (167)	500 (400–1,000)
Dose (mg/kg/dose)		52 (16)	50 (40–100)
Hematologic disease			
Immune thrombocytopenia	6		
Leukemia	3		
Anemia	3		
Infectious mononucleosis syndrome	2		
Agranulocytosis	2		
Other	4		

Notes: Scr: Serum creatinine concentration; eGFR: Estimated glomerular filtration rate.

TABLE 2 | Population PK parameters of cefathiamidine and SIR results.

Parameters	Full dataset		SIR	
	Final estimate	RSE (%)	Median (RSE%)	95% CIs
CL (L/h)				
$CL = \theta1\times(CW/10.25)^{0.75}\times F_{age}$				
$\theta1$	2.20	8.30	2.21 (8.2)	1.87–2.58
V (L)				
$V = \theta2\times (CW/10.25)$				
$\theta2$	3.36	8.2	3.35 (7.9)	2.89–3.96
$F_{age}= (AGE/1.25)^{\theta3}$				
$\theta3$	0.662	21.6	0.651 (22.5)	0.358–0.931
Inter-individual variability (shr) (%)				
CL	25.6 (15.1)	14.3	27.2 (18.2)	18.0–34.5
V	22.4 (28.5)	28.6	23.1 (38.4)	5.00–38.2
Residual variability (shr) (%)				
ERR (1)	22.6 (35.4)	22.2	23.3 (27.7)	9.81–34.7

Notes: CL: clearance; V: volume of distribution; CW: current weight in kilogram; Fage: age factor; AGE: age in years shr: shrinkage in %. In our population, 10.25 kg and 1.25 years are the median current weight and age values on the day of first sampling, respectively.

V, respectively. **Table 2** presents detailed parameter estimates for the final PK model.

The median (range) of weight-normalized CL and V were 0.22 (0.09–0.29) L/h/kg and 0.34 (0.24–0.41) L/kg, respectively. Cefathiamidine CL (L/h) increased allometrically with weight (kg) in infants. Cefathiamidine weight-normalized CL (L/h/kg) also increased with age (years) (**Supplementary Figure S2**). The area under the curve from time 0 to 24 h ($AUC_{0\text{-}24}$) for the prescribed dose ranged from 296 to 1,152 mg*h/L at steady-state.

Model Evaluation

An acceptable goodness-of-fit of the final model was shown in **Figures 1A–D**. In the plots of PRED vs DV and IPRED vs DV, a symmetric distribution of points was observed around the identity line. The plots of CWRES vs PRED and CWRES vs time were randomly distributed around CWRES = 0 within the residuals range from -2 to 2. No bias was observed in goodness-of-fit plots. The dOFV plot showed that the proposal distribution was above the reference Chi square and that the dOFV distributions of the resamples of last two iterations were overlaid. The dOFV plot was shown in **Supplementary Figure S5**. The final parameter estimates were close to the median SIR analysis values and lay within 95% confidence intervals (CIs) obtained from the SIR analysis, demonstrating that the developed model was robust (**Table 2**). The NPDE distribution and histogram comply well with the distribution and density of theory N (0, 1), indicating the model fits well with the individual data (**Figures 1E,F**). The variance and mean of NPDE were 1.14 and 0.09, respectively. The value of Fisher variance test, Wilcoxon signed rank test, Shapiro-Wilks test of normality and global-adjusted *p*-value is 0.533, 0.571, 0.614 and 1, respectively.

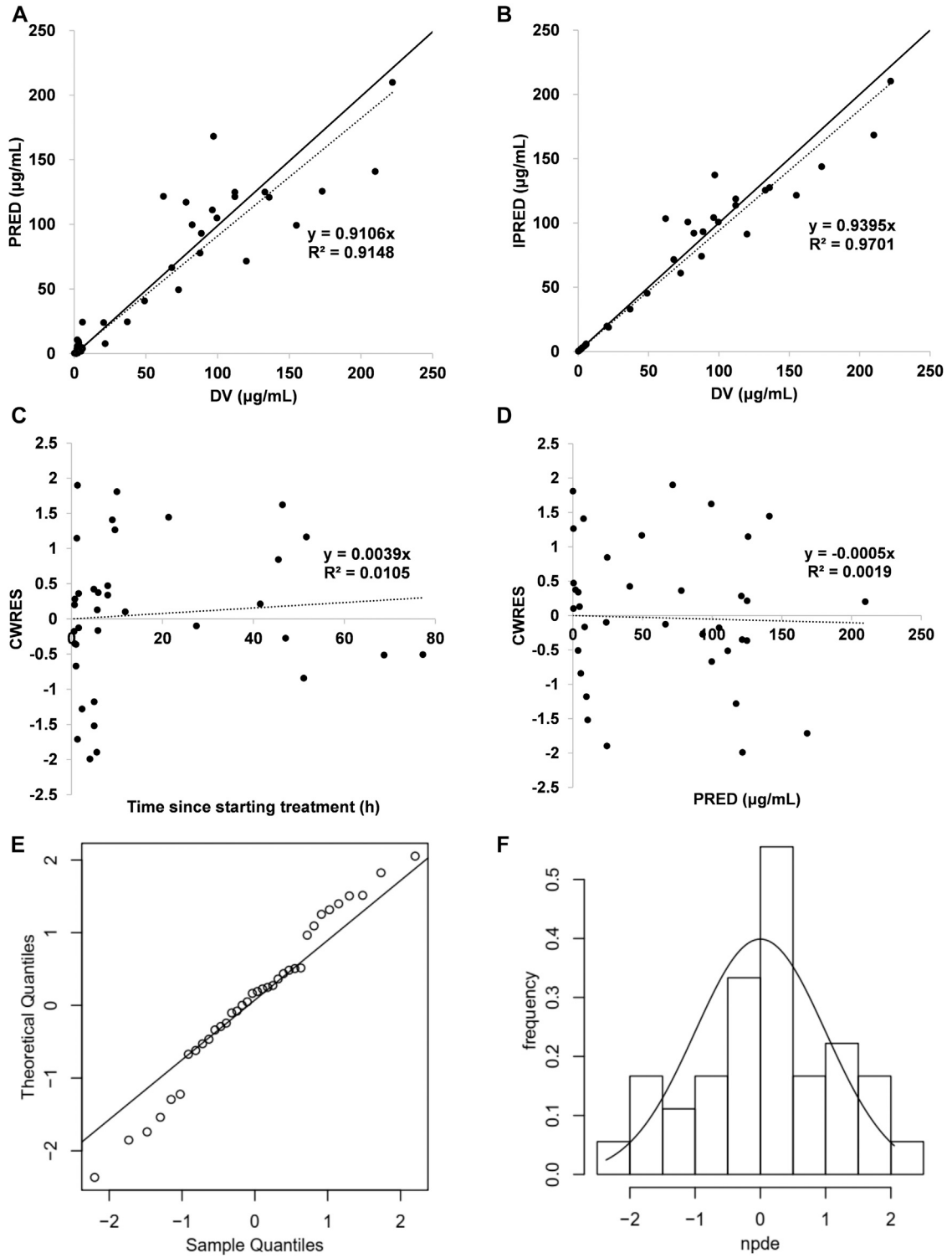

FIGURE 1 | Model evaluation for cefathiamidine **(A)** PRED vs DV **(B)** IPRED vs DV **(C)** CWRES vs time **(D)** CWRES vs PRED **(E)** NPDE QQ-plot vs the theoretical N (0,1) distribution **(F)** NPDE distribution histogram with the density of the standard Gaussian distribution overlaid. In the plot, the solid line is the identity line and the dotted line is the trend line.

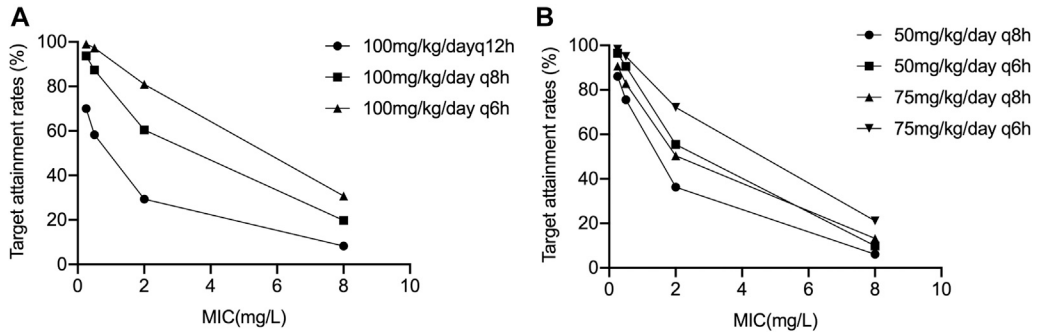

FIGURE 2 | Results of the PTA-based dosing simulations **(A)** 100 mg/kg/day q6 h, q8 h, and q12 h; **(B)** 50 mg/kg/day q6 h, q8 h, and 75 mg/kg/day q6 h, q8 h.

PTA-Based Dosing Regimen Optimization and Evaluation

Results of the PTA-based dosing simulations are showed in **Figure 2**. For the prescribed dose of 100 mg/kg/day q12 h, the target (70% fTMIC) was achieved in 70.1, 58.3, 29.4 and 8.3% of infants for bacteria with a MIC of 0.25, 0.5, 2 and 8 mg/L, respectively. If the dosing interval was shortened to 8 h, the doses of 50 mg/kg/day q8 h resulted in 75.5% (MIC 0.5 mg/L) and 36.3% (MIC 2 mg/L) infants to achieving the target, respectively. If the dosing interval was shortened to 6 h, the doses of 75 mg/kg/day q6 h resulted in 72.1% (MIC 2 mg/L) of infants achieving the target. Nevertheless, the dose of 100 mg/kg/day q6 h resulted in only 30.8% of infants achieving the target for bacteria with a MIC of 8 mg/L, indicating the need for higher dosing or different antibiotics.

DISCUSSION

For the first time a PK model of intravenous cefathiamidine was established in infants with ARC that was also used for dose optimization. A one-compartment model best fitted the PK data obtained from 20 ARC infants. The median CL and V of cefathiamidine in infants aged 0.35–1.86 years were 0.22 L/h/kg and 0.34 L/kg, respectively. The final model was verified by graphics and statistical methods, which showed that the model had a good prediction performance and stability.

Cefathiamidine is primarily eliminated by the renal pathway as the parent compound, and GFR as an indicator of renal function may influence cefathiamidine disposition. Nevertheless, the covariate screening analysis showed that eGFR had no significant influence on cefathiamidine clearance. Only weight with allometric scaling and age were identified as significant covariates. This can be ascribed to a limited range of eGFR (132–413 ml/min/1.73 m^2). The plot between cefathiamidine CL and eGFR shows no trend (**Supplementary Figure S3**).

It is noteworthy that the infants with ARC (eGFR, range 132–413 ml/min/1.73 m^2) were included in the current study. The primary mechanisms underlying ARC are likely to be a result of the systemic inflammatory response, hyperdynamic cardiovascular state, fluid volume loading characterized by increases in cardiac output and renal blood flow (Udy et al., 2010; Cook and Hatton-Kolpek, 2019). ARC is associated with enhanced drug elimination (Zhou et al., 2020) and, as a consequence, underexposure of patients to renally excreted medications. We summarized eight pharmacokinetic models of renally eliminated drugs in pediatric patients with ARC, as shown in **Supplementary Tables S1, S2**. Importantly, clinicians need to be aware of the risk of conventional dosing in patients with ARC because these patients have elevated significant higher CL than the general population without ARC for renally cleared drugs (Udy et al., 2015; Lv et al., 2020). Age and ARC had effects on the pharmacokinetic parameters of renally excreted drugs (Avedissian et al., 2017; Chen et al., 2018; Béranger et al., 2019). The estimated CL (0.09–0.29 L/h/kg) in this study is different from the CL value (0.05–0.43 L/h/kg) in children reported previously. (Zhi et al., 2018). This difference is likely due to the effect of the age groups of infants and children on CL. In this study, we analyzed the CL difference between infants ≤1 year old and those 1–2 years old, with the p value set a priori at 0.05. The mean (SD) of CL values were 0.11 (0.032) L/h/kg and 0.23 (0.034) L/h/kg for infants ≤1 and 1–2 years old, respectively, and the difference between two age groups was statistically significant (independent samples t test, $t = -6.424$, $p < 0.05$).

Simulations showed that the current dosage of cefathiamidine (100 mg/kg/day q12 h) would lead to a high risk of underdosing in infants with ARC for bacteria with a MIC ≥ 0.5 mg/L. To improve the proportion of patients reaching the pharmacodynamic target, increasing the dose and/or dosing frequency have been selected (Shi et al., 2018; Li et al., 2019). As the safety of high doses and toxicity threshold has not been evaluated, increasing the dosing frequency has been primarily considered to avoid possible cefathiamidine related toxicity. The optimal dosing regimens of 50 mg/kg/day q8 h and 75 mg/kg/day q6 h was required to treat bacteria with a MIC 0.5 and 2 mg/L, respectively. When the MIC was 8 mg/L, the therapeutic target is difficult to achieve, and different antibiotics should be taken into consideration in clinical treatment. In this study, the cumulative fraction of response (CFR) was not calculated to

estimate the overall response of microorganisms to cefathiamidine, due to the lack of study on MIC distributions for strains. The MIC distribution for cefathiamidine with respect to strains should be studied in the future. In respiratory infection, the most common microorganisms were *H. influenza* (33.90%), *Streptococcus pneumoniae* (33.55%), *Moraxella catarrhalis* (19.20%) and *Staphylococcus aureus* (3.64%) from 15047 children (Wang et al., 2019). About 90% of the common pathogens had MIC90 ≤ 2 mg/L. The dose of 75 mg/kg/day q6 h was recommended for respiratory infection.

Our study has several limitations. First, the PK model of cefathiamidine was only validated internally due to a limited number of patients. Second, the unbound concentration of cefathiamidine was not measured due to the limited sample volume, and the total concentration was analyzed Given that cefathiamidine has a low protein binding ratio of 23%, albumin collection was not included in the design of the PK study. We eventually adopted a fixed unbound fraction of 77% in dosing simulation. Third, the GFR was estimated based on serum creatinine in our study, because timed urine collection is difficult in infants who are not toilet trained or have bladder dyssynergia. Finally, PK study of cefathiamidine was not available in the non-ARC pediatric population, and further studies should be performed in larger pediatric patients with and without ARC. The clinical application of dose optimization based on PK modeling should be further evaluated in the clinical setting.

CONCLUSION

The population PK model of cefathiamidine was developed in infants with ARC. Weight with allometric scaling and age have been shown to have significant effects on cefathiamidine pharmacokinetics. The prescribed dose (100 mg/kg/day q12 h) could cover bacteria with a MIC ≤ 0.25 mg/L. Based on this developed PK model, 50 mg/kg/day q8h and 75 mg/kg/day q6h were adopted for bacteria with MIC 0.5 and 2 mg/L to achieve the pharmacodynamic target, respectively. As the relationship between high dose and safety remains to be revealed, other antibiotics should be considered for bacteria with a MIC of 8 mg/L and higher.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Board of Children's Hospital of Hebei Province affiliated to Hebei Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WZ and YZ conceived the outline and reviewed and revised the manuscript. BD and YZ analyzed the sample data and drafted the paper. B-HT, Y-EW, X-MY, H-Y S and B-FY collected clinical samples and recorded patient information. D-PY, JA and G-XH provided advice and edited the manuscript. All authors contributed to this article and reviewed and approved the version as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.630047/full#supplementary-material.

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External Evaluation of Vancomycin Population Pharmacokinetic Models at Two Clinical Centers

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Background: Numerous vancomycin population pharmacokinetic models in neonates have been published; however, their predictive performances remain unknown. This study aims to evaluate their external predictability and explore the factors that might affect model performance.

Methods: Published population pharmacokinetic models in neonates were identified from the literature and evaluated using datasets from two clinical centers, including 171 neonates with a total of 319 measurements of vancomycin levels. Predictive performance was assessed by prediction- and simulation-based diagnostics and Bayesian forecasting. Furthermore, the effect of model structure and a number of identified covariates was also investigated.

Results: Eighteen published pharmacokinetic models of vancomycin were identified after a systematic literature search. Using prediction-based diagnostics, no model had a median prediction error of ≤ ± 15%, a median absolute prediction error of ≤30%, and a percentage of prediction error that fell within ±30% of >50%. A simulation-based visual predictive check of most models showed there were large deviations between observations and simulations. After Bayesian forecasting with one or two prior observations, the predicted performance improved significantly. Weight, age, and serum creatinine were identified as the most important covariates. Moreover, employing a maturation model based on weight and age as well as nonlinear model to incorporate serum creatinine level significantly improved predictive performance.

Conclusion: The predictability of the pharmacokinetic models for vancomycin is closely related to the approach used for modeling covariates. Bayesian forecasting can significantly improve the predictive performance of models.

Keywords: vancomycin, population pharmacokinetics, neonates, external evaluation, individualized drug administration

INTRODUCTION

Vancomycin is a glycopeptide antibiotic used as the gold standard treatment for serious infections in adults caused by Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (Pacifici and Allegaert, 2012). Vancomycin is also effective in infants with serious Gram-positive infections. However, the therapy window of vancomycin is narrow, and differences in neonatal development and pathophysiology result in high inter-individual variability in vancomycin pharmacokinetics (Stockmann et al., 2015). Although excessive exposure to vancomycin can lead to side effects including ototoxicity and nephrotoxicity (An et al., 2011), under-dosing is often associated with treatment failure and patient mortality (Rybak et al., 2020). Therefore, despite the challenges, it is imperative to optimize vancomycin regimens in neonates.

Therapeutic drug monitoring is an applicable approach for the pharmaceutical care of vancomycin. According to the American Society of Health-System Pharmacists consensus (2020), the administration target for vancomycin is an area under the concentration-time curve (AUC)/minimum inhibitory concentration of ≥400 h in neonates and infants (Rybak et al., 2020). Although obtaining a sufficiently large number of samples to estimate the AUC is difficult in clinical practice, especially for neonates, a population pharmacokinetic analysis could provide sufficient pharmacokinetic parameters to estimate the AUC through sparse sampling. It is possible to model vancomycin dosing in neonates through reliable individual pharmacokinetic characteristics using Bayesian approaches.

Choosing the appropriate population PK model to estimate the initial and maintenance dosage for vancomycin is essential in clinical practice; however, the performance of most of the published pharmacokinetic models is still unknown. Zhao et al. (2013a) conducted an external evaluation of six models in neonates and found that the analytical method used for serum creatinine (SCR) is a crucial factor in explaining the variability of predictions among different studies. However, more than ten population PK studies have been conducted since then, using several new modeling strategies. Therefore, it is still worth evaluating all the published population pharmacokinetic models for vancomycin in neonates.

Our research aimed to systematically evaluate the published population pharmacokinetic models of vancomycin in neonates, using data from independent cohorts collected from two clinical centers. Moreover, factors that may influence model predictability were also investigated, such as structural model selection and covariate screening approaches, to provide informed guidance for future studies.

MATERIALS AND METHODS

Review of Published popPK Studies

The PubMed, Scopus, and Web of Science databases were systematically searched for population pharmacokinetic analyses of vancomycin published up to October 2020. The key words "vancomycin," "pharmacokinetic" or "pharmacokinetics" or "model" or "nonlinear mixed effect model" were used in the search strategy. The publications were included if 1) the study was a population pharmacokinetic analysis of vancomycin in neonates and 2) the article was written in English.

The publications were excluded if 1) the model was not created using a nonlinear mixed-effects modeling approach, or 2) the model could not be recreated using the published information, or 3) the modeling populations overlapped or the articles were duplicated.

External Evaluation Cohort

Patients

Datasets were derived from published population PK studies conducted in neonates who received vancomycin at Shanghai Children's Hospital between January 2013 and December 2016 (Li et al., 2018), and Suzhou Hospital Affiliated to Nanjing Medical University between September 2011 and March 2016 (Li et al., 2017). Patients included in these two studies were preterm neonates with a postmenstrual age (PMA) of ≤48 weeks and term neonates with a postnatal age (PNA) of ≤28 days. All patients were treated with vancomycin for at least 3 days, and at least one vancomycin level was determined based on routine therapeutic drug monitoring. Patients with extracorporeal membrane oxygenation or who were on continuous renal replacement therapy were excluded from this study.

The following information was collected in each study: gestational age (GA), PMA, PNA, current weight (WT), birth weight, dosing records, measurements of vancomycin levels, and SCR level.

The doses of vancomycin ranged from 10 to 15 mg/kg, administered every 8 h or every 12 h with a 1 h or 2 h infusion duration. Peak samples were collected 1 h after completion of drug infusion, and trough samples were collected half an hour before vancomycin administration in each neonate. Trough and peak levels were determined after at least four repeated doses.

Bioassay

Vancomycin levels were determined using a fluorescence polarization immunoassay with an Architect i2000SR (Abbott Laboratories, Chicago, IL, UNITED STATES). The limit of detection was 1 mg/L, and the calibration range was 3–50 mg/L. The intra-day and inter-day coefficients of variation were <20%.

SCR assays were performed at the Shanghai Children's Hospital using the enzymatic method and were analyzed with a 7,180 automatic analyzer (Hitachi High-Tech Science Systems Corporation, Tokyo, Japan). The calibration range was from 3 to 100 mg/L. SCR assays were performed at the Suzhou Hospital Affiliated to Nanjing Medical University using the enzymatic method and were analyzed with a 7,600 Automatic Analyzer (Hitachi High-Tech Science Systems Corporation, Tokyo, Japan). The calibration range was 0.08–100 mg/L.

Creatinine clearance was calculated using the Schwartz formula as in **Eq. 1** (Schwartz et al., 1984):

$$CLcr\left(\mathrm{mL/min/1.73\times m^2}\right)=\frac{\mathrm{k}\times \mathrm{HT}}{\mathrm{SCR}}, \quad (1)$$

where CLcr represents creatinine clearance, HT (cm) represents height, SCR (umol/L) represents serum creatinine, k is 0.45 for term neonates, and 0.33 for preterm neonates.

SCR was standardized to the enzymatic method (SCR*) if the Jeff method (SCR†) was employed in the external model by **Eq. 2** (Srivastava et al., 2009)

$$\mathrm{SCR} \times (\mu\mathrm{mol/L}) = 1.050 \times 88.41 \times \mathrm{SCR}^{\dagger} \times (\mathrm{mg/dL}) - 0.122. \quad (2)$$

If the method was not clarified in the report, the enzymatic method was used.

External Evaluation

Data were analyzed using a nonlinear mixed-effects modeling program (NONMEM®, Version 7.4; Icon Inc., PA, UNITED STATES) compiled with gFortran (Version 4.9.2; http://www.gfortran.org). Statistical analysis and graphing were performed using R (Version 3.6.1; http://www.r-project.org) and the xpose package.

The reported population pharmacokinetic model was reconstructed based on information extracted from the original articles. The NONMEM code for each model was determined by a double check. The predictabilities of all candidate models were externally evaluated by prediction- and simulation-based diagnosis and Bayesian forecasting (Zhao et al., 2016; Mao et al., 2018; Cai et al., 2020).

Prediction-Based Diagnostics

The predicted population concentrations (PRED) were estimated and compared with the corresponding observations (OBS) by estimating the relative prediction error (PE%) using **Eq. 3**:

$$\mathrm{PE}(\%) = \frac{\mathrm{PRED} - \mathrm{OBS}}{\mathrm{OBS}} \times 100\%. \quad (3)$$

The median prediction error (MDPE) was used to evaluate predictive accuracy, whereas the median absolute prediction error (MAPE) was used to evaluate predictive precision. F_{20} and F_{30} were also calculated as combination indexes of both accuracy and precision, and indicate the percentage of PE that fell within the ±20% and ±30% ranges, respectively. When the standards of MDPE ≤ ± 15%, MAPE ≤30%, F_{20} > 35%, and F_{30} > 50% were reached, the model could be determined as satisfactory and clinically acceptable.

Simulation-Based Diagnostics

A prediction- and variability-corrected VPC (pvcVPC) (Bergstrand et al., 2011) was conducted for simulation-based diagnostics. The pvcVPC takes into account typical population predictions and typical population variabilities compared with the traditional VPC, accounting for the different expected variabilities within individuals. The pvcVPC was conducted with 1,000 simulated datasets generated using the models to be evaluated. The pvcVPC was performed using the Perl speak NONMEM toolkit (PsN, version 4.7.0).

Maximum a posteriori Bayesian (MAPB) forecasting was conducted to assess the influence of prior observations on model predictability. Patients with ≥1, 2, three observations were included in the analysis for Bayesian forecasting using zero, one and two previous observations, respectively. For a patient, the individual prediction (IPRED) of the third observation was predicted using the first and second observations, the second observation was predicted using the first observation, and then compared with the corresponding observations. The relative differences denoted by the individual prediction error (IPE%) were calculated using **Eq. 4** below:

$$\mathrm{IPE}_i(\%) = \frac{\mathrm{IPRED}_i - \mathrm{OBS}_i}{\mathrm{OBS}_i} \times 100 \, (i = 1, 2, 3). \quad (4)$$

To evaluate the predictability of the candidate models when prior information is increased, the standards of an IPE% (MDIPE) ≤ ± 15%, an IPE% (MAIPE) ≤ 30%, an IF_{20} > 35%, and an IF_{30} > 50% were used for MAPB forecasting.

The Impact of Modeling Approaches

Different modeling strategies were used in previous studies, which may affect the predictive performance of the model. To explore the impact of these different modeling strategies, we evaluated the predictability of various structural models and covariate models employed in previous studies. The assessment methods include the aforementioned prediction-based diagnostics and Bayesian forecasting methods.

RESULTS

Review of Published popPK Analysis on Vancomycin

After a systematic literature search, 18 neonatal vancomycin models (Seay et al., 1994; Grimsley and Thomson, 1999; Capparelli et al., 2001; Kimura et al., 2004; Mulla and Pooboni, 2005; Marqués Minñana et al., 2010; Mehrotra et al., 2012; Zhao et al., 2013b; Frymoyer et al., 2014; Li et al., 2017; Sheng et al., 2017; Song et al., 2017; Chen et al., 2018; Li et al., 2018; Moffett et al., 2018; Colin et al., 2019; Germovsek et al., 2019; Moffett et al., 2019) were included in this study. The literature search procedure is shown in **Supplementary Figure S1**. Of the enrolled studies, six were from UNITED STATES, three from the UNITED KINGDOM, five from China, one each from Japan and Spain, and one study enrolled patients from France, Greece, France, and Malaysia. Only 10 models described the analytical method used for the determination of SCR.

Most studies employed sparse sampling strategies. Six models were established with a two-compartment model (2CMT), whereas 12 models were established with a one-compartment (1CMT) model.

Weight, age, and renal function were the most important covariates for clearance identified in the previous studies. Maturation models were employed in 11 studies and could be described by **Eq. 5** (Holford et al., 2013):

$$\mathrm{CL} = \mathrm{CL}_{\mathrm{std}} \times \mathrm{F}_{\mathrm{size}} \times \mathrm{F}_{\mathrm{mat}}, \quad (5)$$

where CLstd represents the baseline clearance, Fsize refers to the body size factor, and Fmat refers to the maturation factor.

Weight (current weight and birth weight) and age (postmenstrual age, PMA; postnatal age, PNA, and GA) were regarded as the main

TABLE 1 | Summary characteristics of published population pharmacokinetic studies of vancomycin in neonates.

Author	Country	Patients/ Samples	SCR (μmol/L) (median, min- max)	WT (kg) (median, min- max)	PMA (weeks) (median, min- max)	PNA(days) (median, min- max)	GA (weeks) (median, min- max)	Serum creatinine measurement
Seay_et al., 1994	UNITED STATES	192/520	NA	1.48 (0.39–4.35)	NA	14.5 (1–73)	29.6 (22–42)	NA
Grimsley and Thomson, 1999	UNITED KINGDOM	59/347	49.0 (18.0–172)	1.52 (0.57–4.23)	NA	19 (2–76)	29 (25–41)	Jaffe method
Capparelli et al., 2001	UNITED STATES	374/1,103	66.9 (NA)	2.82 (NA)	NA	70 (NA)	33.5 (NA)	Jaffe method
Kimura et al., 2004	Japan	19/88	17.7–79.6	NA (0.710–5.20)	NA	NA (3.00–71.0)	NA (24.1–41.3)	Enzymatic method
Mulla and Pooboni, 2005	UNITED KINGDOM	15/NA	79.6 (39.0–180)	3.50 (2.50–4.50)	NA	8.20 (0–28.0)	40.4 (34.3–42.0)	NA
Marqués Minñana et al., 2010	Spain	70/NA	NA	1.70 (0.70–3.70)	34.6 (25.1–48.1)	16.9 (4.00–63.0)	32.2 (24.0–42.0)	NA
Mehrotra et al., 2012	UNITED STATES	134/267	53.1 (17.7–221)	2.50 (0.60–5.30)	36.5 (24.6–44)	26.8 (1–121)	32.7 (23–41)	NA
Zhao et al., 2013a	France	116/207	48.0 (5.00–228)	1.70 (0.46–5.68)	33.8 (24.4–49.4)	26 (1–120)	NA	NA
Frymoyer et al., 2014	UNITED STATES	249/1702	NA (8.8–239)	2.90 (0.500–6.30)	39 (24–54)	19 (0–173)	34 (22–42)	Jaffe method
Li et al. ., 2017	China	80/165	28.3 (5.85–61.6)	2.74 (1.4–5.6)	40.0 (29–47.1)	24 (4–126)	34 (25.7–41.1)	Enzymatic method
Sheng et al., 2017	China	61/72	32.3 (10.4–109)	3.15 (0.95–16.0)	NA	29 (1–354)	NA	Jaffe method
Song et al., 2017	China	102/316	28.6 (12–151)	3.95 (1.25–7.62)	NA	NA	37 (28–41)	NA
Chen et al., 2018	China	213/330	24.8 (9.72–63.7)	2.73 (0.88–5.1)	39.8 (28–47.9)	26 (6–59)	24.8 (9.72–63.7)	NA
Li et al., 2018	China	80/165	32.2 (13.1–54.2)	1.9 (0.81–4.71)	35.02 (28.3–44.0)	17 (4–50)	32.6 (25.7–41.3)	Enzymatic method
Moffett et al., 2018	UNITED STATES	93/NA	49.5 (28.2–89.3)	7.6 (3.7–21.9)	73.2 (41.1–391.2)	233 (25.6–2,446)	49.5 (28.2–89.3)	NA
Colin et al., 2019	Belgium	247/NA	64.5 (34.5–187)	1.20 (0.42–2.63)	31.3 (24–37)	11 (1–27)	NA	NA
	Greece	130/NA	50.4 (23–180)	1.07 (0.51–4.41)	31.3 (26.6–43.8)	13 (3–27)	NA	NA
	France	67/NA	53 (17.7–274.8)	1.06 (0.68–4.45)	31.3 (27.1–45.9)	13 (4–95)	NA	NA
	Malaysia	116/NA	77.8 (29.2–143)	0.90 (0.50–2.00)	28.7 (23.5–33.9)	5 (1–39)	NA	NA
Germovsek et al., 2019	UNITED KINGDOM	54/102	31.0 (18–98)	NA	29 (23.7–41.9)	30 (1–156)	NA	Jaffe method
Moffett et al., 2019	UNITED STATES	261/NA	28.3 (22.1–36.2)	4.8 (3.4–7.4)	54.6 (42.6–76.9)	27 (26–281)	38.7 (37.1–40)	NA

GA, gestational weeks (weeks); PMA, postmenstrual age (weeks); PNA, postnatal age (days); Scr, serum of creatinine (μmol/L); WT, weight (kg); NA, not available.

factors for body size and maturation, respectively. The current weight was used in most of the reported studies. PMA was chosen over GA and PNA as it presented the most parsimonious way to account for both antenatal and postnatal maturation, which can be incorporated as a sigmoid Emax model and asymptotic exponential model, as shown in **Eq. 6** and **Eq. 7** (Salman et al., 2019). Among the included studies, seven out of 18 models applied the sigmoid Emax model:

$$\mathrm{Fmat} = \frac{1}{1 + \left(\frac{\mathrm{PMA}}{\mathrm{TM}_{50}}\right)^{\mathrm{Hill}}}, \tag{6}$$

where TM_{50} is the value of PMA when clearance maturation reaches 50% of adults; Hill is the slope parameter for the sigmoid E_{max} maturation model.

$$\mathrm{Fmat} = e^{\theta \exp \times (PMA - medianPMA)}. \tag{7}$$

Renal function was often presented by SCR in reported studies and was included in nonlinear manner.

The characteristics of each study are summarized in **Table 1**, and the information on population pharmacokinetic models were shown in **Table 2**.

External Evaluation Cohort

The study population consisted of 171 neonates in whom there were 319 assessments of vancomycin levels. Of these, 80 neonates with 165 vancomycin levels were from Shanghai Children's Hospital (SH), and 91 neonates with 154

TABLE 2 | Summary models' information of published population pharmacokinetic studies of vancomycin in neonates.

Author	Structural model		Parameter and formula	BSV% (IOV%)	Residual error
Seay et al.,1994	2CMT	CL	0.059 × WT × 0.46 (if co-therapy with dopamine) × 0.643 (If GA≤32)	40.6%	3.3 mg/L
		V_C	0.44 × WT	16.8%	
		V_{SS}	0.769 × WT	54.1%	
		Q	0.0313 × WT	/	
Grimsley et al., 1999	1CMT	CL	3.56 × WT/ [(SCR+0.12)/1.05]	22%	4.53 mg/L
		V	0.669 × WT	18%	
Capparelli et al., 2001	2CMT	CL	0.006 + WT × [0.028/SCR + 0.000127 × PNA + 0.0123 (If GA>28)]	32%	14%, 3.4 mg/L
		Vss	0.793 × WT +0.01	16%	
		Vc	0.0666 × (0.793 × WT +0.01)	/	
		Q	0.0334 × WT	/	
Kimura et al., 2004	1CMT	CL	0.025 × WT× (88.41/ SCR) × 1.292 (If PCA ≥34 weeks)	22.9%	3.22 mg/L
		V	0.66 × WT	20.8%	
Mulla et al., 2005	2CMT	CL	WT / [(SCR+0.12)/1.05] × 4.3(If PNA >1000 days) × (2.4 + 0.0018 × PNA) (If PNA <1000 days)	25%	12.1%, 2.1 mg/L
		Q	0.09 × WT	91%	
		V_c	WT× 0.45 (If PNA <4000 days) × 0.37 (If PNA >4000 days)	25%	
		V_T	0.25 × WT	48%	
Marqués Minñana et al., 2010	1CMT	CL	0.00192× PMA× WT× 1.65 (If co-therapy with amoxicillin–clavulanic acid)	35.6%	2.69 mg/L
		V	0.572× WT × 0.656 (If co-therapy with spironolactone)	19.3%	
Mehrotra et al., 2012	1CMT	CL	$0.18 \times (WT/2.5)^{0.75} \times (0.42/[(SCR/88.41+0.12)/1.05])^{0.7} \times (PMA/37)^{1.4}$	25.3%	1.5 mg/L,16% (if LOQ = 0.5 mg/L); 5 mg/L(if LOQ = 5 mg/L)
		V	$1.7\times (WT/2.5)^{1.0}$	21.8%	
Zhao et al., 2013	1CMT	CL	$0.0571\times (WT/1.416)^{0.513} \times (bWT/1.01)^{0.599} \times (1+0.282\times PNA/17) \times 1/(SCR/42)^{0.525}$	40.1%	20.3%, 2.28 mg/l
		V	$0.791 \times (WT/1.416)^{0.898}$	17.9%	
Frymoyer et al., 2014	1CMT	CL	$0.345\times (WT/2.9)^{0.75} \times 1/[1+(PMA/34.8)^{-4.53}] \times (1/[(SCR/88.41+0.12)/1.05])^{0.267}$	21.6%	20.5%, 1.3 mg/L
		V	1.75 × (WT/2.9)	10.9%	
Li et al., 2017	1CMT	CL	$4.6\times (WT/70)^{0.75} \times [PMA^{5.46}/(PMA^{5.46}+37.6^{5.46})]\times 1.230/SCR$	24.4%	36.9%
		V	61.1× (WT/70)	/	
Sheng et al., 2017	1CMT	CL	$0.449\times (WT/3.22)^{0.0643}\times (PNA/36.5)^{0.289}$	13.9%	0.281 mg/L
		V	4.45	/	
Song et al., 2017	2CMT	CL	$0.42\times (bWT/3.22)^{0.888}\times (PNA/29)^{0.449}$	46.60%	1.48 mg/L
		Vc	1.27	/	
		Vp	2.422	/	
		Q	1.161	/	
Chen et al., 2018	1CMT	CL	$4.87\times (WT/70)^{0.75} \times [PMA^{4.61}/(PMA^{4.61}+34.5^{4.61})] \times [(SCR/88.41+0.12)/1.05]^{-0.221}$	26.80%	23.9%, 0.688 mg/L
		V	40.7× (WT/70)	/	
Li et al., 2018	1CMT	CL	$0.309\times (WT/2.9)^{1.55} \times (SCR/23.3)^{-0.337}$	37.3%	37.9%
		V	$2.63\times (WT/2.9)^{1.05}$	/	
Moffett et al., 2018	2CMT	CL	$3.96\times (WT/70)^{0.75}\times [0.588/(SCR/88.41+0.12)]^{0.809}\times [1/(1+(PMA/43)^{-0.949}]$	28.8%	19.40%
		Vc	$25.2\times (WT/70)\times 0.932^{(PNA/233.6)}$	94.8%	
		Vp	$32.4\times (WT/70)\times 1.27^{(2.9/ALB)}$	/	
		Q	5.8	/	
Germovsek et al., 2019	1CMT	CL	$5.7\times (WT/70)^{0.632}\times [PMA^{3.33}/(PMA^{3.33}+55.4^{3.33})]$	31.6% (30%)	30%
		V	39.3× (WT/70)	31.6%	
Moffett et al.,2019	1CMT	CL	$7.86\times (WT/70)^{0.75}\times (CLCR/84)^{0.9} \times [1/(1+(PMA/50)^{-0.285}]$	17.4%	19.90%
		V	63.6× (WT/70)	25.5%	
Colin et al., 2019	2CMT	CL	$5.31 \times (WT/70)^{0.75} \times 1/[1+(46.4/PMA)^{2.89}] \times 1/[1+(61.6/(PMA*0.019)^{-2.24}] \times e^{[-0.649\times (SCR/88.41-SCRstd)]} \times 1.292$(if haematological malignancies)] × 0.755 (if heel-prick sampling) $SCRstd = e^{[-1.228+\log 10 (PMA*0.019)\times 0.672+6.27\times e(3.11\times PMA*0.019)]}$	27.9%	21.5%, 1.23 mg/L
		Vc	42.9 × (WT/70) × 0.688 (if heel-prick sampling)	27.3%	
		Vp	41.7 × (WT/70)	97.9%	
		Q	$3.22 \times (WT/70)^{0.75}\times 0.403$ (if heel-prick sampling)	/	

ALB, albumin(g/L); BSV%, the percentage of the value of between subject variation; bWT, birth weight(kg); CMT, compartment; CL, clearance (L/hour); CLCR, creatinine clearance(mL/min); GA, gestational weeks (weeks); IOV, inter-occasion variation; LOQ, limit of quantitation; PCA, postconceptional ages (weeks); PMA, postmenstrual age (weeks); PNA, postnatal age (days); Q, inter-compartmental clearance (L/hour); SCR, serum of creatinine (μmol/L); V, volume of distribution (L); Vc, volume of distribution of central compartment (L); Vss, volume of distribution of steady state; VP, volume of distribution of peripheral compartment (L); VT, the volume of tissue compartment; WT, weight (kg). /: not available.

TABLE 3 | Neonatal characteristics in external evaluation dataset.

Center	SH		SZ		Total dataset	
Variable	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Mean ± SD	Median (range)
No. of patients (male/female)	80 (54/26)	—	91 (54/37)	—	171 (108/63)	—
No. of serum concentration measured	165	—	154	—	319	—
Weight (kg)	2.87 ± 0.89	2.74 (1.4–5.6)	2.19 ± 0.90	1.9 (0.81–4.71)	2.55 ± 2.42	2.42 (0.81–5.6)
Birth weight (g)	2,393 ± 968	2,410 (850–4,000)	2006.48 ± 871.88	1700 (740–3,700)	2,186 ± 907	1,000 (740–4,000)
Height (cm)	46.8 ± 4.72	47 (37–65)	43.26 ± 5.48	42 (26–53)	44.7 ± 5.27	45 (26–65)
Postnatal age, PNA (days)	32.3 ± 24.1	24 (4–126)	18.46 ± 10.28	17 (4–50)	24.7 ± 17.3	20 (4–126)
Gestational weeks, GA (week)	34.7 ± 4.31	34 (25.7–41.1)	33.32 ± 4.11	32.6 (25.7–41.3)	34.1 ± 4.08	33.1 (25.7–41.3)
Postmenstrual age, PMA (week)	39.4 ± 3.60	40.0 (29–47.1)	35.95 ± 3.96	35.02 (28.27–43.99)	37.6 ± 4.04	37.8 (28.27–47.1)
Serum creatinine[a] (μmol/L)	23.2 ± 10.4	28.3 (5.85–61.6)	31.85 ± 9.70	32.20 (13.05–54.2)	26.4 ± 10.4	26.4 (13.05–61.6)
Creatinine clearance (ml/min/1.73m^2)	52.3 ± 17.5	51.4 (21.8–92.5)	36.21 ± 14.88	32.09 (17.63–87.63)	41.2 ± 17.9	45.4 (17.63–92.5)
Blood urea nitrogen, BUN (mmol/L)	4.96 ± 3.89	4.10 (0.40–28.5)	4.01 ± 2.89	3.17 (0.46–15.87)	4.1 ± 3.0	3.49 (0.46–28.5)
First dosage (mg)	45.0 ± 16.4	42 (20–105)	32.20 ± 16.32	25 (8–85)	34.3 ± 17.1	30 (8–105)
Trough concentration (mg/L)	11.2 ± 7.92	9.15 (3.14–42.9)	12.17 ± 6.78	10.48 (3.32–32.23)	11.7 ± 7.37	9.94 (3.32–42.9)
Peak concentration (mg/L)	22.3 ± 11.0	20.3 (4.09–51.9)	—	—	22.3 ± 11.0	20.3 (4.09–51.9)
Albumin, ALB (g/L)	32.4 ± 5.49	32.0 (21.6–46.8)	30.40 ± 4.85	30.49 (13.39–44.09)	31.2 ± 4.80	31.4 (13.39–46.8)

[a]*Schwartz Equation.*

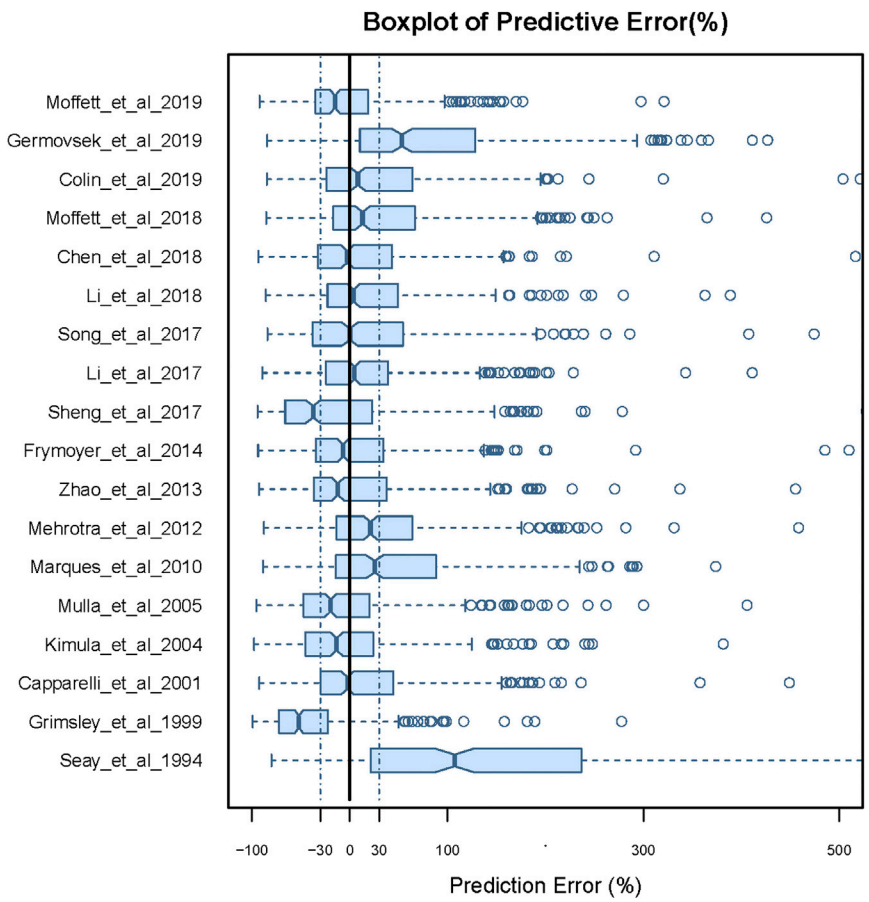

FIGURE 1 | Box plots of the prediction error (PE%) for published population pharmacokinetic models in external data. Black solid lines and blue dotted lines are reference lines indicating PE% of 0% and ±30%, respectively.

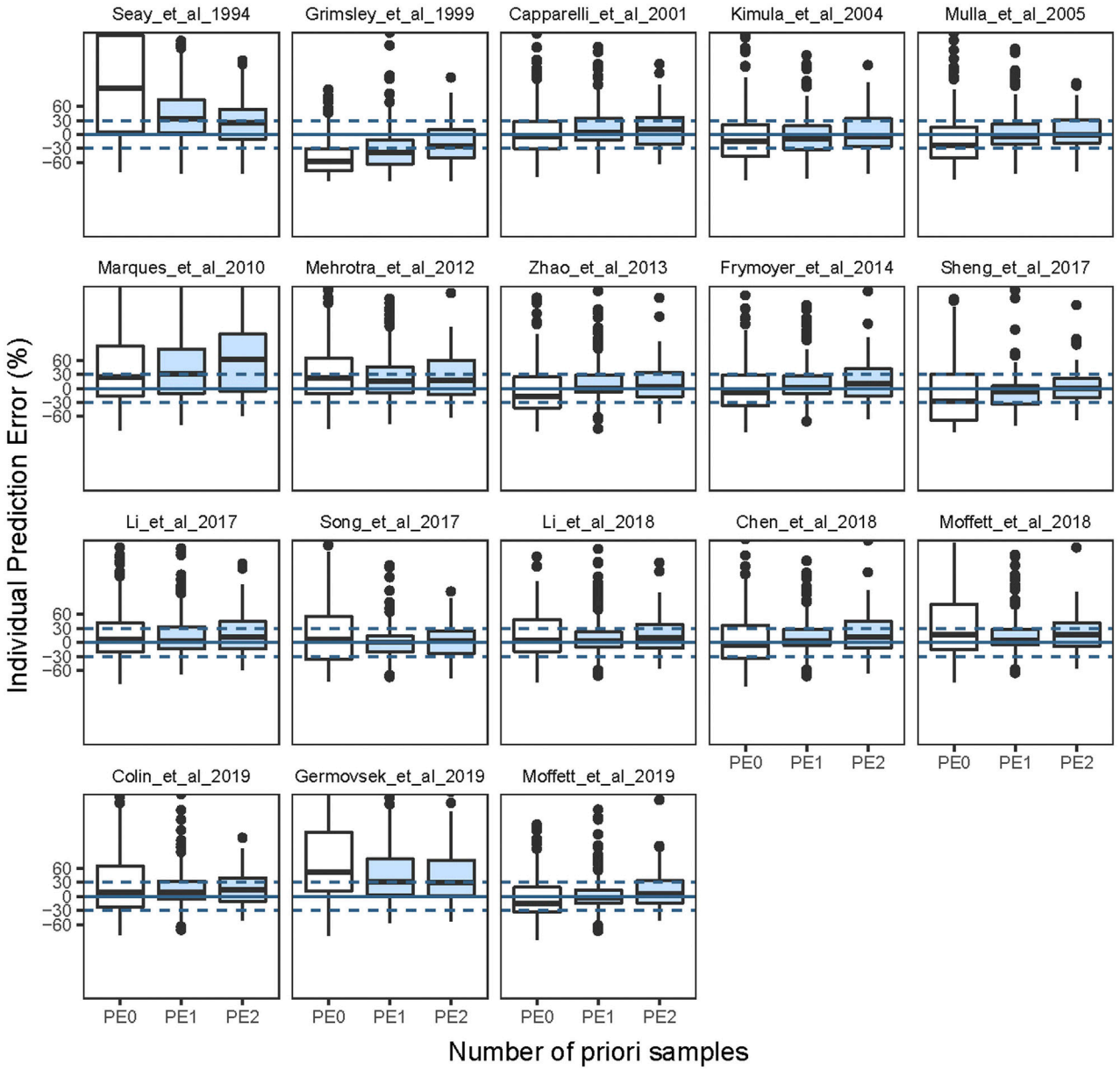

FIGURE 2 | Box plots of individual prediction error (IPE%) in external data with Bayesian forecasting for published population pharmacokinetic models in different scenarios (0 represents predictions without *prior* information and one to two represents with *prior* one to two observations, respectively).

vancomycin levels were from Suzhou Hospital Affiliated to Nanjing Medical University (SZ). The proportion of preterm neonates was larger in the SZ group than in the SH group. The patient demographics of both cohorts are shown in **Table 3**.

External Predictive Evaluations

Prediction-Based Diagnostics

There were large differences in predictability of the different models. As can be seen from the results of the prediction-based diagnostics shown in **Figure 1** and **Supplementary Table S1**, no model satisfied the standards of MDPE ≤ ± 15%, MAPE ≤30%, F_{20} > 35%, and F_{30} > 50%. Nine models showed good predictive accuracy, with an MDPE of less than ±15%. However, MAPE was more than 30% in all models, indicating a poor predictive precision for all models. Of note, the model reported by Moffett et al. (2019) (Moffett et al., 2019) reached the criteria of F_{20} > 30% and F_{30} > 45%, showing better accuracy and precision of predictability than other models. The boxplot for PE% for each model is shown in **Figure 1**.

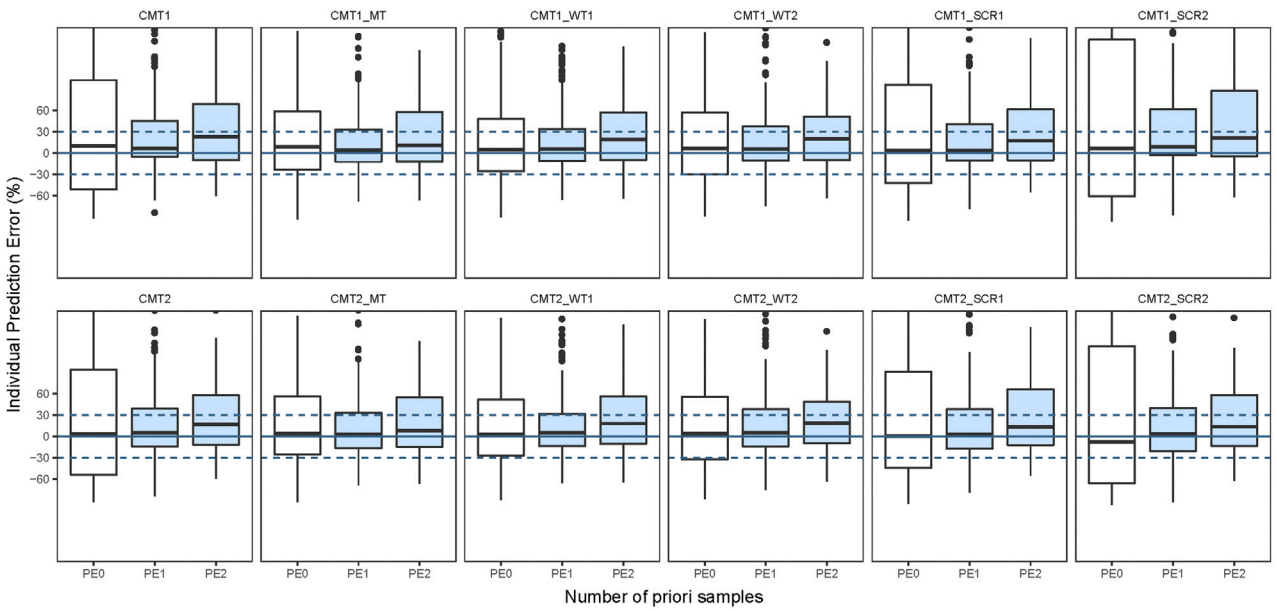

FIGURE 3 | Box plots of individual prediction error (IPE%) in external data with Bayesian forecasting for one compartmental model (CMT1) and two compartmental model (CMT2) and including maturation model (MT), WT on nonlinear model (WT1) and WT on linear model (WT2), SCR on nonlinear model (SCR1) and SCR on linear model (SCR2) in external vancomycin data (0 represents predictions without *prior* information and one to two represents with *prior* one to two observations, respectively).

Simulation-Based Diagnostics

In the case of simulation-based diagnosis, the pvcVPC showed significant differences between observations and model simulations in all reported studies (**Supplementary Figure S2**). A clear tendency of either over- or under-prediction was observed for all models.

Bayesian Forecasting

In total, 171 neonates and 171 observations, 112 neonates and 224 observations, 24 neonates and 72 observations with zero, one, two previous samples, respectively, were included in the Bayesian forecasting. After Bayesian forecasting with one or two prior observations for all models, the mean values of MDPE, MAPE, F_{20}, and F_{30} compared favorably with the prediction-based diagnostics, indicating that the predictive performances had improved, as shown in **Supplementary Table S2**. Furthermore, 12 of the published models showed a median IPE <20%, a median absolute IPE <30%, an IF_{20} > 35%, and an IF_{30} > 50% after Bayesian forecasting with one or two prior observations. The box plots for predictability are shown in **Figure 2**, and the predicted indices are listed in **Supplementary Table S2**.

The Impact of Modeling Approaches

The structural model employed in the previous studies included the 1CMT model or 2CMT model. We evaluated the predictive performance of these two models by establishing 1CMT and 2CMT base models using the external data. Because trough concentrations could not fully describe a two-compartment model, the volume of distribution of the central compartment was fixed at 1.27 L, and the inter-compartmental clearance was fixed at 1.161 L/h in the 2CMT model, according to the study by Song et al. (Song et al., 2017). The MDPE of the 2CMT model was less than that of the 1CMT model (3.49% vs. 10.33%), indicating that the predictive accuracy was better for the 2CMT model (**Figure 3** and **Supplementary Table S3**).

To assess the predictive performance of the various covariate models, we developed models with the identified covariates (WT, PMA, and SCR) and corresponding formulas (a maturation model, a nonlinear model, and a linear model) based on the 1CMT or 2CMT structural models. The maturation model was used by **Eq. 6**, nonlinear model used by **Eq. 8**, and linear model used by **Eq. 9**.

$$P_i = TV(P) \times \left(\frac{COV}{COV_{median}}\right)^{\theta}, \quad (8)$$

$$P_i = TV(P) \times COV. \quad (9)$$

After incorporating body size into the maturation model, the F_{20} and F_{30} were improved significantly compared to the base 1CMT model (F_{20}: 27.65% vs. 14.12% and F_{30}: 44.71% vs. 19.41%), or that of the 2CMT model (F_{20}: 30.0% vs. 14.12% and F_{30}: 43.53% vs. 19.41%). Moreover, the predictive performance of the model with WT and SCR included in a nonlinear fashion was much better than in the model where they were included in a linear fashion (**Figure 3** and **Supplementary Table S2**). With one prior observation, the IF_{20} and IF_{30} values of the base model after Bayesian forecasting were all >35% and 50%, respectively, demonstrating an obvious improvement using Bayesian forecasting. Box plots for the predictive performance in each model are presented in **Figure 3**.

DISCUSSION

This study performed a comprehensive external evaluation of the published population pharmacokinetic models of vancomycin in neonates. Based on prediction- and simulation-based diagnostics, none of the published models had a good predictive performance according to pre-specified standards. However, after Bayesian forecasting with one or two prior measurements of vancomycin levels, the predicted performance improved significantly. This finding is consistent with external evaluation studies of other antibiotics such as rifampicin, voriconazole, and tobramycin (Cheng et al., 2020), and immunosuppressive agents (Zhao et al., 2016; Mao et al., 2018; Cai et al., 2020).

Body size is a pivotal index for the CL and V of vancomycin in neonates. Comparing different covariate modeling approaches, nonlinear models, especially the maturation model, showed much better predictability than the linear model. When the maturation model was adopted, F_{20} and F_{30} improved by 30%–50% compared with the linear model.

For drugs with narrow therapeutic windows, weight-based dosing is most commonly used for neonates because it is easy to perform. However, some studies have reported that there are adverse drug reactions related to weight-based dosage regimens for children, especially for drugs with narrow therapeutic ranges, leading to ineffective treatment outcomes and even fatalities in some cases (Koren et al., 1988; Konstan et al., 1991; Back et al., 2019).

As body weight does not fully describe organ maturity, the maturation model could better explain the physiological status of early, slower growth and subsequent faster growth in neonates (Back et al., 2019). It also allows for a quantification of the relationship between the mass/structure of organs and size (Fsize), which is known to exhibit a nonlinear pattern of growth in neonates (Holford et al., 2013) (Back et al., 2019). Moreover, published population PK analyses that included body size in the maturation models report better forecasting and better clinical use (Andrews et al., 2018; Béranger et al., 2019).

Renal function is also a very important factor affecting the pharmacokinetics of vancomycin, since vancomycin is mainly eliminated via the kidney. Creatinine clearance is used as index to describe renal function in adult patients; however, in neonates, SCR levels are a more reliable indicator of renal function, which is consistent with the findings of previous population PK studies. It has previously been shown that incorporating SCR in CL in a nonlinear fashion is better than incorporating it in a linear fashion. This finding also supports the fact that renal function matures in a nonlinear manner in neonates.

Our study has several limitations. As mentioned previously, the creatinine determination method (Jeff and enzymatic method) has been shown to have a large impact on external predictability (Zhao et al., 2013a). In this study, although we used correction equations to reduce variation between the two methods, several of the previous studies did not clearly state the method used for creatinine determination; therefore, this should be noted in future studies. Moreover, only peak and trough data were collected, and the comparison between the 1CMT and 2CMT models was not fully assessed and so may require further investigation.

CONCLUSION

Based on our study, the published models performed poorly in prediction-based and simulation-based diagnostics. The maturation model based on weight, age, and nonlinear incorporation of SCR had better predictability than other modeling approaches. Moreover, the Bayesian method significantly improved the predictive performance of the published models, and could thus play an important role in vancomycin dosing recommendations and guiding clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Children's Hospital and Suzhou Hospital Affiliated to Nanjing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

Y-XL, ZJ, J-JL, and Z-LL participated in research design. J-JL and Z-LL contributed to acquisition of the evaluation data. Y-XL and ZJ performed the research and analyzed the data, W-JN reviewed the model selected and information verification. Y-XL, ZJ, and HW drafted the manuscript. All authors revised and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.623907/full#supplementary-material.

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ORIGINAL RESEARCH
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Application of a Physiologically Based Pharmacokinetic Model to Characterize Time-dependent Metabolism of Voriconazole in Children and Support Dose Optimization

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Background: Voriconazole is a potent antifungal drug with complex pharmacokinetics caused by time-dependent inhibition and polymorphisms of metabolizing enzymes. It also exhibits different pharmacokinetic characteristics between adults and children. An understanding of these alterations in pharmacokinetics is essential for pediatric dose optimization.

Objective: To determine voriconazole plasma exposure in the pediatric population and further investigate optimal dosage regimens.

Methods: An adult and pediatric physiologically based pharmacokinetic (PBPK) model of voriconazole, integrating auto-inhibition of cytochrome P450 3A4 (CYP3A4) and *CYP2C19* gene polymorphisms, was developed. The model was evaluated with visual predictive checks and quantitative measures of the predicted/observed ratio of the area under the plasma concentration-time curve (AUC) and maximum concentration (C_{max}). The validated pediatric PBPK model was used in simulations to optimize pediatric dosage regimens. The probability of reaching a ratio of free drug (unbound drug concentration) AUC during a 24-h period to minimum inhibitory concentration greater than or equal to 25 ($fAUC_{24h}$/MIC ≥ 25) was assessed as the pharmacokinetic/pharmacodynamic index.

Results: The developed PBPK model well represented voriconazole's pharmacokinetic characteristics in adults; 78% of predicted/observed AUC ratios and 85% of C_{max} ratios were within the 1.25-fold range. The model maintained satisfactory prediction performance for intravenous administration in pediatric populations after incorporating developmental changes in anatomy/physiology and metabolic enzymes, with all predicted AUC values within 2-fold and 73% of the predicted C_{max} within 1.25-fold of the observed values. The simulation results of the PBPK model suggested that different dosage regimens should be administered to children according to their age, *CYP2C19* genotype, and infectious fungal genera.

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Conclusion: The PBPK model integrating CYP3A4 auto-inhibition and *CYP2C19* gene polymorphisms successfully predicted voriconazole pharmacokinetics during intravenous administration in children and could further be used to optimize dose strategies. The infectious fungal genera should be considered in clinical settings, and further research with large sample sizes is required to confirm the current findings.

Keywords: voriconazole, physiologically based pharmacokinetic model, children, gene, dose optimization

INTRODUCTION

Voriconazole is an essential triazole antifungal agent with *in vivo* activity against a broad spectrum of yeasts and filamentous fungi, commonly used for the prophylaxis and treatment of various invasive fungal infections (IFI) (Clancy and Nguyen, 1998; Saravolatz et al., 2013; Perfect et al., 2003). However, a high interindividual plasma variability has been observed partially due to its nonlinear and time-dependent pharmacokinetics (Purkins et al., 2003; Pfizer, 2010). It also exhibits differences in clearance and bioavailability between adults and children (Schulz et al., 2019). All these factors

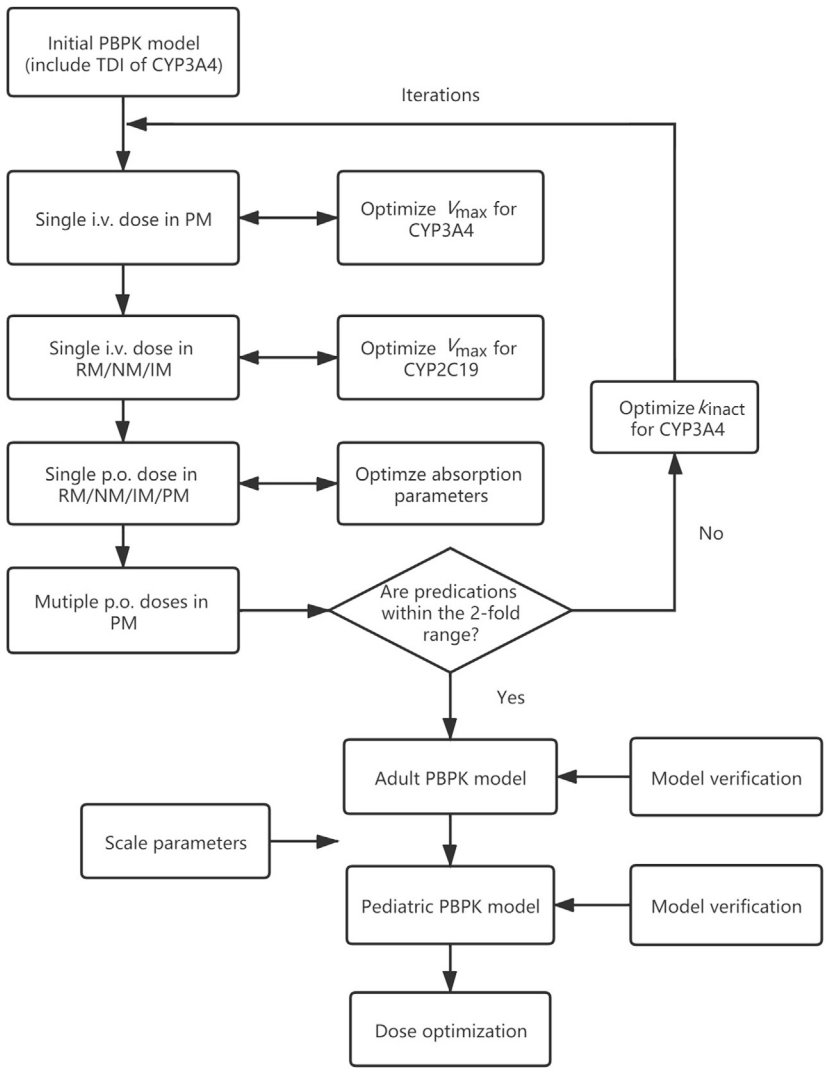

FIGURE 1 | Adult and pediatric modeling workflow. PBPK model, physiologically based pharmacokinetic model; TDI, time-dependent inhibition; i.v., intravenously; p.o., orally; RM, rapid metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; V_{max}, maximum velocity; k_{inact}, maximum inactivation rate constant.

TABLE 1 | Summary of input parameters of voriconazole PBPK model.

Parameter	Unit	Value	Source
Molecular weight	g/mol	349.3	Pfizer Label
fu	%	42	Pfizer Label
log*P*		1.65	Drug bank
pKa		1.76 (base)	Damle et al. (2011)
Solubility (pH)	mg/mL	3.2 (1.0)	Pfizer Canada Inc.
Specific intestinal permeability	cm/s	2.81×10^{-5}	Damle et al. (2011)
Partition coefficients		Poulin and Theil	Damle et al. (2011)
Cellular permeabilities		PK-Sim standard	Li et al. (2020)
CYP3A4 K_m	μmol/L	11	Murayama et al. (2007)
CYP3A4 k_{cat}	min^{-1}	2.3	Optimized
CYP2C19 K_m	μmol/L	3.5	Damle et al. (2011)
CYP2C19 k_{cat}	min^{-1}	1.19	Damle et al. (2011)
CYP2C9 K_m	μmol/L	20	Hyland et al. (2003)
CYP2C9 k_{cat}	min^{-1}	0.0556	Hyland et al. (2003)
GFR fraction		1	
CYP3A4 k_{inact}	min^{-1}	0.04	Li et al. (2020)
CYP3A4 K_I	μmol/L	9.33	Li et al. (2020)
$D_{T,50}$ for tablet	min	30	Li et al. (2020)
Shape factor for tablet		1.29	Li et al. (2020)

fu, fraction of bound drug; logP, log of the partition coefficient between octanol and water; pKa, acid dissociation constant; K_m, Michaelis-Menten constant; k_{cat}, in vitro V_{max} per recombinant enzyme; GFR, glomerular filtration rate; k_{inact}, maximum inactivation rate constant; K_I, the inhibition concentration when reaching 50% of k_{inact}; $D_{T,50}$, the dissolution time when 50% of the substance dissolved; shape factor, the dissolution shape parameter for Weibull function.

complicate the successful therapeutic use of voriconazole in pediatric populations.

Voriconazole is a substrate for cytochrome P450 (CYP) enzymes. CYP2C19 is the primary enzyme that contributes to the main circulating metabolite of voriconazole, voriconazole N-oxide, while CYP3A4 and CYP2C9 are also responsible for its metabolism (Hyland et al., 2003). Only 2% of voriconazole is excreted unmetabolized in the urine (Levêque et al., 2006). The time-dependent inhibition (TDI) of CYP3A4 observed in *in vitro* studies (Li et al., 2020) may play a role in the elevated exposure to voriconazole at multiple doses, which could not be predicted from single-dose data (Purkins et al., 2003). Genetic polymorphisms of *CYP2C19* are also a major determinant of the wide pharmacokinetic (PK) variability in voriconazole. Drug exposures from multiple doses of poor metabolizers (PMs) are almost 3 times higher than those from normal metabolizers (NMs) (Lee et al., 2012). Regarding age-related changes, the total body clearance in children is approximately 2–3-fold higher than that in adults (Levêque et al., 2006). In addition, oral bioavailability in children (45–66%) is only half of that in adults (96%) (Schulz et al., 2019), and this may suggest that primarily gut wall metabolism is also increased in children (Zane and Thakker, 2014). These PK discrepancies may be explained by developmental differences in organs, tissues, and enzymes (Kearns et al., 2003), resulting in an increased ratio of hepatic mass to total body mass and a higher clearance of CYP enzymes in children (Walsh et al., 2010).

The physiologically based pharmacokinetic (PBPK) model combines the knowledge of system-specific factors and drug-specific factors with mathematical modeling methods to quantitatively predict the PK characteristics of drug absorption, distribution, metabolism, and excretion (Maharaj and Edginton, 2014). Previously, an adult and pediatric PBPK model was established with hepatic *in vitro* data (Zane and Thakker, 2014). However, this model could not predict the nonlinear PKs of voriconazole and alterations in its metabolism over time. In another study, a whole-body PBPK model of voriconazole integrating the TDI of CYP3A4 and genetic polymorphisms of CYP2C19 was constructed (Li et al., 2020). It successfully captured the main PK characteristics of the drug in adults but overpredicted exposure to PMs after multiple doses.

Therefore, the objectives of the present study were to 1) establish an adult PBPK model of voriconazole, focusing on improving predictions of multiple-dose administration, especially in PMs; 2) extrapolate this model to children using age-related scaling methods; and 3) conduct simulations to facilitate the dose-optimization process. Due to the lack of data and high interpatient variability in the PK parameters observed following oral (p.o.) administration of voriconazole in children, the adult model was only extrapolated to intravenous (i.v.) administration in the pediatric model.

MATERIALS AND METHODS

Workflow and Software

In this study, a PBPK model of voriconazole was developed and evaluated in the adult population, subsequently extrapolated to the pediatric population, and verified by comparing the simulated plasma exposure with the observed data. The final PBPK model was then used to simulate PK studies for pediatric dose optimization. The workflow of the model development is presented in **Figure 1**.

The modeling work was conducted in PK-Sim® (part of Open Systems Pharmacology (OSP) Suite version 8.0, www.open-systems-pharmacology.org). The published data were digitized by GetData Graph Digitizer version 2.26 (getdata-graph-digitizer.com).

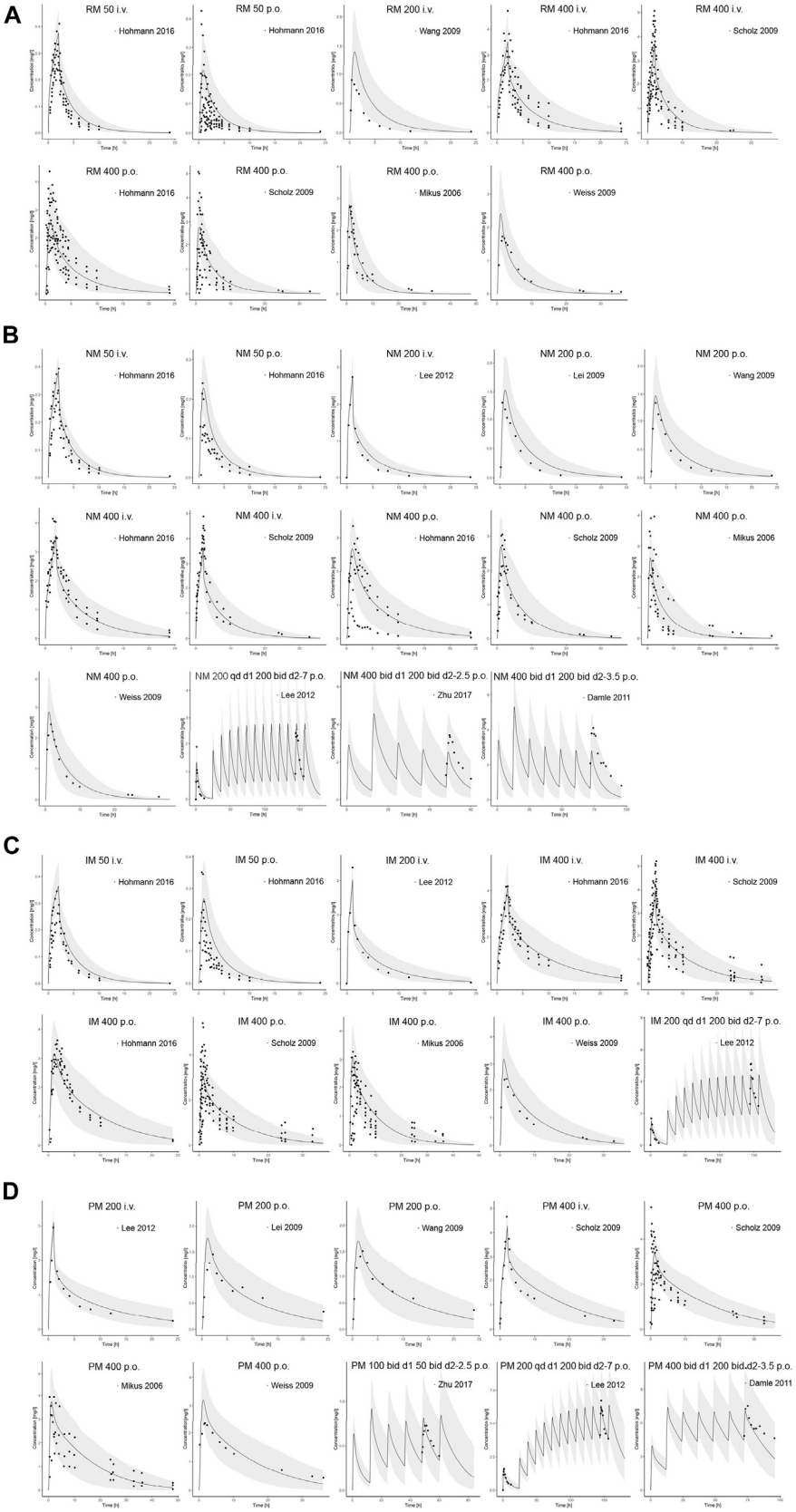

FIGURE 2 | Comparison of adult PBPK model predicted plasma concentration-time profiles (lines) vs. clinical observed data (symbols) in **(A)** RM, **(B)** NM, **(C)** IM and **(D)** PM. PBPK predictions are presented as mean simulated concentrations (black line) with their 5th to 95th percentiles (grey area). i.v., intravenously; p.o., orally; RM, rapid metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Adult Model Development

PK profiles following i.v. and p.o. administration were searched in PubMed, Embase and the Cochrane Library using the terms "voriconazole" and "pharmacokinetic". The clinical trials with dosage, concentration, and *CYP2C19* genotype information in healthy adults were included.

A generic whole-body standard model for small molecules was selected in PK-Sim, and default system-dependent physiological parameters were implemented. With the assumption that CYP2C19, CYP3A4, and CYP2C9 are responsible for the metabolism of voriconazole, reverse transcription-polymerase chain reaction (RT-PCR) profiles were used to determine tissue expression distributions of these three enzymes, with hepatic reference concentrations of 0.76, 4.32, and 3.84 μmol/L, respectively, for CYP2C19 NMs (*1/*1). The abundance of ultrarapid metabolizers (UMs: *17/*17), rapid metabolizers (RMs: *1/*17), intermediate metabolizers (IMs: 1/*2, *1/*3, *2/*17), and PMs (2/*2, *2/*3, *3/*3) of CYP2C19 (Moriyama et al., 2018) was calculated using the scale factor estimated by Steere et al. (2015), and the values were 1.41, 1.36, 0.29(IMs with *1)/0.63(IMs with *17), and 0 μmol/L, respectively. If the genotype was not explicitly distinguished and mentioned, 0.46 was used for IMs. Due to the limited available data for UMs, the adult PBPK model was only built in CYP2C19 RMs, NMs, IMs and PMs.

Drug-specific parameters such as physicochemical properties and PK characteristics describing absorption, distribution, metabolism, and excretion were obtained from the literature, as shown in **Table 1**. Tissue-to-plasma partition coefficients were calculated using the Poulin and Theil method. Cellular permeabilities were predicted using the PK-Sim standard method. The enzymatic clearance process was quantified using Michaelis-Menten kinetics (Michaelis et al., 2011). The initial value of the Michaelis-Menten constant (K_m) for CYP2C19, CYP3A4, and CYP2C9 was 3.5, 11, and 20 μmol/L, and the maximum velocity (V_{max}) was set to 1.19, 2.3, and 0.0556 pmol/min^{-1}/pmol, respectively (Hyland et al., 2003; Damle et al., 2011). As the ratio of AUC within the dosing interval after multiple doses to AUC from zero to infinity after a single dose ($AUC_{\tau(\text{multipole dose})}/AUC_{\text{inf(single dose)}}$) is larger than 2 (Purkins et al., 2003), the time-dependent inhibition of CYP3A4 was integrated into the model using **Eq. 1**.

$$\frac{dE_{cat}(t)}{dt} = k_{deg} * E_0 - \left(k_{deg} + \frac{k_{inact} * I(t)}{K_I + I(t)}\right) * E_{cat}(t), \qquad (1)$$

dE_{cat}/dt describes the turnover of the enzyme, where k_{deg} is turnover rate constant, E_0 is the initial enzyme concentration, I is the inhibitor concentration, k_{inact} is the maximum inactivation rate constant, and K_I is the inhibition concentration when reaching 50% of k_{inact}. The initial values of k_{inact} and K_I were set to 0.04 min^{-1} and 9.33 μmol/L, respectively, according to the results of an *in vitro* inactivity assay (Li et al., 2020). Other parameters related to TDI were set as software default values. The glomerular filtration rate (GFR) fraction was fixed to 1, as there was no evidence for reabsorption and tubular secretion. Initial formulation-related parameters were also obtained from the literature, with the dissolution time when 50% of the substance dissolved ($D_{T,50}$) set to 30 min and dissolution shape parameter for Weibull function (shape factor for tablet) set to 1.29 (Li et al., 2020).

The PBPK model was first established based on the initial values indicated above, and the V_{max} of CYP3A4 was optimized based on a single i.v. dose in CYP2C19 PMs, assuming that CYP3A4 contributes to almost 100% of the metabolism in this population. The propriety of CYP2C19-related parameters was then evaluated based on the observed PK parameters and plasma concentration profiles from a single i.v. dose in CYP2C19 RMs/NMs/IMs. In the next step, the specific intestinal permeability and formulation-related parameters, including $D_{T,50}$ and shape factor for tablet, were inspected using data from studies following a single p.o. administration in RMs/NMs/IMs/PMs. If the fits were deemed inadequate, these three parameters were optimized based on p.o. data. Data from Scholz et al. (2009) was used for the above parameter optimization. The TDI-related parameter was optimized in the final step due to the lack of multiple i.v. clinical studies with genotype information. If the predicted PK parameters from multiple p.o. studies in PMs were within 2-fold of the observed values, the modeling process was complete. Otherwise, k_{inact} for CYP3A4 was optimized and the iterations of the above optimization steps were repeated.

Adult Model Verification

The PK simulation of 100 virtual people for each clinical study was carried out, corresponding to the subject demographics (age range, proportion of male/female, and dosing regimens). The predictive performance was evaluated by visually comparing predicted concentration-time data with the observed data from the literature for initial verification. Ninety percent population prediction intervals covering the observed plasma concentration-time datasets were considered as a visual criterion for good performance. Next, the quantitative assessment was conducted by calculating the mean fold error (MFE) of PK parameters such as the area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{max}), expressed as the ratio of predicted to observed mean values. The model was acceptable if it met the 0.5- to 2.0-fold limit, and a more stringent criterion was the 0.8- to 1.25-fold range.

Pediatric Model Development

PK profiles following i.v. administration were searched in PubMed, Embase and the Cochrane Library using the terms "voriconazole", "pharmacokinetic", and children-related items "infant", "child", "children", "pediatric", and "adolescent". Studies with sufficient information for dosage, concentration, and CYP2C19 genotype were included.

Drug-specific parameters defined in the adult PK data were kept constant for the pediatric PBPK model.

Developmental changes in anatomical and physiological parameters such as weight, height, organ volumes, blood flows, organ composition, and plasma protein concentration in PK-Sim® are based on the population data from previous studies (NHANES III, 1997; ICRP, 2002). These algorithms were used to generate virtual pediatric populations. For the age-dependent hepatic clearance, default CYP2C19, CYP3A4 and

TABLE 2 | Summary of voriconazole pharmacokinetic parameters in clinical studies of healthy adults and comparison with model predicted values.

CYP2C19 genotype	Dose (mg)	Route	Male (%)	Age in years (age range group)	Pharmacokinetic parameters	Predicted	Observed	Pre/ Obs ratio	References
RM	50, sig	i.v. (120)	63	30 (24–53)	AUC_{obs}	1.28	1.02	1.25	Hohmann et al. (2016)
					C_{max}	0.38	0.320	1.19	
	50, sig	p.o. (tab)	63	30 (24–53)	AUC_{obs}	0.76	0.40	1.9	Hohmann et al. (2016)
					C_{max}	0.22	0.167	1.32	
	200, sig	p.o. (tab)	100	21 ± 2*	AUC_{obs}	5.45	3.39	1.61	Wang et al. (2009)
					C_{max}	1.32	1.15	1.15	
	400, sig	i.v. (120)	71	30 (24–53)	AUC_{obs}	15.8	16.5	0.96	Hohmann et al. (2016)
					C_{max}	3.50	3.29	1.06	
	400, sig	i.v. (120)	67	25 (23–28)	AUC_{obs}	17.4	18.8	0.93	Scholz et al. (2009)
					C_{max}	3.72	4.05	0.92	
	400, sig	p.o. (tab)	71	30 (24–53)	AUC_{obs}	13.0	15.3	0.85	Hohmann et al. (2016)
					C_{max}	2.56	3.21	0.90	
	400, sig	p.o. (tab)	67	25 (23–28)	AUC_{obs}	14.6	13.6	1.07	Scholz et al. (2009)
					C_{max}	2.79	2.90	0.96	
	400, sig	p.o. (cap)	0	29 (24–37)	AUC_{obs}	13.9	15.9	0.87	Mikus et al. (2006)
					C_{max}	2.81	2.97	0.95	
	400, sig	p.o. (cap)	100	27 (24–37)	AUC_{inf}	11.3	13.3	0.85	Weiss et al. (2009)
					C_{max}	2.42	2.16	1.12	
NM	50, sig	i.v. (120)	100	35 (24–46)	AUC_{obs}	1.42	1.24	1.15	Hohmann et al. (2016)
					C_{max}	0.38	0.345	1.10	
	50, sig	p.o. (tab)	100	35 (24–46)	AUC_{obs}	0.84	0.53	1.58	Hohmann et al. (2016)
					C_{max}	0.23	0.167	1.38	
	200, sig	i.v. (60)	100	26.7 ± 2.9*	AUC_{inf}	8.33	6.51	1.28	Lee et al. (2012)
					C_{max}	2.76	2.74	1.01	
	200, sig	p.o. (tab)	100	22 ± 1.5*	AUC_{obs}	7.35	5.16	1.42	Lei et al. (2009)
					C_{max}	1.53	1.45	1.06	
	200, sig	p.o. (tab)	100	21 ± 2	AUC_{obs}	7.41	6.18	1.20	Wang et al. (2009)
					C_{max}	1.47	1.65	0.89	
	200, qd, d1	p.o. (NA)	100	26.7 ± 2.9*	AUC_{τ}	6.74	4.64	1.45	Lee et al. (2012)
					C_{max}	1.36	2.32	0.59	
	200, bid, d2-7	p.o. (NA)	100	26.7 ± 2.9*	AUC_{τ}	19.0	19.3	0.98	Lee et al. (2012)
					C_{max}	2.94	3.21	0.92	
	200, bid, d2-2.5 (400, bid, d1)	p.o. (NA)	83	27 (18–45)	AUC_{τ}	15.5	12.9	1.20	Zhu et al. (2017)
					C_{max}	2.49	3.01	0.83	
	200, bid, d2-3.5 (400, bid, d1)	p.o. (NA)	100	29 (22–43)	AUC_{12}	16.8	31.0	0.54	Damle et al. (2011)
					C_{max}	2.79	4.02	0.69	
	400, sig	i.v. (120)	100	35 (24–46)	AUC_{obs}	18.3	21.4	0.86	Hohmann et al. (2016)
					C_{max}	3.57	3.61	0.99	
	400, sig	i.v. (120)	50	31 (24–38)	AUC_{obs}	19.59	18.8	1.04	Scholz et al. (2009)
					C_{max}	3.60	4.05	0.89	
	400, sig	p.o. (tab)	100	35 (24–46)	AUC_{obs}	15.6	13.6	1.15	Hohmann et al. (2016)
					C_{max}	2.67	2.21	1.21	
	400, sig	p.o. (tab)	50	31 (24–38)	AUC_{obs}	16.9	13.6	1.24	Scholz et al. (2009)
					C_{max}	2.68	2.90	0.92	
	400, sig	p.o. (cap)	100	28 (25–31)	AUC_{obs}	16.6	15.9	1.04	Mikus et al. (2006)
					C_{max}	2.63	2.97	0.89	
	400, sig	p.o. (cap)	100	27 (22–31)	AUC_{inf}	16.8	16.4	1.02	Weiss et al. (2009)
					C_{max}	2.85	3.10	0.92	

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TABLE 2 | (*Continued*) Summary of voriconazole pharmacokinetic parameters in clinical studies of healthy adults and comparison with model predicted values.

CYP2C19 genotype	Dose (mg)	Route	Male (%)	Age in years (age range group)	Pharmacokinetic parameters	Predicted	Observed	Pre/ Obs ratio	References
IM	50, sig	i.v. (120)	75	30 (25–34)	AUC_{obs}	1.61	1.13	1.42	Hohmann et al. (2016)
					C_{max}	0.43	0.32	1.34	
	50, sig	p.o. (tab)	75	30 (25–34)	AUC_{obs}	1.04	0.58	1.79	Hohmann et al. (2016)
					C_{max}	0.27	0.22	1.23	
	200, sig	i.v. (60)	100	24.7 ± 2.7*	AUC_{inf}	11.6	10.1	1.15	Lee et al. (2012)
					C_{max}	3.03	3.36	0.90	
	200, qd, d1	p.o. (NA)	100	24.7 ± 2.7*	AUC_{τ}	9.90	7.02	1.41	Lee et al. (2012)
					C_{max}	1.55	1.81	0.86	
	200, bid, d2-7	p.o. (NA)	100	24.7 ± 2.7*	AUC_{τ}	37.7	42.4	0.89	Lee et al. (2012)
					C_{max}	4.60	5.78	0.80	
	400, sig	i.v. (120)	63	26 (24–32)	AUC_{obs}	31.3	37.4	0.84	Scholz et al. (2009)
					C_{max}	3.96	4.33	0.91	
	400, sig	i.v. (120)	75	30 (25–34)	AUC_{obs}	25.8	25.0	1.03	Hohmann et al. (2016)
					C_{max}	4.11	3.82	1.08	
	400, sig	p.o. (tab)	75	30 (25–34)	AUC_{obs}	23.5	23.2	1.01	Hohmann et al. (2016)
					C_{max}	3.12	3.32	0.94	
	400, sig	p.o. (tab)	63	26 (24–32)	AUC_{obs}	29.0	30.9	0.94	Scholz et al. (2009)
					C_{max}	3.00	3.28	0.91	
	400,sig	p.o. (cap)	78	26 (22–33)	AUC_{obs}	27.5	20.7	1.33	Mikus et al. (2006)
					C_{max}	3.12	2.85	1.09	
	400,sig	p.o. (cap)	100	26 (22–33)	AUC_{inf}	27.6	25.7	1.07	Weiss et al. (2009)
					C_{max}	3.17	2.84	1.12	
PM	50, bid, d2-2.5 (100, bid, d1)	p.o. (NA)	100	29 (24–45)	AUC_{τ}	6.32	6.00	1.05	Zhu et al. (2017)
					C_{max}	0.85	0.76	1.12	
	200, sig	i.v. (60)	100	27.3 ± 3.6*	AUC_{inf}	20.8	20.5	1.01	Lee et al. (2012)
					C_{max}	3.10	2.92	1.06	
	200, sig	p.o. (tab)	100	21.6 ± 2.2*	AUC_{obs}	13.9	17.2	0.81	Lei et al. (2009)
					C_{max}	1.77	1.36	1.30	
	200, sig	p.o. (tab)	100	21 ± 2	AUC_{obs}	14.6	16.3	0.90	Wang et al. (2009)
					C_{max}	1.70	1.89	0.90	
	200, qd, d1	p.o. (NA)	100	27.3 ± 3.6*	AUC_{τ}	11.8	9.25	1.28	Lee et al. (2012)
					C_{max}	1.54	2.41	0.64	
	200, bid, d2-7	p.o. (NA)	100	27.3 ± 3.6*	AUC_{τ}	59.8	58.7	1.02	Lee et al. (2012)
					C_{max}	6.42	7.21	0.89	
	200, bid, d2-3.5 (400, bid, d1)	p.o. (NA)	100	29 (22–43)	AUC_{12}	67.4	77.1	0.87	Damle et al. (2011)
					C_{max}	7.14	10.9	0.66	
	400, sig	i.v. (120)	50	30 (20–37)	AUC_{obs}	48.9	44.4	1.10	Scholz et al. (2009)
					C_{max}	4.27	4.30	0.99	
	400, sig	p.o. (tab)	50	30 (20–37)	AUC_{obs}	47.0	41.6	1.13	Scholz et al. (2009)
					C_{max}	3.35	3.91	0.86	
	400, sig	p.o. (cap)	33	29 (19–37)	AUC_{obs}	49.4	42.4	1.17	Mikus et al. (2006)
					C_{max}	3.74	3.24	1.15	
	400, sig	p.o. (cap)	100	31 (19–37)	AUC_{inf}	41.6	45.7	0.91	Weiss et al. (2009)
					C_{max}	3.19	3.13	1.02	

*d, day; sig, single dose; qd, once daily; bid, twice daily; i.v., intravenously; p.o., orally; tab, tablet; cap, capsule; Obs, observed value from clinical studies; Pre, predicted value from PBPK model; RM, rapid metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; AUC_{obs}, area under the concentration-time curve from zero to the maximum observed time; AUC_{inf}, area under the concentration-time curve from zero to infinity; AUC_{τ}, area under the concentration-time curve within the dosing interval; AUC_{12}, area under the concentration-time curve within 12 h; C_{max}, maximum concentration; NA, not available; * mean ± (SD).*

CYP2C9 ontogeny information is described in the online PK-Sim Ontogeny Database Open Systems Pharmacology (2018). In summary, the activity of CYP2C19, CYP3A4 and CYP2C9 increases after birth and reaches the adult level over approximately 1, 4 and 1 year, respectively. The model using these default ontogeny profiles overpredicted the exposure in children; therefore, the ontogeny factors of CYP enzymes were estimated based on a recent meta-analysis using *in vivo* data (Upreti and Wahlstrom., 2016; **Supplementary Figure S1**). These data suggested that in childhood, CYP2C19, CYP3A4, and CYP2C9 exhibit maximal activities beyond the levels in adults.

Pediatric Model Verification

The PBPK model performance in children was evaluated using the quantitative verification described in **Adult Model Verification**. As some pediatric clinical trials (Walsh et al., 2010) did not clearly show results according to the *CYP2C19* genotype as in adults, these data were verified by adding up different genotype results in

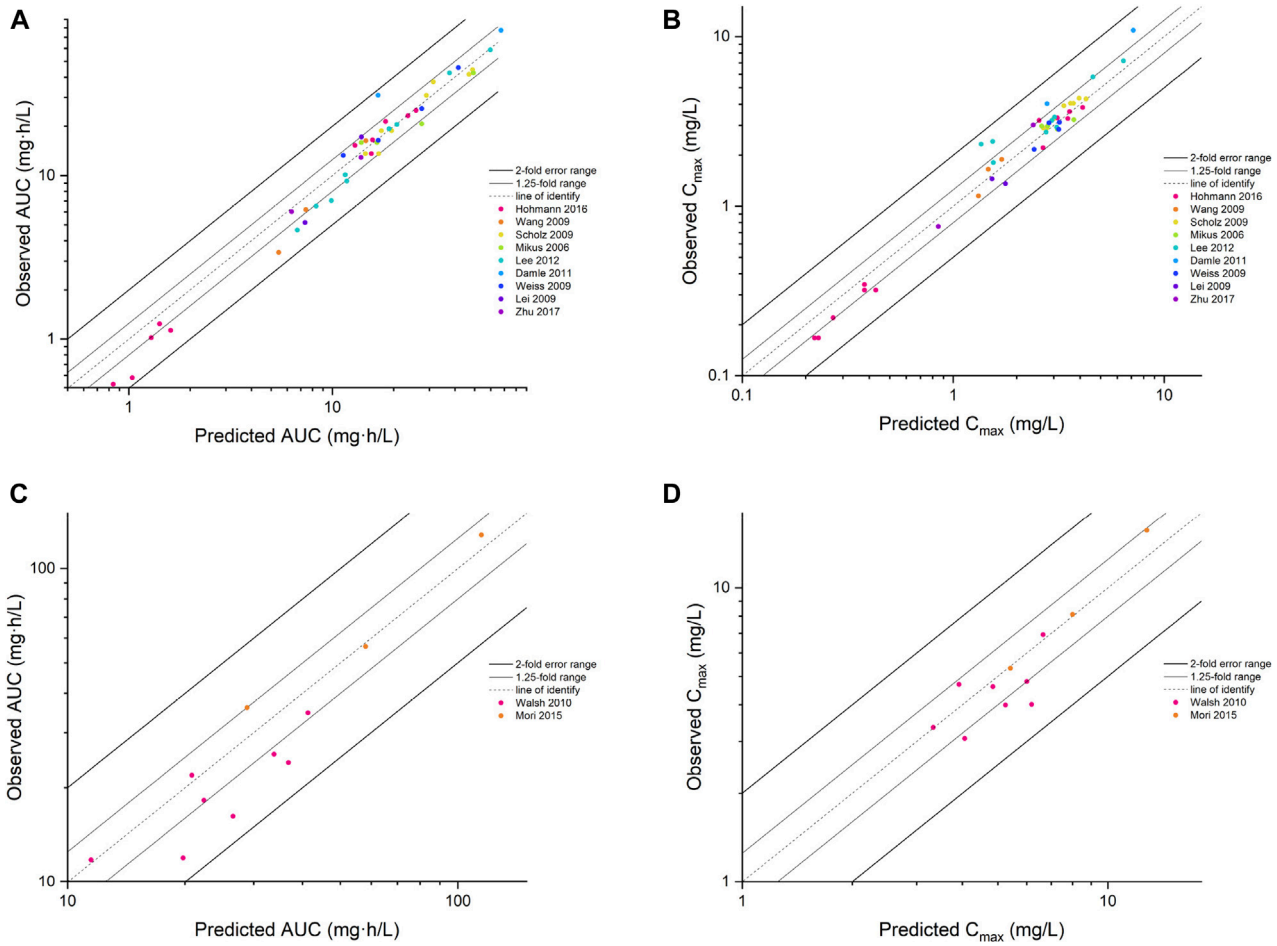

FIGURE 3 | The goodness of fit plot for the PBPK model. Predicted vs. observed AUC for adults **(A)** and children **(C)**, C_{max} for adults **(B)** and children **(D)**. AUC, area under the concentration–time curve; C_{max}, maximum concentration.

the model based on genotype ratios from the literature. The visual check was not conducted due to the lack of available plasma concentration-time curves with gene information.

Pediatric Dose Optimization

A 100-patients simulation was generated for each subpopulation classified by age (2-6 and 6-12 years) and CYP2C19 genotype (NMs, IMs and PMs). The individual AUC_{24h} (AUC during a 24-h period) was estimated.

The probability of reaching a ratio of free drug (unbound drug concentration) AUC_{24h} to minimum inhibitory concentration greater than or equal to 25 ($fAUC_{24h}$/MIC ≥ 25) was considered to be the PK/pharmacodynamic (PD) index (Wang et al., 2015). The fraction of unbound drug was set to 42% (US FDA, 2005), with the assumption that this value is similar between children and adults (Yanni et al., 2008). Voriconazole MIC distributions for *Aspergillus* (4 species) and *Candida* (14 species) infections were obtained from the European Committee on Antimicrobial Susceptibility Testing database (2020); (**Supplementary Figure S2**). The probability of target attainment (PTA) at each MIC and the cumulative fraction of response (CFR) for the overall MIC distribution for each species were calculated. CFR values of all species in one genus larger than or equal to 80% was considered an appropriate dosage regimen (Mangal et al., 2018).

RESULTS

Adult Model Verification

Input parameters of voriconazole PBPK model were summarized in **Table 1**. A proper fit was achieved in the adult model, as shown in **Figure 2**, and most of the observed concentrations fell within the 5% and 95% concentration-time prediction intervals. All PK parameters were predicted to be within the 2-fold difference, with 78% of predicted/observed AUC ratios and 85% of C_{max} ratios within the 1.25-fold difference (**Table 2**; **Figure 3**). The prediction of PMs following multiple doses was satisfactory.

Pediatric Model Verification

The PBPK model well captured the pharmacokinetic features in children after integrating *in vivo* ontogeny profiles. The

TABLE 3 | Summary of voriconazole pharmacokinetic parameters in pediatric clinical studies and comparison with model predicted values.

CYP2C19 genotype	Dose (mg/kg)	Route	Male (%)	Age in years (age range group)	Pharmacokinetic parameters	Predicted	Observed	Pre/obs ratio	References
58% NM + 42% IM	6 bid d1	i.v. (120)	75	3.7 (2–6)	AUC_{τ}	11.49	11.77	0.98	Walsh et al. (2010)
	4 bid d2-d4	i.v. (80)			C_{max}	3.33	3.35	0.99	
	6 bid d5-d8	i.v. (120)	75	3.7 (2–6)	AUC_{τ}	20.82	21.93	0.95	
					C_{max}	3.92	4.69	0.83	
73% NM + 27% IM	6 bid d1	i.v. (120)	75	8.7 (6–12)	AUC_{τ}	19.78	11.95	1.66	
	4 bid d2-d4	i.v. (80)			C_{max}	4.06	3.07	1.32	
	6 bid d5-d8	i.v. (120)	75	8.7 (6–12)	AUC_{τ}	36.83	24.05	1.53	
					C_{max}	6.19	4.01	1.54	
75% NM + 17% IM + 8% PM	6 bid d1-d4	i.v. (120)	45.8	2.8 (2–6)	AUC_{τ}	22.39	18.22	1.23	
					C_{max}	4.85	4.61	1.05	
	8 bid d5-d8	i.v. (160)	45.8	2.8 (2–6)	AUC_{τ}	33.84	25.57	1.32	
					C_{max}	6.00	4.80	1.25	
NM	6 bid d1-d4	i.v. (120)	45.8	8.1 (6–12)	AUC_{τ}	26.57	16.23	1.64	
					C_{max}	5.25	3.99	1.32	
	8 bid d5-d8	i.v. (160)	45.8	8.1 (6–12)	AUC_{τ}	41.30	34.68	1.19	
					C_{max}	6.65	6.92	0.96	
NM	9 bid d1	i.v. (180)	42.9	9.2 (3–14)	AUC_{τ}	28.87	36.0	0.80	Mori et al. (2015)
	8 bid d2-d7	i.v. (160)			C_{max}	5.42	5.32	1.02	
IM	9 bid d1	i.v. (180)	42.9	9.2 (3–14)	AUC_{τ}	58.09	56.4	1.13	
	8 bid d2-d7	i.v. (160)			C_{max}	8.01	8.12	0.99	
PM	9 bid d1	i.v. (180)	42.9	9.2 (3–14)	AUC_{τ}	115	128	0.90	
	8 bid d2-d7	i.v. (160)			C_{max}	12.78	15.70	0.81	

bid, twice daily; d, day; i.v., intravenously; Obs, observed value from clinical studies; Pre, predicted value from PBPK model; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; AUC_{τ}, area under the concentration-time curve within the dosing interval; C_{max}, maximum concentration.

PBPK simulation results were consistent with the observed plasma concentration-time profiles of different dosages after i.v. administration. All corresponding model-predicted concentrations fell within the 2-fold prediction error, with 73% of C_{max} values falling within the 1.25-fold prediction error (**Table 3**; **Figure 3**).

Pediatric Dose Optimization

Twelve pediatric groups were constructed for dose design, and the results are shown in **Table 4**. IMs with *17 have a similar CYP2C19 abundance to NMs and the recommended dosage for NMs can be a reference for this subpopulation. Therefore, the following IM dosage recommendation is for IMs with *1. **Figure 4** shows the contrast of the minimum PTA among different species in two fungal genera at each specific MIC between the following scenarios: one is administered the recommended maintenance dose from the current medication label (8 mg/kg, twice daily (BID)), and the other one is administered the recommended dose determined from the PBPK model. The results suggested that, for the BID dosing regimens, intravenous doses should be adjusted to 12 mg/kg for NMs, 8 mg/kg for IMs, and 5 mg/kg for PMs for 2–6-year-old children infected with *Aspergillus* spp. As children grow older, the recommended dose decreases, specifically 9 mg/kg for NMs, 6 mg/kg for IMs, and 4 mg/kg for PMs infected with *Aspergillus* spp. When the infectious fungal genus is *Candida* spp., approximately half of the above dosages are recommended to attain the appropriate drug exposure using $fAUC_{24h}$/MIC as the indicator, due to notable differences in these two fungi in terms of susceptibility to voriconazole.

DISCUSSION

The adult and pediatric PBPK model of voriconazole, which incorporated the TDI of CYP3A4, gene polymorphisms of *CYP2C19*, and developmental changes in physiology and metabolic enzymes, were able to describe the PKs in both populations. Subsequent simulations revealed that age, *CYP2C19* genotype, and infectious fungal genera influence target PK/PD index attainment and should be considered in dose optimization.

TABLE 4 | Recommended dosages and CFR values with a target value of $fAUC_{24h}/MIC \geq 25$.

Population	Infectious fungal genera			
	Aspergillus spp.		*Candida* spp.	
	Dosage mg/kg	CFR %	Dosage mg/kg	CFR%
Children aged 2–6 years				
NM	12	80.1	6	80.2
IM	8	80.9	5	90.0
PM	5	86.0	3	91.9
Children aged 6–12 years				
NM	9	82.0	4	82.4
IM	6	84.9	3	82.0
PM	4	88.6	2	88.4

$fAUC2_{24h}/MIC \geq 25$, ratio of free drug AUC during a 24-h period to minimum inhibitory concentration greater than or equal to 25; AUC, area under the concentration-time curve; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; CFR, cumulative fraction of response; all the recommended dosages are for the BID dosing regimens.

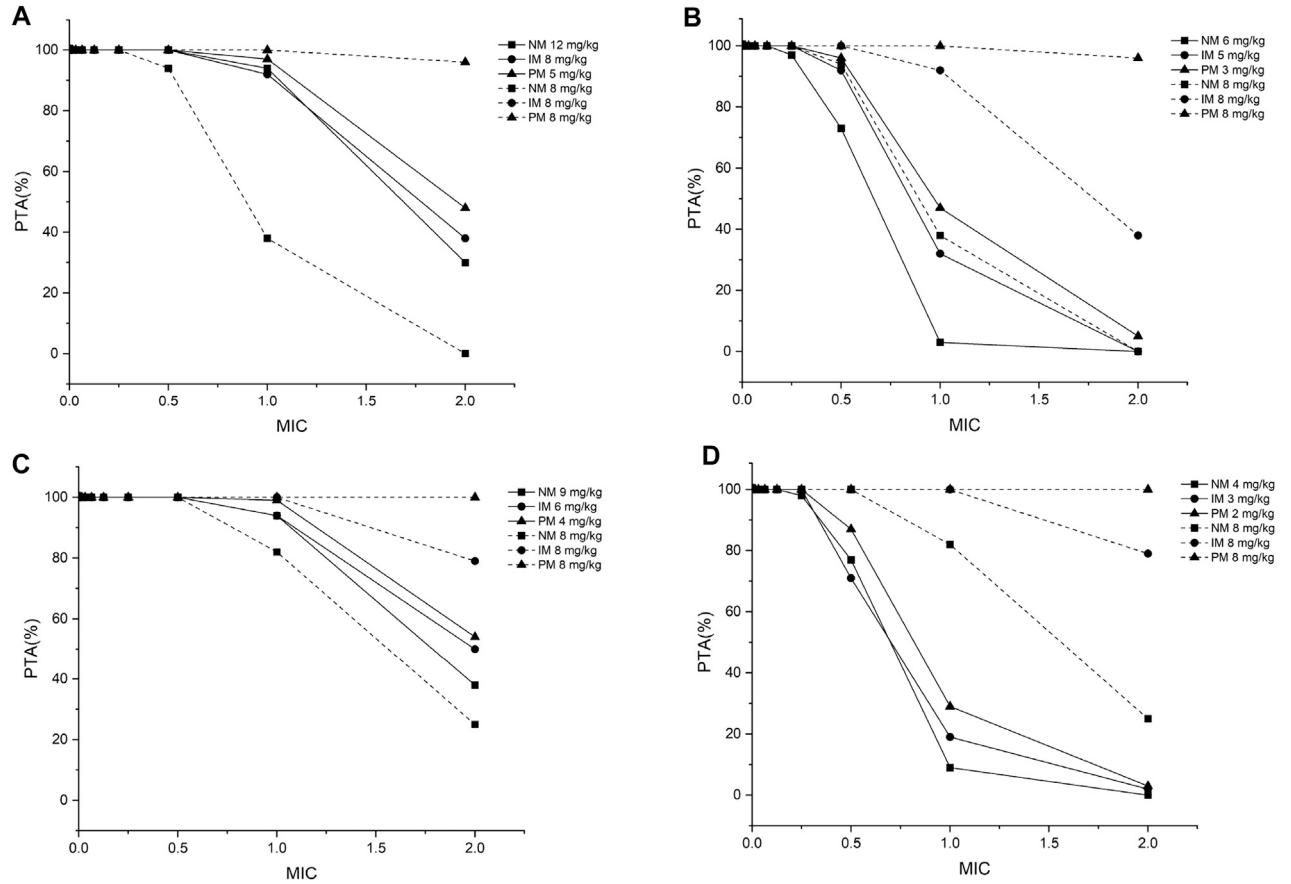

FIGURE 4 | The minimum probability that targets pharmacokinetic/pharmacodynamic index of $fAUC_{24h}$/MIC ≥ 25 among all species achieved at a specific MIC for each *CYP2C19* phenotype at the recommended dosage from the medication label (8 mg/kg) and recommended dose from the PBPK model for **(A)** children aged 2–6 years, infected with *Aspergillus* spp.; **(B)** children aged 2–6 years, infected with *Candida* spp.; **(C)** children aged 6–12 years, infected with *Aspergillus* spp.; **(D)** children aged 6–12 years, infected with *Candida* spp. PTA, probability of target attainment; MIC, minimum inhibitory concentration; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; all the dosages are for the BID dosing regimens.

Voriconazole is often for long-term use, from weeks to months, in the prophylaxis and treatment of IFI (Benitez and Carver, 2019). Therefore, it is essential to elucidate the time-dependent PK characteristics of this medication following multiple doses. To accomplish this goal, the strategy used for model building in this study is slightly different from that used in other studies. TDI-related parameters have always been optimized in the final step in multiple studies. However, the resulting change in these values can affect the previous predictions of single-dose administration. Generally, retrograde clearance can be implemented in the model first, and then sensitivity analysis is conducted to determine the optimal value of uncertain parameters (Wu et al., 2014). However, due to the possible inaccuracies of data digitized from the literature, which may influence the sensitivity analysis, this method was not used. Instead, a "bottom-up" and "top-down" combination strategy incorporating manual iterations was used to facilitate the model building process. The adult PBPK model results showed satisfactory predictive performance for multiple-dose administration in all *CYP2C19* genotype populations.

There was an overprediction of exposure in children when default enzyme ontogeny profiles from *in vitro* experiments were utilized to extrapolate the adult model. Therefore, ontogeny factors based on a meta-analysis of *in vivo* CYP activity with age-related changes (Upreti and Wahlstrom, 2016) were implemented. In this meta-analysis, the maximal activity of CYP2C19, CYP3A4, and CYP2C9 in children exceeded the corresponding adult values. The higher capacity or expression of CYP enzymes in children was also corroborated from a previous *in vitro* experiment using human liver microsomes (Yanni et al., 2010). That experiment showed that the apparent V_{max} for voriconazole conversion to the N-oxide metabolite was approximately 3-fold higher in children than in adults. After incorporating the new ontogeny profiles, the predictive performance of the PBPK model was improved. Moreover, the clearance was approximately 2–3-fold higher in children than in adults in the simulation, which is consistent with a previous study (Walsh et al., 2004).

The final extrapolated model presented the PK features of voriconazole in the pediatric population following i.v.

administration, except that the exposure of several 6–12-year-old children in the study by Walsh et al. was slightly overpredicted. There may be several reasons. First, the predicted PK parameters were calculated from a cohort of children with a certain percentage of different CYP2C19 metabolic types described in the baseline demographic data. However, a few children discontinued treatment due to adverse events. The metabolic types of these children were not disclosed, which may result in differences between the predicted and observed values. Furthermore, although children who were receiving drugs known to interact strongly with voriconazole, such as terfenadine and pimozide, were excluded, concomitant medications that could potentially interact with voriconazole were permitted, which might have resulted in altered PKs that were not considered in the PBPK model.

The results of dose optimization seem to be reasonable. Most of the recommended dosages for NM and IM children aged 2–12 years infected with *Aspergillus* spp. are similar to the dosages adopted by the European Medicines Agency (EMA) for children aged 2–11 years, specifically a loading i.v. dose of 9 mg/kg BID on day 1, followed by a maintenance dose of 8 mg/kg BID (European Medicines Association, 2012). They are also close to the loading dose of 7 mg/kg BID recommended by the Infectious Disease Society of America (IDSA) (Pappas et al., 2009), except for 12 mg/kg, which is the recommended dosage for 2–6-year-old NMs. Although the tolerance of higher dosage up to 10 mg/kg in children has been confirmed (Sano et al., 2016), further validation of this regimen's exposure and safety is needed before implementing it in clinical practice. In other subpopulations, dose adjustment is proposed based on several factors. First, younger children may have a relatively higher enzyme expression or activity (Upreti and Wahlstrom., 2016), contributing to higher metabolism and lower concentration. Thus, higher recommended doses in younger children, especially <5 years old, seem warranted (Soler-Palacín et al., 2011). Second, as CYP2C19 is the major enzyme in the metabolism of voriconazole (Barbarino et al., 2018), lower doses should be administered to people with alleles associated with enzymatic loss-of-function (Moriyama et al., 2017). Third, invasive fungal infection classification should be considered a key factor for antifungal therapy (Wang et al., 2016). The susceptibility of *Candida* spp. to voriconazole is higher than that of *Aspergillus* spp.; therefore, a reduced dose of voriconazole should be sufficient for infections involving the former (Perez-Pitarch et al., 2019).

The recommended dosage in this study should be deemed a reference for the initial dosing regimen because the target CFR value represented the overall distribution of MIC in the population and the clinical data utilized for model validation were mean drug exposure. It cannot completely solve the problem of high PK variability and replace the importance of therapeutic drug monitoring (Gastine et al., 2017). Subsequent dose adjustments should be conducted based on the individual MIC, drug concentration and clinical response (Muto et al., 2015).

One limitation of this study is that the model was established based on some fundamental assumptions. For example, CYP2C19, CYP3A4, and CYP2C9 account for the entire metabolism of voriconazole, and the metabolic pathway is the same in both adults and children. A study of human liver microsomes provided evidence that flavin-containing monooxygenase 3 (FMO3) contributes to higher clearance in children than in adults (Yanni et al., 2010). However, this was not integrated into our model due to the small effect on the main metabolite of voriconazole observed in previous recombinant FMO3 enzyme experiments (Yanni et al., 2008). Moreover, the limited available data on RMs made it impossible to recommend dosage for this subpopulation in children. The established model and the recommended dosage for other subpopulations may also require further verification in carefully designed clinical trials.

In conclusion, the developed PBPK model of voriconazole provides a more accurate description of PK characteristics in adults following single and multiple i.v. and p.o. administrations, especially in PMs. It also predicts exposure in children following i.v. administration with good accuracy. Age, *CYP2C19* genotype, and infectious fungal genera were found to significantly influence the attainment of the PK/PD target in the simulation and thus should be considered for clinical dose selection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YZ and SZ contributed to the study conception and design. YZ, SZ, and CW contributed to PBPK model development and simulations. YZ and PZ drafted the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.636097/full#supplementary-material.

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Serum Creatinine and Serum Cystatin C are Both Relevant Renal Markers to Estimate Vancomycin Clearance in Critically Ill Neonates

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Purpose: Serum creatinine (SCr) is used as a marker of kidney function to guide dosing of renally eliminated drugs. Serum Cystatin C (S-CysC) has been suggested as a more reliable kidney marker than SCr in adults and children. Purpose of this study was to investigate S-CysC as alternative renal marker to SCr for estimating vancomycin clearance in neonates undergoing intensive care.

Methods: Vancomycin pharmacokinetics (PK), SCr and S-CysC data were collected in patients undergoing vancomycin treatment in the neonatal intensive care unit of Robert Debré Hospital - Paris. A population PK analysis was performed utilizing routine therapeutic drug monitoring samples. S-CysC and SCr were compared as covariates on vancomycin clearance using stepwise covariate modeling (forward inclusion [$p < 0.05$] and backward elimination [$p < 0.01$]). Model performance was evaluated by graphical and statistical criteria.

Results: A total of 108 vancomycin concentrations from 66 patients (postmenstrual age [PMA] of 26–46 weeks) were modeled with an allometric one-compartment model. The median (range) values for SCr and S-CysC were 41 (12–153) µmol/l and 1.43 (0.95–2.83) mg/l, respectively. Following stepwise covariate model building, SCr was retained as single marker of kidney function (after accounting for weight and PMA) in the final model. Compared to the final model based on SCr, the alternative model based on S-CysC showed very similar performance (e.g. BIC of 578.3 vs. 576.4) but included one additional covariate: impact of mechanical ventilation on vancomycin clearance, in addition to the effects of size and maturation.

Conclusion: SCr ans S-CysC are both relevant renal markers for individualization of vancomycin dosing in critically ill neonates. Hower, if using S-CysC for this purpose mechanical ventilation needs to be taken into account.

Keywords: serum cystatin C, serum creatinine, population pharmacokinetics, vancomycin, neonates

INTRODUCTION

Kidney function is a major determinant of clearance (CL) of renally eliminated drugs. Markers reflecting kidney function are therefore essential for dosing individualization. Utilizing optimal renal markers for optimizing drug dosing is a current pharmacological challenge in neonatal medicine.

Serum Creatinine (SCr) is used as a marker of glomerular filtration rate (GFR) to guide dosing of drugs eliminated by the kidney across all age groups. However, the use of SCr for this purpose raises two specific issues in neonates. First, SCr concentrations in the first days after birth are influenced by maternal creatinine, because of placenta transfer (Kastl, 2017). Second, SCr may be falsely elevated in the first days to weeks of life in premature neonates, because of tubular reabsorption by the immature kidney (Kastl, 2017).

Serum Cystatin C (S-CysC) has been suggested as a more reliable biomarker than SCr for monitoring kidney function in adults and children (Dharnidharka et al., 2002; Björk et al., 2019). In neonates, S-CysC offers the advantage of limited ability to cross the placental barrier (Allegaert et al., 2015). However, there is limited pharmacokinetic evidence for the usefulness of S-CysC as covariate explaining inter-individual variability of drug renal CL in neonates, especially in those undergoing intensive care treatments.

As vancomycin is one of the drugs primarily eliminated by glomerular filtration, and also highly prescribed in neonates, this glycopeptide antibiotic was used as model drug to answer our research question. The purpose of this pharmacokinetic (PK) study was to investigate S-CysC as alternative renal marker to SCr for explaining inter-individual variability of vancomycin CL in a representative cohort of neonates undergoing intensive care treatment.

MATERIALS AND METHODS

Study Population and Design

This study was conducted in the neonatal intensive care unit (NICU) of Robert Debré University Hospital—Paris (France). Neonates receiving intravenous vancomycin as part of their routine clinical care were enrolled. Vancomycin dosing followed the individualized local guidelines routinely used in the unit (Zhao et al., 2013). A loading dose was infused over 60 min and followed by a maintenance dose administered as a continuous infusion over 24 h.

Vancomycin routine therapeutic drug monitoring (TDM) samples were used for PK modeling. The following data were collected and evaluated as covariates with a potential influence on vancomycin PK: gestational age (GA), postnatal age (PNA), postmenstrual age (PMA, defined as the sum of GA and PNA), birth weight (BW), current weight (CW), SCr and c-reactive protein (CRP) concentrations (both collected within 48 h of TDM sampling), mechanical ventilation, and co-medication of vasopressor agents or aminoglycosides. Patients with missing SCr data were excluded from analysis. S-CysC concentrations were measured on blood samples remaining after routine vancomycin TDM analysis which had been kept frozen at -80°C (maximum storage period of 12 months). No additional blood volume was taken for this non-interventional study. This study was approved by the ethics committee of Robert Debré University Hospital.

Assay of Serum Vancomycin, Creatinine and Cystatin C

Serum vancomycin concentrations were measured by fluorescence polarization immunoassay using a Cobas Integra system (Roche Diagnostics, Meylan, France). The lower limit of quantification for this assay was 0.74 mg/l.

SCr concentrations were determined by an enzymatic method using the Advia 1800 chemistry system (Siemens Medical Solutions Diagnostics, Puteaux, France). The lower limit of quantification was 12 μmol l^{-1}.

S-CysC concentrations were measured by an immunoenzymatic method using the Gentian AS (Moss, Norway) on Beckman Coulter (Beckman Coulter SA, Villepinte, Roissy CDG France). The Gentian Cystatin C immunoassay is a Particle-Enhanced Turbidimetric Immunoassay (PETIA). The lower limit of quantification was 0.4 mg/l.

All assays were performed in Robert Debré University Hospital, Paris.

Population Pharmacokinetic Modeling of Vancomycin

Model Building

PK data for vancomycin were modeled with the software package NONMEM; parameters were estimated by first-order conditional estimation with interaction (FOCE-I).

As a first step, a structural model (without covariates) was developed. One- and two-compartment models were tested. As a second step, a stepwise covariate model building was performed applying a forward selection and backward elimination method (Mandema et al., 1992). The likelihood ratio test was used to test the effect of each covariate on model parameters. Power, exponential and linear models' functions were tested to describe covariate effects of continuous variables. In addition, effect of PMA on CL was tested by means of a sigmoidal maximum effect function (Wang et al., 2019). During the initial step of covariate model building, inclusion of a covariate required a significant ($p < 0.05$; Likelihood ratio test) decrease in the objective function value (OFV; reduction >3.84 according to Chi-square distribution with one degree of freedom) from the basic model and a concomitant reduction in inter-individual variability (IIV) of the PK parameter. All of the significant covariates were then added simultaneously into an intermediate full model, starting with the most significant. Subsequently, each covariate was independently removed from the full model. Covariates were retained in the final model if a significant ($p < 0.01$; Likelihood ratio test) increase (more than 6.635 points) of the OFV was achieved.

As previously described in the literature for primarily renally eliminated antibiotics in neonates, vancomycin CL was finally parameterized as follows (Wilbaux et al., 2016):

$$CL = CLstandard * Effsize * Effmaturation * Effkidney$$

where CLstandard represents the typical value of clearance in the study population, Effsize represents the effect of growth (modeled using allometric scaling approach), Effmaturation represents the effect of age-dependent maturation (antenatal development and postnatal maturation being modeled using maturation functions including either PMA alone, or a combination of GA and PNA, or a combination of BW [as surrogate of GA] and PNA (Grubb et al., 2005)), and Effkidney represents the effect of kidney function.

Reflecting the effect of kidney function, SCr, S-CysC and three preexisting estimates of GFR (Filler and Lepage, 2003; Grubb et al., 2005; Zappitelli et al., 2006) were compared as covariates on vancomycin CL.

Model Evaluation

The performance of developed model was assessed by graphical and statistical criteria. Goodness-of-fit plots were initially used for diagnostic purpose. The stability of the final model was also assessed using a nonparametric bootstrap analysis (Parke and Charles, 2000) with resampling and replacement (500 times). Values of estimated parameters obtained with the bootstrap procedure were compared with respective values estimated with original data set. Then, the final model was evaluated by calculating normalized prediction distribution errors (NPDE) (1,000 datasets were simulated with the final population model parameters) (Comets et al., 2008).

Further Exploration of Differences Between SCr and S-CysC in Respect to Study Purpose

In order to investigate more in depth the relationship vancomycin CL - S-CysC to the relationship vancomycin CL - SCr, two vancomycin PK models were compared: one based on S-CysC (CYS model) and the other based on SCr (CR model). The Bayesian information criterion (BIC) was used to compare these non-nested models (Mould and Upton, 2013).

Additionally, in order to compare the behavior of both renal markers in our population with previous findings from the available literature, we explored effects of age and aminoglycosides on SCr and S-CysC levels. At this step, differences between two groups were assessed by the non-parametric Mann–Whitney–Wilcoxon test. Normality of the distributions was previously analyzed with the Shapiro–Wilk test. Statistical analyses were conducted using R software. A p value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 108 serum vancomycin concentrations from 66 patients were available for PK analysis, after exclusion of two patients because of lack of SCr data. Blood samples were drawn at a median of 33 h (range 5–354 h) after initiation of treatment. One to five PK samples per patient were available for analysis. Vancomycin concentrations ranged from 7.3 to 63.6 mg/l (**Supplementary Figure S1**). Baseline patient characteristics are presented in **Table 1**. GA and PMA ranged from 23 to 41 weeks and from 26 to 46 weeks, respectively. The median SCr and S-CysC concentrations were 41 µmol/l and 1.43 mg/l, respectively. Among the 66 patients, 70% had CRP concentrations >10 mg/l, 48% received mechanical ventilation and 23% were also treated with vasopressor agents at time of first vancomycin dosing.

TABLE 1 | Baseline characteristics of the 66 patients.

	No. of neonates	Median (range)
Demographic data[a]		
Gender (female/male)	37/29	
Gestational age (weeks)		32 (23–41)
Postnatal age (days)		13 (1–106)
Postmenstrual age (weeks)		34 (26–46)
Birth weight (grams)		1590 (512–3950)
Current weight (grams)		1925 (530–3840)
Clinical data[a]		
Mechanical ventilation	32	
Coadministration of vasopressor agent(s)	15	
Coadministration of aminoglycoside(s)	39	
Biological data[b]		
Serum Creatinine concentration (µmol/L)		41 (12–153)
Serum Cystatin C concentration (mg/L)		1.43 (0.95–2.83)
C-reactive protein concentration (mg/L)		30 (5–313)
Vancomycin treatment data		
Loading dose (mg/kg)		10.5 (7.4–20.9)
First maintenance dose (mg/kg/day)		24.8 (10.3–59.3)

[a]*At time of first dosing*
[b]*Within 48 h of first dosing*

Model Building

Data were best fitted by a one-compartment model with first-order elimination. Inter-individual variability could be estimated only for CL (exponential model). A proportional model best described the residual unexplained variability.

The allometric size approach, which consisted of a priori incorporation of CW into the structural model, generated a significant drop in the OFV (−50 units). Allometric exponents of 0.75 and 1 were fixed for CL and volume of distribution, respectively (Holford, 1996); their estimation did not improve the fit of the data. When tested individually, among all above-mentioned tested covariates, the following led to a significant decrease in the OFV from the allometric model: PMA, SCr, S-CysC, mechanical ventilation and co-medication of vasopressor agents. The results of the covariate analysis are presented in **Table 2**. Reflecting the maturation effect, PMA was superior as a covariate on CL, over the combination of BW and PNA and the combination of GA and PNA. Reflecting the effect of kidney function, SCr was superior as a covariate on CL over S-CysC and over all three tested estimates of GFR (Grubb et al., 2005; Filler and Lepage, 2003; Zappitelli et al.,

TABLE 2 | Summary of covariate analysis[h].

Characteristics	Pharmacokinetic parameters	OFV[e]	ΔOFV[f]	IIVCL[g] (%)
Structural model	/	**644.8**	/	**71.0**
Allometric model (effect of size)	**CL, V**			
CW		**594.4**	**−50.4**	**47.3**
Effect of maturation[a]	**CL**			
BW and PNA		576.3	−68.5	40.1
GA and PNA		572.8	−72.0	40.0
PMA		**572.6**	**−72.2**	**40.0**
Effect of kidney function[a]	**CL**			
Grubb eGFR[b]		604.6	−40.2	41.5
Filler eGFR[c]		599.4	−45.4	41.2
Zappitelli eGFR[d]		599.1	−45.7	41.2
S-CysC		577.2	−67.6	40.2
SCr		**560.3**	**−84.5**	**33.8**
Effect of mechanical ventilation[a]	**CL**			
Ventilation		584.9	−59.9	41.8
Effect of maturation and kidney function[a]	**CL**			
PMA and SCr (Final model)		**548.3**	**−96.5**	**30.9**
PMA and SCr and S-CysC		544.6	−100.2	30.6
Effect of maturation, kidney function and mechanical ventilation[a]	**CL**			
PMA, SCr and ventilation		546.3	−98.5	29.9

CW current body weight; BW birth body weight; PNA postnatal age; GA gestational age; PMA postmenstrual age; eGFR estimate of glomerular filtration rate; S-CysC serum Cystatin C concentration; SCr serum Creatinine concentration; CL clearance; V volume of distribution

[a]*Included into the allometric model*

[b]$eGFR = 84.69 \times (S\text{-}CysC)^{-1.680} \times 1.384^{if < 14\ yr}$ *(Grubb et al., 2005)*

[c]$eGFR = 91.62 \times (S\text{-}CysC)^{-1.123}$ *(Filler and Lepage, 2003)*

[d]$eGFR = 75.94 \times (S\text{-}CysC)^{1.17} \times 1.2^{if\ renal\ transplant}$ *(Zappitelli et al., 2006)*

[e]*Objective function value*

[f]*Variation in objective function value*

[g]*Inter-individual variability of vancomycin clearance*

[h]*The characteristics in boldface were retained in the final population model.*

2006). Inclusion of SCr and S-CysC into the allometric model reduced inter-individual variability of vancomycin clearance (IIVCL) from 47 to 34% and 40%, respectively. Relationships between covariates and vancomycin CL were best fitted by power models functions for both SCr and S-CysC.

After integration of SCr into the allometric model, PMA caused a further significant drop in the OFV (- 12 units). Other covariates were then rejected during the forward selection step because of insufficient decrease of the OFV. In particular, further introduction of S-CysC did not significantly improve the model (drop in the OFV of 3.7 units). The final model (CR model) included CW, PMA, and SCr as significant covariates on vancomycin CL (**Table 3**).

TABLE 3 | Final estimates of population pharmacokinetic parameters of vancomycin and bootstrap results—from the final model based on Serum Creatinine (CR model).

Parameters	Final model		Bootstrap (n = 500)		
	Mean estimate	RSE (%)	Median	5th %ile	95th %ile
CL (L/h)					
$CL = CLTV \times (CW/1925)^{0.75} \times Effage \times Effkidney$					
CLTV	0.11	4.4	0.11	0.10	0.12
$Effage = (PMA/34)^{k1}$					
k1	1.47	23.3	1.51	0.94	2.12
$Effkidney = (1/(SCR/41))^{k2}$					
k2	0.50	18.3	0.51	0.34	0.65
V (L)					
$V = VTV \times (CW/1925)$					
VTV	0.47	44.8	0.48	0.14	1.30
Inter-individual variability (%)					
CL	30.9	27.3	29.8	23.0	36.6
Residual variability (%)	29.8	18.1	28.4	22.0	33.5

CL clearance; CLTV typical value of clearance; CW current body weight (grams); Effage effect of age; Effkidney effect of kidney function; PMA postmenstrual age (weeks); SCR Serum Creatinine concentration (μmol/L); V volume of distribution; VTV typical value of volume of distribution.

Model Evaluation

No major bias in the goodness-of-fit plots was observed (**Supplementary Figure S2**). The median parameter estimates resulting from the bootstrap procedure closely agreed with the respective values from the final model (**Table 3**). The mean and variance of NPDE were 0.03 (Wilcoxon signed rank test p = 0.89) and 1.05 (Fisher variance test p = 0.70), respectively.

Further Exploration of Differences Between SCr and S-CysC in Respect to Study Purpose

When S-CysC was selected instead of SCr as biomarker reflecting kidney function, the covariate selection process led to an alternative vancomycin PK model including CW, PMA,

TABLE 4 | Final estimates of population pharmacokinetic parameters of vancomycin and bootstrap results—from the alternative model based on Serum Cystatin C (CYS model).

Parameters	Final model		Bootstrap (n = 500)		
	Mean estimate	RSE (%)	Median	5th %ile	95th %ile
CL (L/h)					
$CL = CLTV \times (CW/1925)^{0.75} \times Effage \times Effkidney \times Effventilation$					
CLTV	0.15	6.2	0.14	0.13	0.16
$Effage = (PMA/34)^{k1}$					
k1	1.72	19.7	1.76	1.17	2.42
$Effkidney = (1/(SCYS/1.43))^{k2}$					
k2	0.97	20.1	0.98	0.59	1.31
Effventilation = k3					
k3	0.69	9.5	0.69	0.58	0.81
V (L)					
$V = VTV \times (CW/1925)$					
VTV	0.48	40.3	0.48	0.14	1.22
Inter-individual variability (%)					
CL	30.3	24.6	29.2	22.2	34.9
Residual variability (%)	29.6	21.1	28.1	20.8	33.6

CL clearance; CLTV typical value of clearance; CW current body weight (grams); Effage effect of age; Effkidney effect of kidney function; Effventilation effect of mechanical ventilation; k3 scaling factor applied for patients receiving mechanical ventilation; PMA postmenstrual age (weeks); SCYS Serum Cystatin C concentration (mg/L); V volume of distribution; VTV typical value of volume of distribution.

S-CysC and mechanical ventilation as covariates on CL (CYS model, **Table 4**). After integration of PMA and S-CysC into the allometric model, mechanical ventilation (associated with 30% reduced vancomycin CL) caused a further significant drop of 14 units in the OFV and a further reduction in IIVCL from 36.1 to 30.3%.

The typical estimated values of vancomycin CL were very similar between CR and CYS models (i.e. 0.11 and 0.15 L/h for the CR and CYS models, respectively, with <10% relative standard errors of CL for both models). CL estimates (mean ± SD) obtained from CR and CYS model were 0.068 ± 0.025 l/h kg and 0.070 ± 0.025 l/h kg, respectively. **Table 5** shows the high similarity between individual vancomycin CL estimates from CR and CYS models for four typical patients with different PMA. Both CR and CYS models showed very similar performance in terms of visual goodness of fit (**Supplementary Figures S2 and S3**), stability (**Tables 3** and **4**), NPDE results (for CYS model, the mean and variance of NPDE were 0.01 [p = 0.95] and 1.05 [p = 0.69], respectively), and BICs values (i.e. 576.4 and 578.3 for the CR and CYS models, respectively). To summarize, compared to the final model based on SCr, the alternative model based on S-CysC provided a very similar fit of the data but included the effect of mechanical ventilation on vancomycin CL as additional covariate.

Based on this finding, we further explored effects of mechanical ventilation on SCr and S-CysC. **Figure 1** showed that SCr levels were higher in patients undergoing mechanical ventilation (median levels increasing from 25 to 48 µmol/l; p < 0.001) while S-CysC concentrations remained stable with and without mechanical ventilation (median levels of 1.46 and 1.43 mg/l, respectively; p = 0.68).

Additionally, as shown in **Figure 2**, regardless of GA group, SCr levels decreased gradually with PNA during the first two months of life while S-CysC concentrations remained relatively stable over the same time period. Then, S-CysC levels were significantly lower in patients treated with aminoglycosides (median levels decreasing from 1.56 to 1.35 mg/l; p < 0.001) while SCr concentrations were not impacted by aminoglycosides exposure (p = 0.73).

DISCUSSION

In the present study, a population PK analysis was performed to compare SCr and S-CysC as covariates on vancomycin CL in neonates undergoing intensive care treatment. The inclusion of SCr into the allometric model reduced IIVCL from 47 to 34%, while S-CysC reduced IIVCL from 47 to 40% (**Table 2**). Following stepwise covariate model building, SCr was retained as single marker of kidney function (after accounting for weight and PMA) in the final model. Compared to the final model based on SCr, the alternative model based on S-CysC showed very similar performance (e.g. BIC of 578.3 vs. 576.4) but included, besides the effects of size and maturation, the impact of mechanical ventilation as additional covariate on vancomycin CL.

Kidney function is the determining factor of dosing optimization for drugs predominantly eliminated by the kidney. Brou et al. recently reviewed the available PK studies comparing the impact of S-CysC and SCr on the CL of renally eliminated drugs (Brou et al., 2015). Among the 14 studies identified, only one was conducted in children, with the youngest patient being 4 years of age (Halacova et al., 2008). The present study is to our knowledge the first population PK study comparing S-CysC and SCr as covariates on drug CL in neonates undergoing intensive care treatment.

TABLE 5 | Individual vancomycin clearance estimates from CR and CYS models for four typical patients (1,000 simulations).

	Patient 1	Patient 2	Patient 3	Patient 4
Postmenstrual age (weeks)	**26**	**31**	**34**	**39**
CL estimates from CR model	0.048 [0.047–0.049]	0.057 [0.056–0.058]	0.086 [0.085–0.088]	0.123 [0.120–0.125]
CL estimates from CYS model	0.039 [0.038–0.040]	0.047 [0.046–0.048]	0.096 [0.095–0.098]	0.128 [0.125–0.130]

*CL, vancomycin clearance (mean [95% confidence interval] in L/h*kg); CR model, final model based on Serum Creatinine; CYS model, alternative model based on Serum Cystatin C.*

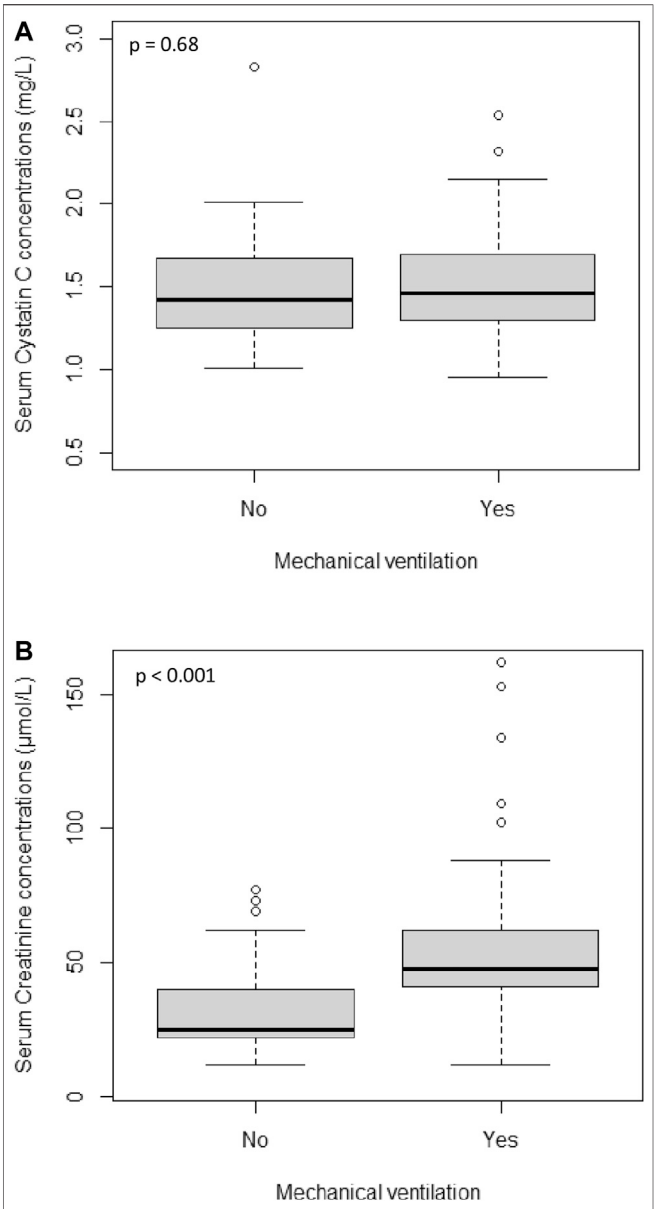

FIGURE 1 | Distribution of Serum Cystatin C concentrations **(A)** and Serum Creatinine concentrations **(B)** in patients treated with and without mechanical ventilation.

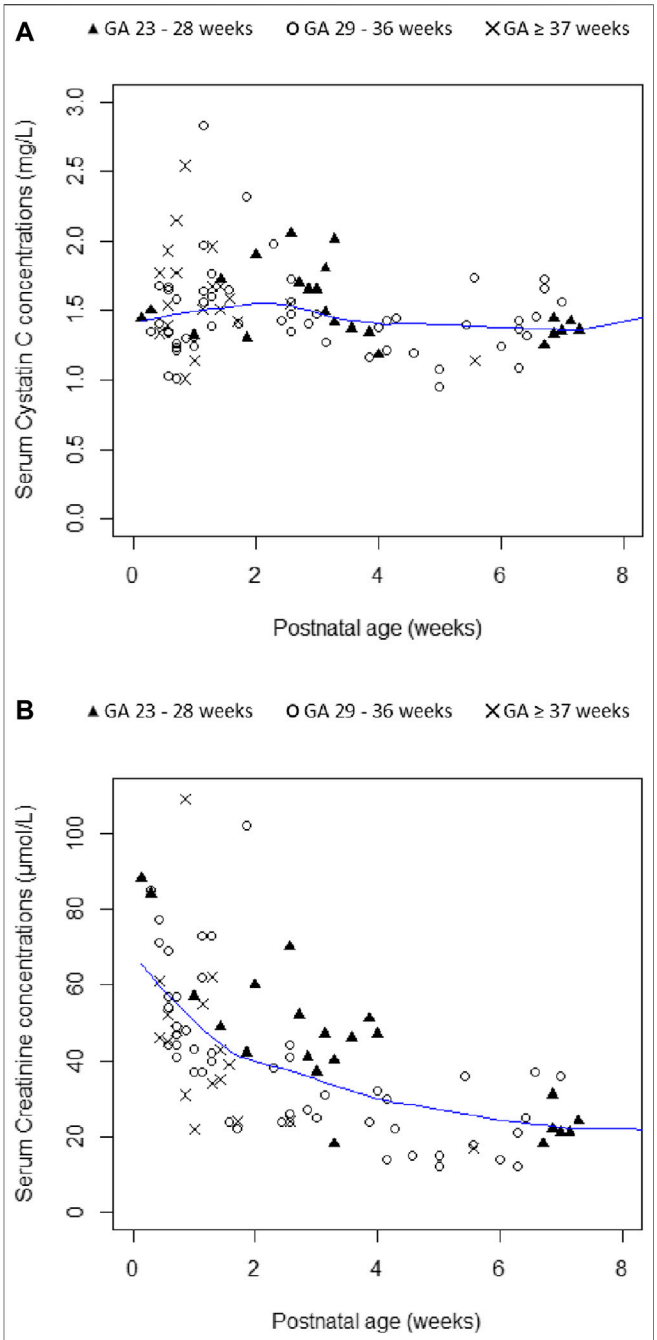

FIGURE 2 | Plots of Serum Cystatin C concentrations **(A)** and Serum Creatinine concentrations **(B)** according to gestational age (GA) and postnatal age. Smooth lines are represented in blue color.

SCr and S-CysC concentrations measured in this study were in the range of reference values previously reported in neonates (Finney et al., 2000; Allegaert et al., 2015; Wilhelm-Bals et al., 2019). Given available data, our covariate analysis led to retain SCr rather than S-CysC as single marker of kidney function in the final vancomycin PK model. Our results are in agreement with recent findings of Wilhelm-Bals et al. showing that inulin CL correlated with SCr but not with S-CysC in a neonatal population with similar ranges of GA (26–40 weeks vs. 23–41 weeks in our population), S-CysC concentrations (0.87–2.4 mg/l vs. 0.95–2.8 mg/l in our population) and SCr concentrations (28–163 µmol/l vs. 12.0–153 µmol/l in our population) (Wilhelm-Bals et al., 2019).

The behavior of SCr and S-CysC levels in our population is in agreement with previous findings from the available literature. First, in the present study, SCr was shown to be impacted by PNA while S-CysC concentrations were stable during the first two months of life. In agreement with previous reports, SCr decreased gradually with PNA (**Figure 2**) because of residual maternal creatinine and tubular reabsorption by the immature kidney in early life (Abitbol et al., 2014; Kastl, 2017). Whatever differences

in post-natal profile of SCr and S-CysC concentrations, antenatal and postnatal kidney maturation is reflected by PMA, a significant covariate on vancomycin CL in both CR and CYS models. Second, in accordance with previous findings by Abitbol et al. (2014), aminoglycosides exposure was associated with lower S-CysC values in our population. As previously suggested, this could be due to a competition between S-CysC and aminoglycosides both being ligands of the megalin receptor in the proximal tubule (Konopska et al., 2013). In other words, S-CysC concentration may be lowered in the presence of aminoglycosides independent of underlying kidney function. Clinicians should be aware of this potential confounding factor to interpret S-CysC for kidney assessment.

In this study, the inclusion of SCr into the allometric model reduced IIVCL from 47 to 34% while S-CysC reduced IIVCL from 47% to only 40% (**Table 2**). The comparison of CR and CYS models leads to the hypothesis that mechanical ventilation could at least partly explain this finding. Our results showed that the portion of IIVCL dependent on the effect of mechanical ventilation on kidney function was better reflected by SCr than by S-CysC. A 30% lower vancomycin CL was shown in neonates undergoing mechanical ventilation (factor 0.69 in CYS model). This is consistent with previous data from Perkins et al. showing that mechanical ventilation is a well-documented cause of decrease in cardiac output, hepatic and renal blood flow, GFR, and urine flow (Perkins et al., 1989). Vancomycin CL may be reduced in patients undergoing mechanical ventilation because of decreasing renal blood flow or GFR. Interestingly, the decrease in vancomycin CL due to mechanical ventilation stayed significant after integration of other covariates in the CYS model but not in the CR model. Indeed, accounting for mechanical ventilation further improved predictive performance of the CYS model (causing a further significant drop of 14 units in the OFV and a concomitant reduction in IIVCL from 36.1 to 30.3%) but did not significantly improve CR model (**Table 2**). This may suggest that S-CysC is less sensitive than SCr to the changes of GFR due to mechanical ventilation (**Figure 1**). Additional studies are needed to further explore this hypothesis.

As recently highlighted by the review of Muhari-Stark et al., currently available GFR-estimating formulas raise issues for neonatal use (Muhari-Stark and Burckart, 2018). Only two of the SCr-based GFR-estimates developed for paediatric use were derived from data in preterm and term neonates (Brion et al., 1986; Wilhelm-Bals et al., 2019). Their applicability is limited by the fact that SCr values were determined using the Jaffe method rather than the enzymatic one. None of the S-CysC-based GFR-estimates reported to date has been validated in neonates. In our population, none of the three tested GFR-estimates was superior to SCr alone as covariate on vancomycin CL (**Table 2**). We were not able to test GFR-estimates based on height as height was not available in all study subjects.

The vancomycin CL estimates based on both CR and CYS models are in accordance with values previously reported (de Hoog et al., 2004; Jacqz-Aigrain et al., 2019). Although comparison of BIC values cannot be interpreted statistically, a drop of 2 is often admitted as a threshold for considering one model over another (Mould and Upton, 2013). As shown by the ΔBIC of 1.9 between CYS and CR models, the use of S-CysC rather than SCr as single marker of kidney function provided a similar fit of our vancomycin data. However, for similar performance, CYS model required the inclusion of one additional covariate compared to CR model, which was only based on CW, PMA, and SCr. The pragmatic implications of these findings have to be considered for neonatal clinical practice. Due to the wide IIVCL shown in neonates, vancomycin dosage individualization is imperative. However, especially in NICUs, vancomycin treatment is frequently urgently needed, requiring simple, "easy to use" dosing recommendations. This is also a way to minimize prescriptions errors. Thus, leading to similar goodness of fit, the simplest model (CR model) might be preferred for implementation in clinical practice.

A limitation of our study is the sparse PK sampling. However, as reflected by the satisfying relative standard error of parameter estimates (i.e. <30% for CLTV, Effage, Effkidney and Effventilation—**Tables 3** and **4**) and other above-mentioned parameters of goodness of fit, this is expected to have limited impact on the primary objective of drug CL estimation. Second, both SCr and S-CysC levels might be affected by the assays used in this study. Different methods were previously reported to quantify these markers with between assay differences (Allegaert et al., 2015; Wilhelm-Bals et al., 2019). Finally, further investigations are needed to explore more in depth the pathophysiological differences between SCr and S-CysC, especially in patients undergoing mechanical ventilation.

CONCLUSION

Population PK analysis led to retain SCr as single marker of kidney function to estimate vancomycin CL in neonates undergoing intensive care treatment. Compared to the final model based on SCr, the alternative model based on S-CysC showed very similar performance but included the effect of mechanical ventilation on vancomycin CL, as additional covariates to S-CysC, CW and PMA. SCr and S-CysC are both relevant renal markers for individualization of vancomycin dosing in critically ill neonates. However, if using S-CysC for this purpose mechanical ventilation needs to be taken into account.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Robert Debré University Hospital.

Written informed consent from the participants' legal guardian/next of kin was not required to participate in this

study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SL, WZ, and EJ-A designed the study. VB organized and followed the study in the NICU. Patients' data were collected by DZ and VB. SL performed the analysis, which was discussed with EJA, MP, JvDA, and VG. SL wrote the first draft of the manuscript, which was first discussed with EJ-A and MP. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Contribution of Population Pharmacokinetics of Glycopeptides and Antifungals to Dosage Adaptation in Paediatric Onco-hematological Malignancies: A Review

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The response to medications in children differs not only in comparison to adults but also between children of the different age groups and according to the disease. This is true for anti-infectives that are widely prescribed in children with malignancy. In the absence of pharmacokinetic/pharmacodynamic paediatric studies, dosage is frequently based on protocols adapted to adults. After a short presentation of the drugs, we reviewed the population pharmacokinetic studies available for glycopeptides (vancomycin and teicoplanin, $n = 5$) and antifungals (voriconazole, posaconazole, and amphotericin B, $n = 9$) currently administered in children with onco-hematological malignancies. For each of them, we reported the main study characteristics including identified covariates affecting pharmacokinetics and proposed paediatric dosage recommendations. This review highlighted the very limited amount of data available, the lack of consensus regarding PK/PD targets used for dosing optimization and regarding dosage recommendations when available. Additional PK studies are urgently needed in this specific patient population. In addition to pharmacokinetics, efficacy may be altered in immunocompromised patients and prospective clinical evaluation of new dosage regimen should be provided as they are missing in most cases.

Keywords: paediatrics, malignancy, onco-hematology, glycopeptides, antifungals, population pharmacokinetics, drug dosage

INTRODUCTION

Child specific challenges of treatment include 1) frequent off-label/unlicensed use (which increases the risk of adverse drug reactions and lack of efficacy), 2) limited pharmacokinetic (PK) and/or pharmacodynamic (PD) age group and disease specific data, 3) considerable variation in drug dosages, and 4) an increased risk of medication errors (Gore et al., 2017; Jong, et al., 2001).

According to pharmacoepidemiologic studies, anti-infective drugs are widely prescribed in children (de Bie et al., 2016) but paediatric pharmacokinetic/pharmacodynamic (PK/PD) studies are limited and dosage frequently based on protocols adapted to adults. However, the response of children to medication differs in comparison to adults and also between different paediatric age

groups and between diseases. Data are also missing in many paediatric subpopulations presenting with frequent specific diseases.

In the past 20 years, several initiatives were undertaken in the United States and in Europe to encourage paediatric research and drug development (Choonara, 2007). Although the number of paediatric investigation plans and marketing authorisations increased, studies evaluating dosage regimen and therapeutic strategies in children presenting with frequent specific conditions are sparse and require public-private fundings (Turner et al., 2014; Ruggieri et al., 2015). This is particularly true in paediatric malignancies, representing specific diseases different from adults.

We selected paediatric onco-hematologic malignancies as a key area where anti-infectives are used regularly to manage infections complicating chemotherapy. However, dosage recommandations based on PK/PD targets originate frequently for adult studies. In this context, we reviewed the population PK (PopPK) studies available for currently prescribed glycopeptides (vancomycin and teicoplanin) and antifungals (posaconazole, voriconazole, and amphotericin B) to report on the key variables impacting PK parameters in children and analyze available dosage recommendations.

PHARMACOKINETIC/PHARMACODYNAMIC BIOMARKERS OF ANTI-INFECTIVES

PK-PD indices represent the quantitative relationship between pharmacokinetic measures the test drug (such as area under the curve AUC) and a microbiologic measure of susceptibility (minimum inhibitory concentration - MIC). The microbiological data from animal or *in vitro* experiments provide initial insight into PK-PD most likely to be associated with efficacy.

A concentration-dependent pattern of activity may be observed and $AUC_{0\text{-}24}$/MIC ratio and/or the Cmax/MIC ratio are the PK/PD indices that usually predict efficacy in PK-PD models.

A time-dependent pattern of bactericidal activity may be observed and time > MIC and/or AUC_{0-24}/MIC ratio are the indices that usually predict efficacy in PK-PD models.

Glycopeptides are time-dependent/concentration-independent antibiotics with moderate persistent killing, active against susceptible strains of methicillin-resistant (beta-lactam resistant) staphylococci. For azole antifungals, the PK/PD index that best relates to the outcome is the AUC_{0-24}/MIC (European Medicines Agency, 2015; Gómez-López, 2020).

PRESENTATION OF PHARMACOLOGICAL PROPERTIES AND AVAILABLE PK DATA OF GLYCOPEPTIDES AND ANTIFUNGALS

Glycopeptides: Vancomycin and Teicoplanin

The first line treatment for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections is a glycopeptide antibiotic, either vancomycin (a glycopeptide) or teicoplanin (a lipoglycopeptide). Both are often prescribed to broaden initial empirical antibiotic in case of persistent fever in paediatric and adult patients with HM (Libuit et al., 2014; Lehrnbecher et al., 2017). Teicoplanin is not inferior to vancomycin with regard to efficacy and is associated with a lower adverse event rate than vancomycin (Menichetti et al., 1994; Finch and Eliopoulos, 2005).

Vancomycin

Vancomycin is a large, hydrophilic molecule with poor oral absorption. Hence it is given intravenously to treat systemic infections. Vancomycin is 25–50% protein-bound, mainly to albumin and immunoglobulins, and protein binding changes non-linearly with vancomycin concentrations. It is almost exclusively eliminated by the renal route via glomerular filtration and to some extent via active tubular secretion. Elimination half-life is 6–12 h. Factors that affect its clinical activity, include variable tissue distribution, inoculum size, and emerging resistance.

The AUC_{0-24}/MIC ratio is the best predictor of vancomycin efficacy in adults. Various studies have shown that a vancomycin AUC_{0-24}/MIC ratio >400 best predicts treatment outcomes for invasive MRSA infection in adults.

Many vancomycin PK studies and reviews are available in adults, including PopPK studies and report that both vancomycin clearance (CL) and volume of distribution were higher in cancer than non-cancer patients (Yasuhara et al., 1998; Buelga et al., 2005; Jarkowski et al., 2012). PK studies also reported large variability in vancomycin disposition in children (neonates excluded) (Chang, 1995; Krivoy et al., 1998; Wrishko et al., 2000; Marsot et al., 2012; Hadi et al., 2016; Tkachuk et al., 2018).

Teicoplanin

Similarly to vancomycin, teicoplanin needs to be administered intravenously as bioavailability is extremely low, it is 25–50% protein bound and also exclusively eliminated by the renal route (Marsot et al., 2012).

PopPK studies available in adults receiving the drug for various indications, showed high variability in drug disposition (Yu et al., 1995; Lortholary et al., 1996; Soy et al., 2006). In children, different classical PK studies but with a relatively low number of patients (12,13, and 6, respectively, in the three studies) provided conflicting conclusions on the impact of age on teicoplanin PK parameters (Tarral et al., 1988; Terragna et al., 1988; Reed et al., 1997).

Antifungals: Voriconazole, Posaconazole, and Amphotericin B

Invasive fungal disease (IFD) is an important cause of morbidity and mortality in immunocompromised children receiving chemotherapy for cancer and those undergoing hematopoietic stem cell transplant (HSCT). Its incidence varies according to chemotherapy regimen and supportive care practices (Lehrnbecher et al., 2009; Groll et al., 2014).

Antifungal chemoprophylaxis is therefore recommended for high risk patients with prolonged neutropenia, prolonged use of steroids or in different subgroups of leukemia, taking into account the local epidemiology, patient comorbidity or specific treatment modalities (Fisher et al., 2018).

There are no major differences between children and adults in the choice of treatment of established infections and triazole antifungal agents are potential choices both for prophylaxis and treatment of probable and proven IFDs.

Voriconazole

Voriconazole is a recent triazole antifungal agent with potent activity against a wide range of clinically significant pathogens, including Aspergillus and Candida. Voriconazole may be administered orally and intravenously. Bioavailability has been estimated to be >90% in healthy volunteers, substantially lower in adults and even more in children with malignancies (Karlsson et al., 2009). A potential mechanistic explanation could be that paediatric patients exhibit greater systemic metabolism but also greater first-pass metabolism than that of adults.

Voriconazole is extensively metabolized by polymorphic cytochrome P450 (CYP) isoenzymes CYP2C9, CYP2C19 and CYP3A4. The prevalence of CYP2C19 poor metabolizers is 3–5% among Caucasians and black Africans, 15–20% among Asian populations. Only <2% of the dose is excreted unchanged in the urine. AUC/MIC ratio >20–25 was previously proposed as the PK/PD target to optimize voriconazole dosing (Andes, 2003). Previously published reports in adult patients suggested aiming at a plasma trough drug concentration between 1 and 5.5 mg/L for efficacy and limiting toxicity (Pascual et al., 2008). PopPK studies on voriconazole have been conducted in adults, either healthy volunteers or sick patients (Vehreschild et al., 2012; van Iersel et al., 2018; Liu et al., 2019; Shi et al., 2019) and available studies were recently reviewed (Shi et al., 2019), reporting marked IIV in PK parameters and only limited intraindividual variation.

Posaconazole

Posaconazole is licensed for prophylaxis of IFD in 1) patients with prolonged neutropenia and who are at high risk of developing IFD complicating HM, 2) patients at high risk of developing IFD following HSCT and under immunosuppressive therapy for graft-versus-host disease.

Posaconazole showed potent dose-dependent *in vivo* antifungal activity on prophylaxis and treatment against most fungal infections. PK studies were predominantly performed in healthy volunteers and hematological adult patients and were recently reviewed (Chen et al., 2019). Bioavailability was reported to be around 50% in healthy volunteers with the suspension and delayed-release tablet (Chen et al., 2019), but lower in patients receiving the posaconazole suspension (Dolton et al., 2014). It is bound to plasma proteins for more than 98%. It is predominantly eliminated unchanged in feces or in urine. Elimination by glucuronidation (UGT1A4) is only limited (less than 20%).

Different biomarkers of efficacy are reported in adults, 1) the AUC/MIC showed the strongest correlation with therapeutic success, 2) the posaconazole average plasma concentration (Cavg) ≥ 1.25mg/L at steady-state was fixed as a valid cut-off value for IFD treatment as it was associated with 75% successful response rates in patients with invasive aspergillosis (Chen et al., 2020), while Cavg of 0.7 mg/L is accepted as a target for prophylaxis. Trough concentrations (Cmin) proved to be well correlated with Cavg or AUC 0–24 are biomarkers easier to use for monitoring.

According to the European marketing authorization, safety and efficacy are not established in children aged below 18 years (**Table 1**). Posaconazole can be administered as an oral suspension (40 mg/ml), a delayed-release tablet (100 mg), and more recently as intravenous formulation (18 mg/ml): only the oral formulations are licensed for paediatric patients. Prophylactic posaconazole was shown superior to fluconazole or itraconazole in reducing IFD and fungal related mortality in patients with graft vs. host disease (Ullmann et al., 2007). In addition, acceptability is high. Dosing information depends on the formulation, patient's age and indication (prophylaxis or treatment). No PK/PD data exist on tablets and intravenous formulation for all paediatric age groups.

Amphotericin B

Amphotericin B is a highly lipophilic drug administered intravenously as it is poorly absorbed orally. Amphotericin B-deoxycholate (D-AmB), a mixed micellar dispersion with deoxycholate, has been the cornerstone for the management of life-threatening fungal infections. This formulation has suboptimal clinical success and frequent nephron-toxic effects at usual recommended doses. It was replaced in the 1990 by the lipid-based formulations (L-AmB) encapsulating amphotericin B into liposomes or binding the drug to lipids (Walsh et al., 1999; Chen et al., 2020). L-AmB is less toxic and has limited infusion-associated reactions, increased therapeutic index and can be administered at higher dosages (Janoff, 1990; Moreau et al., 1992). AmB exhibits concentration-dependent killing of fungal organisms, with a long post-antifungal effect (Andes et al., 2003).

Standard PK studies, comparing the pharmacokinetics and tolerability of amphotericin B administered in a conventional 5% dextrose (glucose) (5% D) solution and in a 20% fat emulsion formulation (Intralipid; 20% IL) were initially conducted in adults. Differences in PK profile between the two formulations resulted in higher distribution volume, decreased Cmax and AUC, and increased CL with the 20% IL form (Ayestarán et al., 1996). A possible reason for the PK differences between the two methods of administration is the larger particle size of AmB in lipid emulsion.

The first PK studies in neutropenic adults showed dose-related, non-linear, saturation-like PK. The Cmax/MIC ratio of 2 may provide sufficient antifungal efficacy. The first population PK in adults (75 patients received 0.5–8.0 mg/kg of body weight of amphotericin B colloidal dispersion for 28 days) showed that plasma CL and volume of distribution increased with escalating doses, but without net change in renal function (Amantea et al., 1995).

REVIEW OF THE POPULATION PHARMACOKINETIC STUDIES OF GLYCOPEPTIDES AND ANTIFUNGALS IN PAEDIATRIC ONCO-HEMATOLOGICAL MALIGNANCIES

Methods

We search for PopPK studies of anti-infectives (glycopeptides and antifungals) in onco-hematological malignancies (leukemia or

TABLE 1 | Indications and European marketing authorization status of glycopeptides and antifungals in the different paediatric age groups.

Drug	Indications	Marketing authorization in Europe
Glycopeptides		
Vancomycin	Serious infections due to Gram-positive bacteria such as methicillin-resistant staphylococcus aureus (MRSA), resistant to other antibiotics	All patients; dosage based on age and weight
Teicoplanin	Serious infections due to Gram-positive bacteria	All patients; dosage based on age and weight
Antifungals		
Voriconazole	Treatment of 1) invasive aspergillosis 2) candidemia in non-neutropenic patients 3) fluconazole-resistant serious invasive Candida infections (including C. krusei) 4) serious fungal infections caused by Scedosporium spp. and Fusarium spp. Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant recipients	Adults and children aged 2 years and above
Posaconazole	Treatment of 1) invasive aspergillosis in patients with disease that is refractory or intolerant to amphotericin B or itraconazole 2) oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised Prophylaxis of invasive fungal infections 1) in patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes at risk of prolonged neutropenia and invasive fungal infections 2) in hematopoietic stem cell transplant recipients under high-dose immunosuppressive therapy for graft-versus-host disease, at high risk of invasive fungal infections	Safety and efficacy not established in children aged below 18 years
Amphotericin B–lipid formulation	1) Systemic mycotic infections due to susceptible organisms 2) Fever of unknown origin in neutropenic patients	Patients who are one month to 18 years old; dosage based on weight

lymphoma or multiple myeloma or malignant disease) affecting paediatric patients (neonates excluded), published up to August 31, 2020, using Pubmed to identify the PopPK studies of glycopeptides/vancomycin/teicoplanin, antifungals/voriconazole/posaconazole/amphotericinB, in children/paediatric patients with hemato-oncology malignancy/acute leukemia/lymphoma. We selected the studies on one of our five anti-infectives of interest and selected additional articles by reviewing the bibliography of the selected publications. Tables were built to summarize the PopPK studies, presenting the study drug, patients' characteristics (number, age, and weight), underlying disease and indication of treatment, number of samples, software, covariates analyzed, and retained in the PK model, PK/PD target used for simulations and dosage recommendations.

Results

Studies Selection

A total of 19 paediatric PopPK studies were identified and 14 included in this review: five for glycopeptides (vancomycin $n = 3$ and teicoplanin $n = 2$) and 9 for antifungals (voriconazole $n = 4$, posaconazole $n = 1$, amphotericin B $n = 4$) administered in children with malignancy.

Population Pharmacokinetics of Glycopeptides in Paediatric Onco-hematological Malignancies

The PopPK studies of glycopeptides in paediatric HM are presented in **Table 2**.

During our review process, two vancomycin PopPK studies in sick children were excluded as the underlying disease and indications of treatment were missing, or patients with various diseases were included (Lamarre et al., 2000; Hahn et al., 2015). We identified and analyzed three vancomycin PopPK studies (Zhao et al., 2014; Marsot et al., 2018; Guilhaumou et al., 2016) including two PopPK studies in paediatric HM and 1 being an external validation (Guilhaumou et al., 2016) of one of them (Marsot et al., 2018). Data are presented in **Table 2**. The number of patients included were 70 (Zhao et al., 2014) and 121 (Marsot et al., 2018), with a wide range of both ages and weights. Concentrations were obtained during therapeutic drug monitoring (TDM). Among all covariates tested, weight (with fixed or estimated allometric coefficients) was always significant, creatinine CL was significant only in the model by Zhao (Zhao et al., 2014), type of disease and coadministration of cyclosporin were significant only in the model by Guilhaumou (Guilhaumou et al., 2016). The primary PK/PD target used for simulations was AUC/MIC ≥400 h in one case and the steady-state concentration of 20–25 mg/L in the other one. After accounting for significant covariates, the mean value of the interindividual variability (IIV) in vancomycin CL was 34.8 and 31.1%, respectively, in the two studies. Both studies showed that higher doses are required in cancer paediatric patients. Dosage adaptation might use either a patient tailored dose or a proposed chart, taking into account the identified variables. In both cases, drug monitoring is still recommended.

We identified and analyzed two teicoplanin PopPK studies in children with cancer (Ramos-Martín et al., 2014; Zhao et al., 2015). Two additional studies population PK studies are available but in children without malignancy treated in intensive care or

TABLE 2 | Population pharmacokinetic studies of glycopeptides in paediatric onco-hematological malignancies.

	Vancomycin		Teicoplanin	
Author	Zhao 2014 Zhao et al. (2014)	Guilhaumou 2016 and Marsot 2018 Marsot et al. (2018), Guilhaumou et al. (2016)	Ramos 2014 Ramos-Martín et al. (2014)	Zhao 2015 Zhao et al. (2015)
Study location	France	France	United Kingdom	France
Underlying disease (number of patients)	HM including - ALL n=64 - AML N=48	Malignant diseases including - HM n=32 - SM n=30	Predominantly malignant diseases (not detailed)	HM including - ALL n=65 - AML n=27
Indication	Suspected or proven infection	Suspected infection (Febrile neutropenia)	At the discretion of the treating physician	Suspected infection
Number of patients	70	121	39	85
Age (years) mean ± SD	6.8 ± 4.8	HM: 9.1 ± 5.7 SM: 7.1 ± 5.4	4 ± 4.3	8.4 ± 4.6
Weight (kg) *mean ± SD*	25.7 ± 15.5	HM: 31.6 ± 18.6 SM: 25.0 ± 16.4	17.3 ± 13.3	32.3 ± 17.8
Intravenous drug dose	40–60 mg/kg/24 h in four divided doses (over 1 h)	10–15 mg/kg LD (over 1 h) followed by MD 30–40 mg/kg/24 h continuous infusion	10 mg/kg BID for 3 LD followed by MD 10 mg/kg/24 h ("current dosage")	10 mg/kg BID for 3 LD (over 3–5 min) followed by MD 10 mg/kg/24 h
PK sampling design	TDM sampling	TDM sampling	Specific PK study sampling	TDM and opportunistic sampling
Number of samples	98	301	298	143
Software	NONMEM	NONMEM	Pmetrics	NONMEM
Number of compartment(s)	1	1	2	2
Significant covariate on CL	WT (Alloestcoef function, MEDcentred), CrCL	WT (Allofixcoef function, 70 kg centred) Type of disease (HM or SM) Cyclosporin coadministration in case of HM	WT (linear function, noncentred)	WT (Allofixcoef function, MEDcentred), CrCL
Significant covariate on V	WT (Alloestcoef function, MEDcentred)	None	None	WT (Allofixcoef function, MEDcentred)
Covariates tested without significant effect on PK parameters	Age, serum creatinine, type of disease (leukaemia or lymphoma), and bone marrow transplantation	Age, gender, serum creatinine, and comedications (acyclovir, aminoglycoside, foscavir, and liposomal amphotericin b)	Height, age, serum creatinine, and comedications	Age, serum creatinine, and type of disease (leukaemia or lymphoma)
CL estimates	Typical value: 4.3 L/h for a patient weighing 20 kg Mean (range) individual values: 0.22 (0.04–0.73) L/h/kg	Typical value: 4.7 L/h standardised to a 70 kg individual with HM and without cylcosporin coadministration Mean individual value: 0.084 L/h/kg	Median individual value: 0.019 L/h/kg	Median individual values (L/h/kg): Infants: 0.028, Children: 0.019 Adolescents: 0.015
Validation	Internal and External (20 children, 25 samples)	Internal and External (77 children, 289 samples)	Internal	Internal and External (15 children, 15 samples)
PK/PD target used for dosing optimization (simulations)	1) $AUC_{0\text{-}24}$/MIC ≥400 h 2) C_{min} of 10–20 mg/L at SS	SS concentrations of 20–25 mg/L	C_{min} > 10 mg/L	1) $AUC_{0\text{-}24}$: 750 mg/h/l 2) C_{min} of 10–30 mg/L at SS
Dosage recommendation based on results of modelling and simulation	Patient tailored dose based on WT and CrCL	Chart based on WT and coadministration of cyclosporine (administration via continuous infusion after a LD of 15 mg/kg)	"Current dosage" based on WT is adequate but TDM is highly recommended	Patient tailored dose based on WT and CrCL

HM, hematological malignancy; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; SM, solid malignancy; LD, loading dose; MD, maintenance dose; PK, pharmacokinetic; TDM, therapeutic drug monitoring; CL, clearance; V, volume of distribution; WT, weight; Allofixcoef function, weight included as an allometric power function using fixed coefficients of 0.75 for CL and one for V; Alloestcoef function, weight included as an allometric power function using estimated coefficients for CL and V; MEDcentred, centred on the median weight of the population; 70kgcentred, normalized according to data for a 70kg individual; CrCL, creatinine clearance; Internal validation, diagnostic plots +/– visual predictive checks +/– bootstrap +/– NPDE +/– weighted-mean error and bias-adjusted weighted-mean-squared error; PD, pharmacodynamic; AUC area under the concentration-time curve; MIC, minimum inhibitory concentration; C_{min}, trough concentration; SS, steady-state.

with renal dysfunction (Lukas et al., 2004; Gao et al., 2020). Results of the analyzed PopPK studies showed that weight and renal function (quantified by creatinine CL) are covariates explaining part of the observed variability. PK/PD targets used for simulations were different between the two studies. A patient tailored dose based on weight and creatinine CL might reduce variability in teicoplanin AUC and trough concentration (Cmin) values compared with the $mgkg^{-1}$ basis dose (Zhao et al., 2015). Drug monitoring is still recommended.

Population Pharmacokinetics of Antifungals in Paediatric Onco-hematological Malignancies

The PopPK studies of antifungals in paediatric onco-hematological malignancies are presented in **Tables 3**, **4**.

TABLE 3 | Population pharmacokinetic studies of the antifungals Voriconazole and Posaconazole in paediatric onco-hematological malignancies.

	Voriconazole				Posaconazole
Author	Walsh 2004 Walsh et al. (2004)	Karlson 2009 Karlsson et al. (2009)	Muto 2015 Muto et al. (2015)	Gastine 2017 Gastine et al. (2017)	Boonsathorn Boonsathorn et al. (2019)
Study location	United Kingdom/United States/ Costa rica/Panama	Europe	Japan	Germany	United Kingdom
Underlying disease (number of patients)	Malignant diseases including - leukaemia n=7	Malignant diseases including - leukaemia n=56	Malignant diseases including - leukaemia n=21	Allogeneic HSCT	Predominantly bone marrow transplant n=86
Indication	Prophylaxis or treatment of systemic FI	Prophylaxis of systemic FI	Prophylaxis of systemic FI	Prophylaxis of systemic FI	Prophylaxis or treatment of systemic FI
Number of patients	35	82	21	23	117
Age (years) *mean or **median (range)	*6.2 (2–11)	(2–11)	**10 (3–14)	Age≤12: **8 (0.5–12) Age>12: **14 (13–21)	**5.7 (0.5–18.5)
Weight (kg) *mean or **median (range)	*23.4 (12–54)	*22.8 (10.8–54.9)	**31.5 (11.5–55.2)	Age≤12: **27 (7–44) Age>12: **56 (39–85)	**17.8 (6.05–74.8)
Drug dose (mg/kg)	Single IV doses: 3 to 4 Multiple IV doses: LD 6 BID followed by MD 3 to 4 BID	Single IV doses: 3 to 4 Multiple doses: LD 6 BID IV, followed by MD 3 to 8 BID IV, and then 4 to 6 BID PO (suspension)	Multiple doses: LD 6 to 9 BID IV, followed by MD 4 to 8 BID IV, and then 9 mg/kg or 200 mg BID PO (suspension)	Age≤12: 7 BID IV Age>12: LD 6 BID IV, followed by MD 4 BID IV, and then 200 mg BID PO (suspension)	Median 13.11 (range, 2.67–48.95) PO (tablets and suspension)
PK sampling design	Specific PK study sampling	Specific PK study sampling from 3 studies	Specific PK study sampling	Specific PK study sampling	TDM sampling
Number of samples	355	1274	276	187	338
Software	NONMEM	NONMEM	NONMEM	NONMEM	NONMEM
Number of compartment(s)	2 with linear elimination	2 with Michaelis-Menten elimination	2 with mixed linear and non-linear elimination (model previously developed by Friberg et al. (2012), Hong et al. (2006)	2 with Michaelis-Menten elimination	1
Significant covariate on CL	WT CYP2C19 genotype status ALT, ALKP	WT (linear function, noncentred) CYP2C19 genotype status ALT	WT (Allofixcoef function, 70 kg centred), CYP2C19 genotype status, and age	WT (Allofixcoef function, 70 kgcentred)	WT (Allofixcoef function, 70 kgcentred)
Significant covariate on V	WT	WT	WT (Allofixcoef function, 70 kg centred)	WT (Allofixcoef function, 70 kgcentred)	WT (Allofixcoef function, 70 kgcentred)
Significant covariate on suspension bioavailability		None	None	None	Diarrhoea, co-medication with PPI, dose
Covariates tested without significant effect on PK parameters	Age	Age, gender, height, ethnic origin, serum creatinine, ALKP, GGT, albumin, total bilirubin, and total protein levels Co-medications (CYP2C19 inh, CYP2C9 inh, CYP3A4 inh, CYP450 ind), underlying disease, and presence of mucositis	Gender, liver function parameters	Age, gender, body surface area, CRP, bilirubin, AST, ALT, GGT, ALKP, and serum creatinine	Age, treatment/prophylaxis, co-medications (other than PPI)
CL and/or Vmax estimates (typical values)	CL 0.40 L/h/kg	CL 0.582 L/h/kg in CYP2C19 homozygous extensive metabolizers and km 3.03 ng/ml	CL 2.35 L/h and Vmax at 1h 46.1 mg/h for a patient weighing 20 kg	Vmax 51.5 mg/h standardised to a 70 kg individual	Tablet apparent CL 15 L/h standardised to a 70 kg individual
Validation	NA	Internal	Internal	Internal	Internal
PK/PD target(s) used for dosing optimization (simulations)	AUC Cmean Objective: to achieve similar exposures to those observed in adults receiving MD 3 mg/kg BID	AUC: Objective: to achieve similar exposures to those observed in adults receiving approved dosing regimens	AUC: Objective: to achieve similar exposures to those observed in non-Japanese children receiving the same dosing regimen	1) Trough concentrations of 1–6 mg/L 2) AUC/ MIC >32.1	Steady-state trough concentrations of >0.7 mg/L for prophylaxis and >1 mg/L for treatment

(Continued on following page)

TABLE 3 | (*Continued*) Population pharmacokinetic studies of the antifungals Voriconazole and Posaconazole in paediatric onco-hematological malignancies.

	Voriconazole				Posaconazole
Dosage recommendation based on results of modelling and simulation	IV: MD 4 mg/kg BID PO: 200 mg BID (no LD)	IV: 7 mg/kg BID (no LD)	- Age [2–12 [or [12–15 [years and WT < 50 kg: LD 9 mg/kg BID IV for 1day, followed by MD 8 mg/kg BID IV for 6 days, and then MD 9 mg/kg BID PO for 7 days- Age [12–15 [years and WT ≥ 50 kg: LD 6 mg/kg BID IV for 1 day, followed by MD 4 mg/kg BID IV for 6 days, and then MD 200 mg BID PO for 7 days	Age 2–12 years: LD 9 mg/kg TID IV for 3 days, followed by MD 8 mg/kg BID IV	Initial treatment dose: age 6 months to 6 years: 200 mg suspension QID- age 7–12 years and cannot take tablets: 300 mg suspension QID- age 7–12 years and can take tablets: 200 mg suspension TID- age 7–12 years and cannot take tablets: 300 mg suspension TID- age 7–12 years and can take tablets: 200 mg tablets TID

HSCT, hematopoietic stem cell transplantation; FI, fungal infection; IV, intravenous; LD, loading dose; MD, maintenance dose; PO, per os; BID, twice a day; TID, three times a day; QID, four times a day; PK, pharmacokinetic; TDM, therapeutic drug monitoring; CL, clearance; V, volume of distribution; Km, Michaelis Menten constant; Vmax, maximum elimination rate; WT, weight; Allofixcoef function, weight included as an allometric power function using fixed coefficients of 0.75 for CL and 1 for V; 70kgcentred, normalized according to data for a 70kg individual; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GGT, gamma glutamyl transferase; PPI, proton pump inhibitors; CYP, cytochrome; inh, inhibitor; ind, inducer; CRP, C reactive protein; Internal validation: diagnostic plots +/− visual predictive checks +/− bootstrap; NA, not available; PD, pharmacodynamic; AUC area under the concentration-time curve; Cmean, geometric mean concentrations in plasma; MIC, minimum inhibitory concentration.

In children, voriconazole PK studies demonstrated high IIV with no apparent relationship to dose in immunocompromised children (Walsh et al., 2010; Pieper et al., 2012). Bioavailability is substantially lower in children than in adults with HM (20 and 59.4%, respectively) (Karlsson et al., 2009).

Four PopPK studies in children were analyzed and summarized in **Table 3** (Karlsson et al., 2009; Walsh et al., 2004; Muto et al., 2015; Gastine et al., 2017), the larger one being by Karlsson (Karlsson et al., 2009). An additional one was excluded because of missing information (Carlesse et al., 2019). Data were obtained from rich sampling in patients receiving voriconazole in experimental settings in all four cases. Voriconazole was modeled either with linear or non-linear or mixed of both linear and non-linear elimination. The following covariates were significant in 1–4 of the analyzed models: weight, CYP2C19 genotype status, alanine aminotransferase (ALT), alkaline phosphatase (ALKP) and population age groups (adolescent or child). CYP2C19 deficient genotypes and increased levels of ALT were the most important determinants of voriconazole CL, associated with lower CL values. The additional importance of age was evidenced in the recent study by Yan, showing that, in the paediatric population, the patients younger than 3years, might need higher doses to reach the same trough concentrations and exposure than patients over 3years (Yan et al., 2018). Simulations conducted in the four analyzed studies led to the conclusion that the dose required in children was higher than in adults. However, recommended dosages differed from one study to one other for the same age group (Muto et al., 2015; Gastine et al., 2017). Only one Posaconazole PopPK study was conducted in children (Boonsathorn et al., 2019): weight, formulation (suspension or tablet), dose, diarrhea and coadministration of proton pump inhibitors had a significant impact on PK parameters. The estimated values of CL/F and V/F related to the delayed-release tablet formulation and standardized to a 70 kg individual were comparable to those reported in adults. These children showed a higher IIV on CL/F compared to adults (63.0 vs. 24.2 or 37.9%) (van Iersel et al., 2018; Petitcollin et al., 2017) suggesting a potential age-associated maturation of hepatic UGT1A4. Suspension had poor and saturable bioavailability, which decreased with increasing dose. Diarrhea and proton pump inhibitors were also associated with reduced bioavailability of the suspension. Based on the probability of target attainment (PTA) of trough concentration >1mg/L in fungal infection treatment, the authors issued dosage recommendations in children up to 6 years and between 7 and 12 years with an initial dose of 200 and 300 mg suspension four times daily, respectively. When tablets can be used in patients aged seven or over, 200 mg tablets three times daily are required. Dosage have then to be adapted to TDM after the initial phase of treatment.

For amphotericin B, the first PopPK study in children by Nath (Nath et al., 2001) compared D and L-Amb, and then analyzed the two formulations separately (**Table 4**). This study was conducted with significant number of patients and samples, in a wide range of ages, and showed that weight and formulation (D or L-AmB) had a significant impact on PK parameters. Only one of the four PopPK

TABLE 4 | Population pharmacokinetic studies of dextrose and lipid Amphotericin B (D and L-AmB) in paediatric onco-hematological malignancies.

	D- and L-AmB	L-AmB	L-AmB	L-AmB
Author	Nath 2001 Ayestarán et al. (1996)	(Hong et al. 2006) (87)	Ohata 2015 Ohata et al. (2015)	Lestner 2016 Lestner et al. (2016)
Study location	Australia	Australia	Japan	United Kingdom/United States
Underlying disease (number of patients)	Malignant diseases including - ALL n=22 - AML n=19	Malignant diseases (not detailed)	Malignant diseases including - ALL n=71 - AML n=5	Malignant diseases including - HM n=52
Indication	Suspected or proven FI (Fever/ neutropenia)	Suspected or proven FI (Febrile neutropenia)	Suspected or proven FI (e.g., febrile neutropenia	Suspected or proven FI
Number of patients	57	39	39	35
Age (*months or **years) mean ± SD	74.5 (9–190.5)*	7.1 ± 5.1**	8.4 ± 4.5**	8.7 ± 4.6**
Weight (kg) mean ± SD	21.6 ± 10.2	28.8 ± 19.8	27.1 ± 14.1	26.9 ± 14.0
Intravenous drug dose mg/kg/24h	1 (over 2 h)	0.8 to 5.9 (over 1 h)	1 to 5 (over 1–2 h)	2.5 to 10 (over 1 h)
PK sampling design	Specific PK study sampling	Specific PK study sampling	Specific PK study sampling	Specific PK study sampling
Number of samples	581	637	159	NA (7–12 per patient within each sampling period)
Software	PPharm	NONMEM	NONMEM	PMetrics
Number of compartments	2	2	2	2
Significant covariate on CL	WT (Allofixcoef function, noncentred) Method of AmB administration (D- or L-AmB)	WT (exponential function, MEDcentred)	WT (linear function, MEDcentred)	WT (Allofixcoef function, 70 kg centred)
Significant covariate on V	WT (Allofixcoef model, noncentred)	WT (exponential function, MEDcentred)	WT (linear function, MEDcentred)	None
Covariates tested without significant effect on PK parameters	Age, height, gender, diagnosis, history of prior bone marrow transplant, coadministration of total parenteral nutrition, co-medications: acyclovir, cyclosporin, ondansetron, morphine, diuretics, and promethazine	Age, height, and gender	Serum creatinine, BUN, AST ALT, K, Mg, co-medications	Liver function, serum albumin, white blood cell count, total protein concentrations, use of parenteral nutrition, and concomitant steroids
CL estimates **mean ± SD individual values or **typical value*	D-Amb: *0.038 ± 0.015 L/h/kg L-Amb: *0.052 ± 0.021 L/h/kg	**0.44 L/h for a patient weighing 21 kg	**0.25 L/h for a patient weighing 23 kg	**0.67 L/h standardised to a 70 kg individual
Validation	External (26 patients/83 samples)	Internal	Internal	Internal
PK/PD target used for dosing optimization (simulations)	NA	Suggested target: Cmax,ss/MIC (no threshold available)	NA	NA
Dosage recommendation based on results of modelling and simulation	NA	NA	NA	NA

D-AmB, dextrose amphotericin B; L- AmB, lipid amphotericin B; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HM, hematological malignancy; FI, fungal infection; PK, Pharmacokinetic; NA, not available; CL, clearance; V, volume of distribution; WT, weight; Allofixcoef function, weight included as an allometric power function using fixed coefficients of 0.75 for CL and 1 for V; MEDcentred, centred on the median weight of the population; 70kgcentred, normalized according to data for a 70kg individual; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; K, blood potassium; Mg, blood magnesium; Internal validation: diagnostic plots and bootstrap; PD, pharmacodynamic; Cmax,ss/MIC, peak concentration at steady state over the minimum inhibitory concentration.

studies identified resulted in dosage recommendation. Using their previously developed model (Nath et al., 2001), Nath et al. proposed weight-based dosage recommendation for D-AmB (i.e., 1.25–1.5, 1, and 0.75 mg/kg/day for children weighing 10–25, 25–45, and 45–55 kg, respectively) targeting the 0.76–1.05 mg/L range of through level at steady-state (Nath et al., 2007). Lestner and co-authors showed the absence of correlation between absolute dose and exposure (maximum concentration–Cmax, minimum concentration–Cmin, or AUC_{0-24}) but a significant correlation between steady-state exposure (AUC_{0-24}) and change in serum creatinine. In Japanese paediatric patients (Ohata et al., 2015), the predicted parameters Cmax/dose and AUC_{0-24}/dose were similar to those in the non-Japanese paediatric patients (Kohno et al., 2013) and Japanese adult patients at 1.0, 2.5, and 5.0 mg/kg/day given as 1 h infusion.

DISCUSSION

In this review, we analyzed the population pharmacokinetics of five anti-infectives in paediatric patients with onco-hematological

diseases. The studies, based on a nonlinear mixed effects modeling approach, aimed to estimate the typical population PK parameters, their variability between patients, and the variability between occasions and within patients, and to identify the covariates with significant impact on variability in PK.

Most PK studies conducted in children focus on age and organ maturation/function to explain variability in drug disposition. In addition to these key covariates, studies focusing on the potential impact of the disease underlying infection on anti-infective PK are sparse in the paediatric field. Data are missing in many paediatric subpopulations presenting with specific diseases. In paediatric malignancies, most paediatric chemotherapy regimens are intensive with high risk of infection complicating profound neutropenia and requiring anti-infectives at effective and non-toxic doses. We focused our research on the frequently administered glycopeptides (vancomycin and teicoplanin) and antifungals (posaconazole, voriconazole and amphotericin B). Our review shows that data on anti-infectives are limited in children with cancer and that their optimal dosing regimen remains controversial or undefined.

PK and PopPK determine the relation dose/concentration and participate to identify and quantify the impact of covariates on drug disposition. Exposure to anticancer drugs, most of them having a narrow therapeutic range, is central to optimize cure rate of paediatric patients with malignant diseases. However, during treatment, induced immunosuppression is at high risk of infection and anti-infective dosage, if inadequate, may result in infection-related morbidity and increased mortality, making optimization of dosing regimen essential. According to regulatory guidelines, antimicrobial agents are good examples of drugs for which modelling and simulation techniques can be used to develop dosage recommendations in children. PK/PD surrogate markers of efficacy that are used for this purpose include 1) a PK parameter (AUC, Cmax, Time) (Kearns et al., 2003), 2) a PD parameter (MIC) which is function of the germ responsible for the infection, and based either on identification of the germ or more frequently on local germ epidemiology if infection is only suspected.

PK and PopPK of glycopeptides in children with HM diseases are sparse.

IIV in vancomycin disposition in children (neonates excluded) was reported to be primarily linked to patient's age, type of disease and clinical condition (e.g., renal function, proven infection) (Chang, 1995; Krivoy et al., 1998; Wrishko et al., 2000; Marsot et al., 2012; Hadi et al., 2016; Tkachuk et al., 2018). The impact of malignancy on vancomycin disposition was initially reported by Chang, who showed that vancomycin CL in 33 paediatric patients with malignancy was significantly larger than in 31 patients without cancer while the volumes of distribution were similar (Chang, 1995). The impact of febrile neutropenia was tested in only one study including 109 children with hematological and solid malignancies (Keita et al., 2016), using the model previously developed in adults by Yasuhara (Yasuhara et al., 1998). Multilinear regression analysis of individual patient CL identified age and estimated glomerular filtration rate (eGFR) as covariates affecting drug disposition. Febrile neutropenia did not show any significant impact on CL. Accordingly, in children with malignancy, higher doses than the currently used dosage regimen of 30–40 mg/kg/24 h, are needed to increase the percentage of patients reaching the PK/PD vancomycin AUC/MIC breakpoint of at least 400 h (value determined in adults with *Staphylococcus aureus* pneumonia (Moise-Broder et al., 2004)) or the steady-state target concentration of 20–25 mg/L, while limiting the risk of emergence of vancomycin-resistant microorganisms (Seixas et al., 2016). Optimal doses have to be adapted to weight, creatinine CL, type of disease and co-administration of cyclosporin if any, but remain to be validated prospectively, both in terms of safety and efficacy.

In the teicoplanin PK studies in paediatric malignancy, children had more variability in drug exposures than the adults. The two PopPK studies on paediatric malignancies confirmed that teicoplanin CL was higher in paediatric cancer patients than in children without cancer, with weight and creatinine CL being significant covariates (Ramos-Martín et al., 2014; Zhao et al., 2015). This is most probably related to high glomerular filtration secondary to hyperhydration which is included in HM protocols. In addition, the complex composition of generic teicoplanin products may have a potential impact on both biological analysis and PD. Additional data showed that current weight-based dosage was associated with a low proportion of patients attaining minimum recommended serum drug concentrations at steady state (Cmin value of 10 mg/L) (Dufort et al., 1996; Sánchez et al., 1999; Strenger et al., 2013). According to these data, teicoplanin individualized dosing regimen needs to be recommended for different renal function groups and TDM remains recommended in HM patients.

For antifungals, data are even more limited.

For voriconazole, high paediatric variability is partially explained by body weight, cytochrome P450 2C19 genotype, liver function, and concomitant medications. However, although the genotyping status helps to explain the variability in voriconazole exposure, the CYP2C19 genotyping status alone does not warrant dose adjustment as the voriconazole exposures varied widely within each genotype and overlap considerably across CYP2C19 genotypes. Voriconazole monitoring remains recommended. Therefore, experts advise TDM, in particular in younger children (Chen et al., 2012).

For posaconazole, and according to data obtained in children with malignancy, weight and formulation (suspension or tablet) have an important impact on bioavailability. However, data are extremely limited, did not explore additional covariates already identified in adults such as pharmacogenetic biomarkers and additional studies are particularly needed to validate posaconazole use in paediatric malignancies. Although used in children, this drug is prescribed off-label, as the marketing authorization stated that "safety and efficacy are not established in children aged below 18years" (**Table 1**).

Amphotericin B is formulated as amphotericin B-deoxycholate (D-AmB) and lipid emulsions (L-AmB). In children, a classical dose escalation study including 40 immunocompromised paediatric patients (2.5, 5.0, 7.5 or 10 mg

per kg L-AMB) concluded that L-AMB could be administered to paediatric patients at dosages similar to those of adults but azotemia may develop, especially in those receiving ≥5.0 mg/kg/day (Seibel et al., 2017). In children, Lestner and co-authors (Lestner et al., 2016) showed the absence of correlation between absolute dose and exposure (Cmax, Cmin, or AUC_{0-24}) but a significant correlation between steady-state exposure (AUC_{0-24}) and change in serum creatinine. Weigt-based dosage recommendation to reach the target through level at steady-state were issued for D-AmB but not for L-AmB (Nath et al., 2001; Nath et al., 2007). When immunocompromised children experience fever that persists in spite of broad-spectrum antibiotic therapy, they receive D-AmB by the standard dose of 1 mg/kg/day that may be insufficient to prevent fungal surinfection or to control clinically detected or undetected fungal infection. Here again, additional PK and efficacy studies are required for a safer use in cancer children.

As illustrated by the present review, PopPK studies on antibiotics and antifungals including in paediatric malignancy are limited for well-known reasons, ethical and technical. The major barriers to paediatric PK studies are the relatively large volumes of blood loss during the study period, difficulty in timing of PK samples due to the critical clinical condition and a relatively low rate of informed parental consent (Baker et al., 2018). For this reason, many drugs are used off-label and enter the paediatric care protocols because clinicians perceive them to have a more useful spectrum of activity and/or better profile of tolerance than the currently used anti-infectives.

Population PK allows to determine PK parameters with a formal PK design with planned (pre-selected) sampling times, with opportunistic samples or a combination of planned and opportunistic samples (Leroux et al., 2015). In our review, it should be noted that, in most PopPK studies, sometimes retrospective and based on TDM, the number of patients was limited (lower than 100), and age range and malignant underlying disease were variable. Only a few studies performed a meta-analysis of data from different studies, as previously done in neonates (Jacqz-Aigrain et al., 2019) allowing to combine sufficient data to reach a larger number of patients, increase study power and identify covariates.

Most studies used a nonlinear mixed effects mathematical method, estimating PopPK parameters (CL and V) and their variability, based on the significant impact of covariates. Covariates in the context of paediatric malignancy include age, weight, organ maturation and function, but also other determinants such as underlying disease groups, comedications, and pharmacogenetics. Allometric scaling is an empirical examination of the relationships between the PK parameters and size (body weight). Allometric power parameters are often fixed at values of 0.75 for CL and 1 for distribution volume on the basis of physiologic consideration of size impact on metabolic processes (Anderson et al., 1997; Anderson and Holford, 2011). As shown here, the allometric coefficients need to be estimated in a limited number of cases (Johnson, 2008). The covariates renal function (reflected by creatinine or creatinine CL), hepatic function (reflected by ALT and ALKP) and pharmacogenetics were frequently tested. In the case of voriconazole, CYP2C19 genetic polymorphism, identified in adults affecting voriconazole disposition was not identified as a significant contributor to variability in children. As illustrated with this example, the role of pharmacogenetic biomarkers in variability may not be significant when the number of patients of deficient metabolizer genotypes is low, when PK overlap exists between the different genotypes and/or when genotype expression did not reach maturation (Lestner et al., 2016).

Once the PK model is developed, internal validation (using the same dataset) and external validation (requiring additional independent patients) are required. In most paediatric studies, validation was internal, predominantly based on goodness of fit plots and bootstrapping. In the studies that we analyzed, external validation was the exception, although it is more stringent.

Simulations of dosing regimens based on the validated model aim to inform optimal dosing in children that achieves target exposure comparable to that of adults. Of note, the adult PK/PD target thresholds do not take into account developmental aspects of immunocompetence; indeed, the immune system gradually changes during infancy to mature and expand during growth and to respond efficiently to acute infections (Anderson and Holford, 2011; Friberg et al., 2012). In addition to reduced immunocompetence due to incomplete immune maturation, the role of therapeutic immunosuppression would require to be explored. As illustrated in this review, different PK/PD targets may be used for dosing optimization of the same drug, with a lack of consensus regarding which target is optimal for this purpose. Efforts should be made to further explore this issue.

Before implementation of the new dosing regimen into the clinics, validation of exposure, safety, and tolerability in a carefully designed clinical trial will be needed. However, for most if not all studies, the clinical validation is not available, although response to anti-infectives is known to depend not only on drug exposure but also on age, associated therapies and type of disease.

CONCLUSION

In conclusion, many antibiotic and antifungal compounds are not approved for children or their optimal dosage is unknown, although differences in drug disposition may be anticipated in children compared to adults. We showed that PopPK data of the frequently prescribed glycopeptides and antifungals are very limited in children, although they are prescribed in most patients with hematologic malignancy. A few inform variability in disposition, identify significant impact of weight and additional covariates (organ function, disease subgroups) and led to dosage recommendations taking into account the identified variables. This review highlighted the lack of consensus regarding PK/PD targets used for dosing optimization, and regarding dosage recommendations when available. Additional PopPK and PK/PD studies are needed in this specific population of patients. In addition, clinical studies should be performed to prospectively validate the dosing regimens adapted to infection in paediatric patients with malignancy.

AUTHOR CONTRIBUTIONS

EJ-A initiated the review and identified the PopPK studies of interest, SL and EJ-A analysed the different PopPK studies and wrote the first version of the review, FM-H provided her expertise in treatment of paediatric malignancies, all three authors finalized the manuscript and agreed on the submitted version.

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Modeling Approach to Optimizing Dose Regimen of Vancomycin for Chinese Pediatric Patients with Gram-Positive Bacterial Infections

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The aim of this study was to establish the population pharmacokinetics (PK) model of Vancomycin for Chinese pediatric patients which can extrapolate to whole age periods by bridging the published adult population PK model and the established pediatric population PK model. The final consolidated population PK model was used to explore the correlation of pharmacokinetics/pharmacodynamics (PK/PD) indices and efficacy of vancomycin and to provide evidence for the optimized regimen of vancomycin in Chinese pediatric patients with Gram-positive bacterial infection. 108 pediatric patients with Gram-positive infections from 2 pediatric hospitals in China in the first period of the prospective multi-center vancomycin clinical observational study were enrolled to establish the population PK model. A one-compartment population PK model was established and validated. The correlation between vancomycin PK/PD indices [trough concentration (C_{min}), peak concentration (C_{max}), 0–24 h area under the curve (AUC_{0-24}) and the area under the curve to minimum inhibitory concentration ratio (AUC_{0-24}/MIC)] and the overall clinical outcomes (clinical efficacy and microbiological efficacy) in Chinese pediatric patients were evaluated. There is no significant correlation between PK/PD indices and clinical efficacy or microbiological efficacy. Considering the high clinical effective rate (>90%) and median AUC_{0-24}/MIC values of 200–300, Chinese pediatric patients with Gram-positive bacterial infection may be suitable for lower AUC_{0-24}/MIC target value compared to the target value of 400–600 recommended by IDSA guideline. Different optimal dose regimen of vancomycin for Chinese pediatric patients should be considered. Further evaluation in more prospective studies will be needed.

Keywords: vancomycin, pediatric, pharmacokinetics/pharmacodynamics, population pharmacokinetics, external validation

INTRODUCTION

Since the 1980s, vancomycin has been the first-line treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. However, vancomycin has the characteristics of narrow therapeutic window, high inter-individual pharmacokinetic (PK) variability, and potential nephrotoxicity and ototoxicity. Therapeutic drug monitoring (TDM) has been routinely used in clinical practice to optimize efficacy and safety of vancomycin. In March 2020, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious Diseases Pharmacists (SIDP) published the revised consensus guideline for therapeutic monitoring of vancomycin for MRSA infection (Rybak et al., 2020). In this consensus guideline, predictive target value of the area under the curve to minimum inhibitory concentration ratio (AUC_{0-24}/MIC) based on population pharmacokinetic analysis combined with Bayesian approaches was recommended for therapeutic drug monitoring, and trough concentration monitoring alone is no longer recommended. The target value of AUC_{0-24}/MIC recommended by the consensus guideline is 400–600, for both adults and pediatric patients.

However, the recommended target value of AUC_{0-24}/MIC and trough concentration has always been controversial due to insufficient evidence for efficacy and safety (Lodise et al., 2009; Rybak et al., 2009; Kullar et al., 2012; Gawronski et al., 2013; Holmes et at., 2013). The investigations of vancomycin pharmacokinetics/pharmacodynamics (PK/PD) in Chinese patients are mostly based on retrospective observational clinical studies, which provided limited clinical efficacy and safety evidence. There are even fewer vancomycin PK/PD studies conducted in Chinese pediatric patients. Most of these studies only established population PK model in newborn patients and did not evaluate PK/PD combined with clinical outcome or microbial efficacy. There is an urgent need to conduct a prospective large sample size clinical research to provide evidence for optimizing dose regimen of vancomycin for adults and pediatric patients in China.

Our research is to establish population PK model utilizing the clinical data of pediatric patients from a prospective, pathogen diagnosis–based, multicenter, observational study (Liang et al., 2018; Shen et al., 2018), assess the clinical and microbiological efficacy of vancomycin, and recommend optimized dose regimen of vancomycin in Chinese pediatric patients.

METHOD

Study Design

The research data were from a prospective, multicenter, randomized, open label clinical observational study (Period I) of vancomycin for the treatment of patients with Gram-positive bacterial infection. All the patients had clinical and microbiological evidence (clinical symptoms, signs, laboratory tests, and microbiology culture) for the diagnosis. Patients from 13 hospitals in China including 2 pediatric hospitals with Gram-positive infections who received vancomycin therapy ≥5 days and who were under therapeutic drug monitoring (TDM) were enrolled in this study. Patients received any other agents that are effective against Gram-positive bacterial infection for ≥24 h within 72 h of receiving vancomycin therapy and patients who were considered to have Gram-positive bacteria colonization were excluded.

The study was approved by the medical ethics committee of each study center and was performed in accordance with the ethical standard established by the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all enrolled patients or their legally authorized representatives. The study was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn, number ChiCTR-OPC-16007920).

Laboratory Test

The TDM concentration data of therapeutic drugs in adults and pediatric patients with Gram-positive bacterial infection were collected. Serum samples were collected within 0.5 h before the fifth dose of vancomycin, and at any point from 0.5–1 h after the fifth dosing of vancomycin. The bioanalysis method for vancomycin TDM was a fluorescence polarization immunoassay (FPIA) or a chemiluminescence immunoassay (CMIA) with a calibration range of 3.00~100 mg/L. The minimum inhibitory concentrations (MIC) of vancomycin was verified by the agar dilution method in a CHINET microbiology laboratory. Clinical Laboratory Standards Institute (CLSI) protocols M07-A9 and M100-S24 were performed as MIC testing standards. MIC_{50} and MIC_{90} values were defined as the lowest concentration of vancomycin at which 50 and 90% of the isolates were inhibited, respectively.

Clinical Outcomes Evaluation

Both clinical efficacy (improvement of symptoms and signs of infection) and microbiological response (bacteria eradication) were evaluated in all the eligible patients. The clinical efficacy was evaluated centrally by the investigator with double check. The eradication of bacteria was defined as the inability to culture the original pathogen at the primary infection site and the absence of the need for anti-gram-positive bacterial antibiotic within 7 days after the end of the vancomycin treatment.

Population PK Modeling and Simulation

The population PK model of vancomycin for adults and pediatric patients were established respectively to investigate the difference of covariates using NONMEM 7.3.0 (ICON Development Solutions, Ellicott City, MD). The population pharmacokinetics model was composed of a structural model and random effect models using the first-order conditional estimation method (FOCE) with interaction. Demographic variables (e.g., gender, age, weight, height, body mass index [BMI]), renal function descriptors (serum creatinine, eGFR, creatinine clearance rate [CLCr], and albumin, etc.), and disease conditions (e.g., surgery or injury, chronic kidney disease, diabetes, cancer) were tested as potential covariates. Covariates were evaluated using the stepwise forward-selection

TABLE 1 | Demographic and baseline characteristics of the pediatric patients included in the population PK analysis (n = 108).

Variables	Mean ± SD	Median (range)
Age (years)	1.47 ± 2.63	0.456 (0.0164–13.0)
Body weight (kg)	8.47 ± 9.22	5.40 (0.900–55.0)
Height (m)	0.688 ± 0.278	0.600 (0.300–1.70)
BMI (kg/m^2)	14.1 ± 4.66	14.7 (3.60–34.3)
BSA (kgm^2)	0.388 ± 0.287	0.289 (0.132–1.65)
S_{CR}(umol/L)	25.6 ± 14.3	20.0 (9.00–83.0)
TBIL (umol/L)	29.8 ± 43.4	9.05 (2.00–218)
ALT (U/L)	21.9 ± 23.9	13.0 (1.00–129)
AST (U/L)	34.1 ± 43.3	24.0 (7.00–418)
ALB (g/L)	35.1 ± 6.19	36.0 (2.90–47.0)
WBC (e^9/L)	6.56 ± 2.93	6.00 (2.41–11.4)
ENC (%)	47.8 ± 14.3	48.3 (1.20–93.3)

BMI: body mass index; BSA: body surface area; S_{CR}: serum creatinine; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; WBC: white blood cell; ENC: eosinophils cell.

method and backward elimination. The population PK model for adults and pediatric patients were evaluated respectively and the model parameters were compared. In order to unify the population PK model for adults and pediatric patients, the datasets were merged and the covariates were consolidated and reevaluated. By introducing body weight as scaling factor, an unified final population PK model for the pooled data of adults and pediatric patients was established and validated. External validation was performed using part of the data from Period II of the vancomycin observational study. The established population PK model was used to simulate individual PK parameters (C_{min}, C_{max}, AUC_{0-24}) by Bayesian feedback method for the further PK/PD evaluation.

Utilizing Monte Carlo simulation, the PK/PD index of AUC_{0-24}/MIC of vancomycin for Chinese pediatric patients at different ages under different administration scheme were simulated. The optimal dose regimens were recommended for the treatment of Gram-positive bacterial infection in Chinese pediatric patients at different ages.

Statistical Analysis

Multivariate logistic regression analysis was carried out with SAS 9.4 (SAS Institute, Inc: Cary, NC) to evaluate the correlation between the PK/PD indices (C_{min}, C_{max}, AUC_{0-24} and AUC_{0-24}/MIC) of vancomycin and the overall efficacy (clinical efficacy and microbial efficacy). The $\chi 2$ test was used to compare categorical variables. $p < 0.05$ was considered significant.

RESULTS

In total, 108 pediatric patients with Gram-positive infections from 2 pediatric hospitals in China from the prospective multi-center vancomycin clinical observational study were enrolled to establish the population PK model, and the dataset for model development used 251 observations, including trough and peak concentrations at steady state. The demographics and baseline clinical characteristics of patients were shown in **Table 1**. In our study, most of the pediatric patients were neonates and infants (<3 years old, n = 90). There were 16 patients from 3 years old to 12 years old, and only 2 cases were older than 12 years old.

To minimize the distribution bias of different age period, extrapolation from adult population PK model to pediatric population PK model was investigated. In our previous research, a population pharmacokinetic model of vancomycin in Chinese adult patients was established using 380 adult patients from the prospective multi-center vancomycin clinical observational study (Shen et al., 2018). The population PK datasets of adults and pediatric patients were combined and evaluated the covariates related to age and physiology (such as CLCr, weight, body surface area, etc.) and finally established a unified population PK model for adults and pediatric patients. By comparing the unified population PK models and original model, the weight was introduced as the covariate on the basis of the population PK model of adults. The final population model and typical pharmacokinetic parameters are as follows:

$$\mathrm{CL}\,(L/h) = 3.83 \times \left(\frac{\mathrm{CLCr}}{90.28}\right)^{0.516} \times \left(\frac{\mathrm{WT}}{58.25}\right)^{0.646} \times e^{\eta_{CL}} \quad (1)$$

$$V\,(L) = 44.7 \times \left(\frac{\mathrm{AGE}}{55}\right)^{0.33} \times \left(\frac{\mathrm{WT}}{58.25}\right)^{0.349} \times e^{\eta_{V}} \quad (2)$$

The parameter estimates of the final model and bootstrap confidence intervals were shown in **Table 2**. The results showed that the estimated values of the final model parameters and the 95% confidence interval are very similar to the bootstrap results of 1,000 times of simulation, indicating that the performance of the model is very stable. External validation was also performed using the extra 23 pediatric patients from the 2nd period of the observational study and showed good consistency between the predicted individual concentration and the observed concentration.

The goodness-of-fit plots for final population PK model were shown in **Figure 1**. A good agreement between the predicted concentrations and the observed concentrations was observed. The visual predictive check (VPC) for the final population PK model (**Figure 2**), showed that the model can predict the central tendency of the observed PK concentrations well. In general, the final population PK model has good prediction performance and can be used for further PK/PD evaluation.

Among the enrolled pediatric patients, the total cases with evaluable clinical efficacy was 108, and the number of cases with evaluable microbiological efficacy was 102. MRSA isolates from the pediatric patients had a vancomycin MIC_{50} = 1 mg/L and MIC_{90} = 1 mg/L. Both methicillin resistant coagulase-negative staphylococci (MRCNS) and *Enterococcus* species had vancomycin MIC_{50} = 1 mg/L and MIC_{90} = 2 mg/L.

The correlation between the PK/PD index of vancomycin (C_{min}, C_{max}, AUC_{0-24} and AUC_{0-24}/MIC) and the overall clinical outcomes (clinical efficacy and microbial efficacy) were analyzed by multivariable logistic regression analysis (**Tables 3** and **4**). There were no significant correlation between the PK/PD indices of vancomycin and clinical/microbiological efficacy ($P > 0.05$).

TABLE 2 | Parameter estimates and bootstrap of the final population PK model of vancomycin for adults and pediatric patients.

Parameters		Final model				Bootstrap	
		Estimate	RSE (%)	95% CI	Shrinkage (%)	Median	95% CI
$\theta 1$	CL (L/h)	3.83	2.3	3.655–4.005	–	3.82	3.64–4.00
$\theta 2$	V (L)	44.7	3	42.093–47.307	–	44.8	42.2–47.5
$\theta 3$	CLCr effect on CL	0.516	7.1	0.444–0.588	–	0.519	0.450–0.593
$\theta 4$	Body weight effect on CL	0.646	4.1	0.594–0.698	–	0.644	0.590–0.696
$\theta 5$	Age effect on V	0.33	15.7	0.229–0.431	–	0.331	0.223–0.435
$\theta 6$	Body weight effect on V	0.349	30.4	0.141–0.557	–	0.347	0.129–0.567
$\omega 1$	CL IIV	0.204	9.8	–	9.6	0.201	0.164–0.242
$\omega 2$	V IIV	0.0427	41	–	56.2	0.0416	0.00598–0.0914
$\sigma 1$	Residual error	0.0749	99.7	–	19.9	0.0746	0.0586–0.0893

RSE: relative standard error; CL: clearance; V: volume of distribution; BSA: body surface area; eGFR: estimated glomerular filtration rate; ALB: albumin; IIV: inter-individual variability.

Table 5 summarized bacterial response of vancomycin and AUC_{0-24}/MIC by the most common infection sites and bacteria, which compared the difference (*P* value shows the statistical significance level) between the bacterial classifications. Although the results in **Table 5** showed that the AUC_{0-24}/MIC of different bacterial classification are statistically different ($p < 0.05$) in bloodstream, lung and urinary tract infections, there is no statistically significant difference in bacterial response between the different bacterial classifications. Therefore, the difference of AUC_{0-24}/MIC between different bacterial classifications has no clinical significance.

The median value of AUC_{0-24}/MIC was between 200 and 300, which did not reach the target value of 400, but the overall clinical effective rate was 92.6%. It suggested that the AUC_{0-24}/MIC value of Chinese pediatric patients may not need to reach the target level (above 400) required by the guidelines. This observation is similar as the results of our previous research in adult patients (Shen et al., 2018).

Table 6 listed the results of the population PK model predicted probability of target attainment (PTA) of vancomycin in pediatric patients at different ages under different dosing regimens and different target values. It can be seen that lower daily dose in the

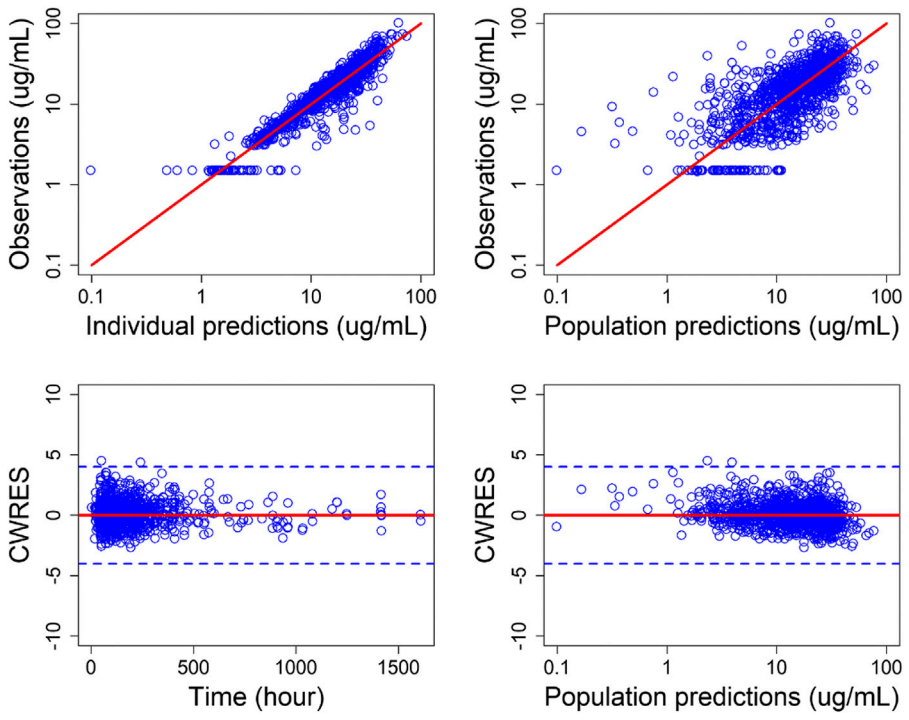

FIGURE 1 | Goodness-of-fit plots for final population PK model. Top: Individual predicted (IPRED) serum concentrations vs. observed concentrations **(left)** and population predicted (PRED) serum concentrations vs. observed serum concentrations **(right)**. Bottom: conditional weighted residuals (CWRES) vs. time **(left)** and PRED **(right)**. Points are individual data. Red solid lines represent the unit diagonal **(top)** or line at zero **(bottom)**. Blue dashed lines represent |CWRES| of 4.

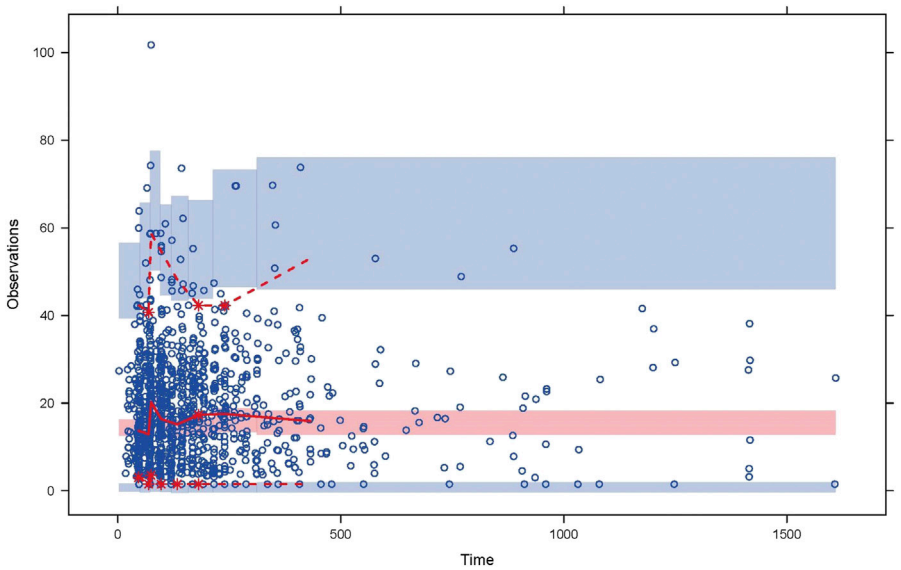

FIGURE 2 | Visual predictive check for the final population pharmacokinetic model. The circles are the observations. The solid and dashed lines represent the median, 2.5th, and 97.5th percentiles of the observations; the shaded pink and blue areas represent the 95% confidence interval of the median, 2.5th, and 97.5th percentiles predicted by the model.

>12-year-old age group can achieve the same target value compared with the <12-year-old age group.

Combined with the actual clinical efficiency, the optimal dose regimen for the treatment of in Chinese pediatric patients with Gram-positive infections is recommended to be 60–80 mg/kg/day every 6 or 8 h for <12-year-old and 50–60 mg/kg/day every 6 or 8 h for >12-year-old pediatric patients.

DISCUSSION

Vancomycin is mainly excreted through the kidneys. In the previous adult population PK model (Zhou et al., 2016; Shen et al., 2018), creatinine clearance (CLCr) was identified as a major covariate affecting the clearance (CL) of vancomycin. However, among the previous reported the pediatric vancomycin population PK models (Liu et al., 2017; Zane et al., 2017), only a small part of the models believe that creatinine clearance is a factor affecting vancomycin CL. The is mainly due to the children's serum level of creatinine does not fully reflect the level of kidney function. In this study, the adult population PK model of vancomycin and the pediatric population PK model were firstly established and validated independently, and the covariate effects in adult and pediatric infection patients were investigated respectively. In the unified model of adults and pediatric patient, both CLCr and weight are considered as covariates. Zhou et al. (2016) studied the establishment of population PK model of renal clearance drugs, in which the vancomycin population PK model used CLCr and body weight as the main covariates to extrapolate from adult to children, which is the same as this study.

TABLE 3 | Multivariable logistic regression analyses on clinical/microbiological efficacy of vancomycin therapy.

Variable	Bacterial eradication		Clinical efficacy	
	Wald $\chi 2$	*P* Value	Wald $\chi 2$	*P* Value
Infection sites	9.9627	0.1907	0.4141	0.9997
Bacterial classification	0.8128	0.9992	7.5118	0.4825
$C_{min,\ ss}$	1.0589	0.3035	0.1499	0.6987
$C_{max,\ ss}$	0.4599	0.4977	1.9485	0.1628
AUC_{0-24}	0.0507	0.8218	1.7681	0.1836
AUC_{0-24}/MIC	1.1411	0.2854	NA	NA

$C_{min,\ ss}$: trough concentration at steady state; $C_{max,\ ss}$: peak concentration at steady state; AUC_{0-24}: 0–24 h area under the curve; AUC_{0-24}/MIC: the area under the curve to minimum inhibitory concentration ratio.

In this study, we successfully established the unified population PK model of vancomycin for adults and pediatric patients, and verified it as a tool model to extrapolate from adults to children, which meets the needs of different physiological mechanisms and therapeutic drug monitoring in clinical practice. In clinical practice, adult PK data is easier to obtain than children. Generally, the integrity and sufficiency of PK data of adult patients better than that of pediatric patients. At the same time, it can reduce the sampling bias caused by the uneven age distribution of pediatric PK dataset. The Bayesian feedback method can better predict the individual PK parameters of pediatric patients, and can also be used to extrapolate the PK/PD index of pediatric patients at different ages.

This study evaluated not only the clinical efficacy but also the microbiological efficacy, which was relatively rare in previous studies. In this study, univariate and multivariate logistic

TABLE 4 | Comparison of pharmacokinetic parameters and clinical efficacy (improvement of clinical signs and symptoms) by the most common infected sites.

Infected site	PK parameters	Improved	Not improved	*P* value
Overall	Responding, n (%)	100 (92.6)	8 (7.4)	
	$C_{min,ss}$ (mg/L),Median (IQR)	1.50 (1.50, 5.75)	1.50 (1.50, 4.92)	0.8206
	$C_{min,ss}$ (mg/L),Median (IQR)	21.50 (16.89, 27.12)	26.02 (22.01, 28.67)	0.1146
	AUC_{0-24}, (hr*mg/L), median (IQR)	217.5 (172.87, 286.34)	212.6 (204.20, 314.50)	0.4082
Bloodstream	Responding, *n* (%)	49 (96.1)	2 (3.9)	
	$C_{min,ss}$ (mg/L),Median (IQR)	1.50 (1.50, 5.95)	1.50	0.2650
	$C_{max,ss}$ (mg/L),Median (IQR)	23.32 (17.20, 26.57)	26.02	0.3693
	AUC_{0-24}, (hr*mg/L), median (IQR)	215.9 (172.33, 305.85)	225.0	>0.9999
Pulmonary	Responding, *n* (%)	27 (90.0)	3 (10.0)	
	$C_{min,ss}$ (mg/L),Median (IQR)	3.02 (1.50, 6.17)	3.32	0.8553
	$C_{max,ss}$ (mg/L),Median (IQR)	20.24 (16.24, 28.07)	22.60	0.6783
	AUC_{0-24}, (hr*mg/L), median (IQR)	219.2 (183.44, 266.38)	213.1	0.5802
Urinary tract	Responding, *n* (%)	16 (94.1)	1 (5.9)	
	$C_{min,ss}$ (mg/L),Median (IQR)	1.50 (1.50, 5.99)	1.50	0.4930
	$C_{max,ss}$ (mg/L),Median (IQR)	22.08 (15.80, 25.63)	29.18	0.1846
	AUC_{0-24}, (hr*mg/L), median (IQR)	196.2 (145.03, 287.92)	212.1	0.9187
Central nerve system	Responding, *n* (%)	10 (90.9)	1 (9.1)	
	$C_{min,ss}$ (mg/L),Median (IQR)	4.77 (1.50, 10.58)	1.50	0.3315
	$C_{max,ss}$ (mg/L),Median (IQR)	28.11 (24.75, 30.66)	21.41	0.4292
	AUC_{0-24}, (hr*mg/L), median (IQR)	303.3 (204.97, 386.18)	200.1	0.4292
Endocarditis	Responding, *n* (%)	6 (100.0)	0 (0.0)	
	$C_{min,ss}$ (mg/L),Median (IQR)	1.50 (1.50, 3.63)		
	$C_{max,ss}$ (mg/L),Median (IQR)	21.50 (17.20, 23.70)		
	AUC_{0-24}, (hr*mg/L), median (IQR)	213.4 (195.3, 239.1)		

$C_{min,ss}$: trough concentration at steady state; $C_{max,ss}$: peak concentration at steady state; AUC_{0-24}: 0–24 h area under the curve; AUC_{0-24}/MIC: the area under the curve to minimum inhibitory concentration ratio; IQR: interquartile range.

Data are presented as the median (IQR) or n *(%); IQRs were not reported for* n < 5.

TABLE 5 | Summary of bacterial response of vancomycin and AUC_{0-24}/MIC by the most common infection sites and bacteria.

Bacterial classification	*N*	Bacterial eradication		AUC_{0-24}/MIC	
		n (%)	*P* value*	Median (IQR)	*P* value**
Bloodstream			1.0000		0.0039
SA	8	8 (100.0)		315.0 (215.5, 367.0)	
CoNS	32	31 (96.9)		187.0 (152.0, 250.5)	
Enterococcus	7	7 (100.0)		214.0 (184.0, 528.0)	
Other	4	4 (100.0)		553.5 (470.0, 746.0)	
Pulmonary			1.0000		0.0382
SA	24	23 (95.8)		220.5 (201.0, 301.0)	
CoNS	1	1 (100.0)		186.0 (186.0, 186.0)	
Enterococcus	1	1 (100.0)		69.0 (69.0, 69.0)	
Other	3	3 (100.0)		833.0 (660.0, 1060.0)	
Urinary tract			NA		0.0322
SA	2	2 (100.0)		138.0 (137.0, 139.0)	
CoNS	2	2 (100.0)		261.5 (233.0, 290.0)	
Enterococcus	11	11 (100.0)		179.0 (145.0, 286.0)	
Central Nerve System			0.0909		0.2012
SA	1	0 (0.0)		200.0 (200.0, 200.0)	
CoNS	2	2 (100.0)		276.0 (166.0, 386.0)	
Enterococcus	2	2 (100.0)		512.0 (178.0, 846.0)	
Other	6	6 (100.0)		1082.5 (820.0, 1313.0)	
Endocarditis			NA		0.7633
SA	1	1 (100.0)		195.0 (195.0, 195.0)	
CoNS	1	1 (100.0)		240.0 (240.0, 240.0)	
Enterococcus	1	1 (100.0)		196.0 (196.0, 196.0)	
Other	3	3 (100.0)		462.0 (188.0, 478.0)	

**Fishers' Exact test.*

***Maximum likelihood ratio test.*

SA: Staphylococcus aureus*; CoNS:* Coagulase-Negative Staphylococcus*; AUC_{0-24}/MIC: 0–24 h area under the curve to MIC ratio; IQR: interquartile range; NA: not applicable.*

TABLE 6 | Population PK model predicted probability of target attainment (PTA) of vancomycin in pediatric patients at different ages under different dosing regimens and different target values.

AUC_{0-24}/MIC target value	Age period	Dose regimen (q6h, q8h or q12h) (mg/kg/day)	MIC (mg/L)				
			0.125	0.25	0.5	1	2
200	0–3m	40	**100**	**100**	**98.6**	66.7	17.4
		50	**100**	**100**	**100**	81.9	31.9
		60	**100**	**100**	**100**	89.9	44.2
		70	**100**	**100**	**100**	**94.2**	57.2
		80	**100**	**100**	**100**	**98.6**	66.7
	3m–12y	40	**100**	**100**	**100**	76.7	26.1
		50	**100**	**100**	**100**	88.9	43.3
		60	**100**	**100**	**100**	**96.1**	56.7
		70	**100**	**100**	**100**	**99.4**	65.6
		80	**100**	**100**	**100**	**100**	76.7
	12y -17y	40	**100**	**100**	**100**	**91.0**	46.5
		50	**100**	**100**	**100**	**99.0**	66.0
		60	**100**	**100**	**100**	**100**	79.5
		70	**100**	**100**	**100**	**100**	85.5
		80	**100**	**100**	**100**	**100**	**91.0**
250	0–3m	40	**100**	**100**	**92.0**	50.7	9.4
		50	**100**	**100**	**98.6**	66.7	17.4
		60	**100**	**100**	**100**	81.2	30.4
		70	**100**	**100**	**100**	87.7	39.1
		80	**100**	**100**	**100**	**92.0**	50.7
	3m–12y	40	**100**	**100**	**97.8**	61.1	16.7
		50	**100**	**100**	**100**	76.7	26.1
		60	**100**	**100**	**100**	86.7	38.9
		70	**100**	**100**	**100**	**92.2**	50.6
		80	**100**	**100**	**100**	**97.8**	61.1
	12y -17y	40	**100**	**100**	**100**	83.0	26.5
		50	**100**	**100**	**100**	**91.0**	46.5
		60	**100**	**100**	**100**	**97.0**	61.0
		70	**100**	**100**	**100**	**100**	75.0
		80	**100**	**100**	**100**	**100**	83.0
300	0–3m	40	**100**	**100**	84.1	35.5	3.6
		50	**100**	**100**	**93.5**	54.3	10.1
		60	**100**	**100**	**98.6**	66.7	17.4
		70	**100**	**100**	**100**	79.0	26.8
		80	**100**	**100**	**100**	84.1	35.5
	3m–12y	40	**100**	**100**	**90.6**	47.2	8.9
		50	**100**	**100**	**98.3**	62.8	18.3
		60	**100**	**100**	**100**	76.7	26.1
		70	**100**	**100**	**100**	85.0	36.1
		80	**100**	**100**	**100**	**90.6**	47.2
	12y–17y	40	**100**	**100**	**99.5**	70.5	17.5
		50	**100**	**100**	**100**	83.5	29.5
		60	**100**	**100**	**100**	**91.0**	46.5
		70	**100**	**100**	**100**	**96.5**	58.5
		80	**100**	**100**	**100**	**99.5**	70.5
400	0–3m	40	**100**	**98.6**	66.7	17.4	0.7
		50	**100**	**100**	81.9	31.9	2.9
		60	**100**	**100**	89.9	44.2	5.8
		70	**100**	**100**	**94.2**	57.2	10.9
		80	**100**	**100**	**98.6**	66.7	17.4
	3m–12y	40	**100**	**100**	76.7	26.1	3.3
		50	**100**	**100**	88.9	43.3	7.8
		60	**100**	**100**	**96.1**	56.7	14.4
		70	**100**	**100**	**99.4**	65.6	19.4
		80	**100**	**100**	**100**	76.7	26.1
	12y–17y	40	**100**	**100**	**91.0**	46.5	5.5
		50	**100**	**100**	**99.0**	66.0	14.0
		60	**100**	**100**	**100**	79.5	23.5
		70	**100**	**100**	**100**	85.5	34.0
		80	**100**	**100**	**100**	**91.0**	46.5

q6 h: every 6 h; q8h: every 8 h; q12 h: every 12 h. Bold text: target attainment above 90%.

regression analysis was carried out on the correlation between (C_{min}, C_{max}, AUC_{0-24} and AUC_{0-24}/MIC) with clinical efficacy (clinical efficacy + microbiological efficacy). In general, there was no significant correlation between vancomycin (C_{min}, C_{max}, AUC_{0-24} and AUC_{0-24}/MIC) according to different infection sites and bacterial types. The clinical/microbiological effective in this study were very high (>90%), and only very few ineffective cases, which may be the reason of no significant correlation could be found between effectiveness and PK/PD indexes. Further evaluation will be needed based on accumulative data generated from the larger population in more prospective studies.

Based on the predicted AUC_{0-24}/MIC target value and trough concentration of vancomycin in children with population PK model, combined with the actual clinical effective rate of Chinese children with infection, it is recommended that the optimal dosage regimen for the treatment of Chinese pediatric patients with Gram-positive infections is 60–80 mg/kg/day every 6 or 8 h (<12 years old), and 50–60 mg/kg/day every 6 or 8 h (>12 years old). The optimal dose regimen for Chinese pediatric patients younger than 12 years old is basically consistent with the recommended dose of IDSA, while the recommended dose for Chinese pediatric patients over 12 years old is slightly lower compared with the IDSA guideline. More prospective studies need to be performed to confirm these results.

CONCLUSION

No significant correlations were identified between the PK/PD indices of vancomycin and clinical or microbiological efficacy in Chinese pediatric patients with Gram-positive infections in this prospective study. Based on our research, Chinese pediatric patients with infection may be suitable for lower AUC_{0-24}/MIC target value compared to the IDSA guideline, and different optimal dose regimen of vancomycin for Chinese pediatric patients should be considered.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Huashan hospital, Fudan university. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KS, YF, MY, YC, JZ performed the major research. The manuscript was written mainly with the efforts of KS and JZ. The clinical data were collected by YF, JT, GL, HZ and QH.

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Predicting Adverse Drug Events in Chinese Pediatric Inpatients With the Associated Risk Factors: A Machine Learning Study

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The aim of this study was to apply machine learning methods to deeply explore the risk factors associated with adverse drug events (ADEs) and predict the occurrence of ADEs in Chinese pediatric inpatients. Data of 1,746 patients aged between 28 days and 18 years (mean age = 3.84 years) were included in the study from January 1, 2013, to December 31, 2015, in the Children's Hospital of Chongqing Medical University. There were 247 cases of ADE occurrence, of which the most common drugs inducing ADEs were antibacterials. Seven algorithms, including eXtreme Gradient Boosting (XGBoost), CatBoost, AdaBoost, LightGBM, Random Forest (RF), Gradient Boosting Decision Tree (GBDT), and TPOT, were used to select the important risk factors, and GBDT was chosen to establish the prediction model with the best predicting abilities (precision = 44%, recall = 25%, F1 = 31.88%). The GBDT model has better performance than Global Trigger Tools (GTTs) for ADE prediction (precision 44 vs. 13.3%). In addition, multiple risk factors were identified via GBDT, such as the number of trigger true (TT) (+), number of doses, BMI, number of drugs, number of admission, height, length of hospital stay, weight, age, and number of diagnoses. The influencing directions of the risk factors on ADEs were displayed through Shapley Additive exPlanations (SHAP). This study provides a novel method to accurately predict adverse drug events in Chinese pediatric inpatients with the associated risk factors, which may be applicable in clinical practice in the future.

Keywords: pediatric, machine learning, prediction, Chinese children, adverse drug event (s)

INTRODUCTION

Rising attention has been paid to the early warning of adverse drug events (ADEs) in hospitalized children. ADEs are defined as medication-related patient injury caused during any stage of the medication process, some of which are preventable due to errors, whereas some are adverse drug reactions (ADRs) and non-preventable (Desireé et al., 2009; Marcum et al., 2013; Malladi, 2016). The World Health Organization defines an ADR as a response to a noxious and unintended drug (Smyth et al., 2012). Events such as overdose, drug abuse,

treatment failure, and drug administration errors are excluded from ADRs. In this study, we considered ADEs including ADRs and drug administration errors. ADEs can be manifested by signs, symptoms, or laboratory abnormalities, which are important causes of iatrogenic morbidity and mortality (Desireé et al., 2009).

As a special population, pediatric patients commonly have complicated situations, and the incidence of ADEs is hard to predict. A systematic review of 102 studies concluded that the incidence rates for ADRs causing pediatric admission ranged from 0.4 to 10.3% (Sakuma et al., 2014). Another study on Japanese pediatric inpatients found frequent ADEs with an incidence of 37.8 per 1,000 patient-days, and most were non-preventable (Morimoto et al., 2011). Surprisingly, the incidence of ADEs was around two times higher in admitted children than in adults (37.8 vs. 17.0 per 1,000 patient-days), and the incidence of medication errors was about eight times higher in admitted children than in adults (65.1 vs. 8.7 per 1,000 patient-days) (Poole, 2008). The possible reasons may be complexities in the pediatric medication process, which needs specific dosage calculation based on the age and weight of individual child; moreover, children are difficult to express and describe the symptoms of ADEs (Takata et al., 2008; Morimoto et al., 2011).

So far, the Global Trigger Tool (GTT), developed by the Institute for Healthcare Improvement (IHI), is a commonly used method for identifying potential ADEs among pediatric populations in the United States, the United Kingdom, Norway, Australia, and Japan (Grifn and Resear, 2009; Morimoto et al., 2011; Kirkendall et al., 2012; Chapman et al., 2014; Solevag and Nakstad, 2014; Hibbert et al., 2015; Ji et al., 2018). In China, Ji et al. explored the associated risk factors to predict ADEs using the GTT in children through stepwise logistic regression. The GTT uses "triggers" to identify ADEs, presenting as the ordering of certain medications, change of clinical status or symptoms, abnormal laboratory values, and abrupt stop orders (Resar et al., 2003; Marcum et al., 2013). However, based on previous research, pediatric patients have remarkable differences with regard to the risk factors associated with ADEs. Some found that gender, the number of drugs, use of antibacterial drugs, length of hospital stay, and general anesthesia were associated with ADEs in children. These findings still create controversy (Star et al., 2011; Rashed et al., 2012; Tiesen et al., 2013; Saedder et al., 2015; Andrade et al., 2017).

In our study, we aimed to apply machine learning methods to explore the associated risk factors for ADEs in Chinese pediatric inpatients. The rapidly developing machine learning methods can promote data-driven estimation when screening from multiple variables and capture nonlinear relations to achieve high accuracy in predicting clinical outcomes. We proposed to make a comparison between the study outcome and the findings of Ji et al., in order to find an optimal model to accurately predict pediatric ADEs and take effective prevention measures.

METHODS

Study Design and Population

We enrolled pediatric inpatients from January 1, 2013, to December 31, 2015, in the Children's Hospital of Chongqing Medical University, which is a large tertiary children's hospital in China. Data were collected from the electronic medical records through the medical record system and the bar code system for medication administration. In order to compare the final results with those of the study by Ji et al., we applied the same criteria to select patients. The inclusion criteria were patients aged >28 days and <18 years, whose length of hospital stay >1 day and who were discharged or died between January 1, 2013, and December 31, 2015. The exclusion criteria were as follows: patients who had no drug exposure or were from the PICU, neonatal ward, hematology department, or oncology department (they were excluded because they had special treatment regimens that needed different triggers for ADE research). Samples were randomly selected from eligible patients using a random equidistant sampling method, obtaining a total of 1,800 patients. The whole dataset was then divided into derivation and test cohorts at the ratio of 8:2.

Data Processing

Data were collected from medical records including patient's basic information, diagnostic and treating procedures, medication charts, laboratory values, surgical records, nurse's records, physician's records, and admission and discharge records. One pharmacist and two pediatricians were assigned to examine the data and determine the occurrence of ADEs. If there was a disagreement, the final decision was made based on a consensus after team discussion. If the patient got actual harm that was related to medication, then the event was deemed as an ADE. Herein, harm was defined as an accidental body injury that needed medical care with additional monitoring, treatment, or hospitalization, including permanent injury or death. To be specific, the following symptoms or diseases were deemed as the occurrence of ADEs: gastrointestinal disorders (e.g., diarrhea, constipation, and vomiting), nervous system disorders (e.g., convulsions, convulsions grand mal, and over-sedation/hypotension), resistance mechanism disorders (e.g., candidiasis and fungal infection), metabolism and nutrition disorders (e.g., hyperkalemia, hypokalemia, hypoglycemia, hyperglycemia, and hyponatremia), respiratory system disorders (e.g., respiratory depression, bronchospasm, and dyspnea), rash, hepatotoxicity, nephritis, coagulopathy, leukopenia, allergic reactions, and so forth. The number of ADEs per case = the total number of ADEs/the number of cases.

Selection of Risk Factors

Based on the data of pediatric inpatients' records, the risk factors were screened from multiple patient characteristics. To be specific, we included patients' demographic information (such as gender, age, weight, and height), status at birth (such as natural delivery/cesarean, premature birth, and weight at birth), information about admission (such as the number of medical

diagnoses, admissions, admissions in the previous 1 year, and the length of hospital stay), and treatment information (such as surgical operation, number of drugs and doses, and the use of antibacterial, sedative analgesic, and anesthetic drugs). We set "the occurrence of ADEs" as the target variable to analyze which characteristic had remarkable influence on it. Subsequently, machine learning methods were applied to calculate the importance score of all risk factors according to patient characteristics, represented as a ranking figure. A factor with a higher risk score indicates more impact on the occurrence of ADEs. Based on the selected factors, we visually displayed the Shapley Additive exPlanations (SHAP) figure to demonstrate the positive or negative correlations between risk factors and the occurrence of ADEs (Lundberg and Lee, 2017).

Model Establishment and Comparison

Using the selected risk factors as covariates, seven machine learning models were first established and analyzed through algorithms including eXtreme Gradient Boosting (XGBoost), CatBoost, AdaBoost, LightGBM, Random Forest (RF), Gradient Boosting Decision Tree (GBDT), and TPOT. The prediction metrics of the seven models were evaluated and compared in terms of the receiver operating characteristic (ROC) curve and the value of area under the curve (AUC), which represented the overall ability of classification and prediction. In order to compare the results with those of the study by Ji et al., precision/positive predictive value (PPV), recall, and F1 values of the prediction model were calculated. Precision/PPV indicates the number of times a risk factor independently identified an ADE divided by the number of times a risk factor was identified as positive. Ultimately, the algorithm with the best performance was selected to establish the model to predict the occurrence of ADEs in Chinese pediatric inpatients.

Statistical Analysis

Data were analyzed by using Python 3.6.4 and WPS Office. Algorithms including XGBoost, CatBoost, AdaBoost, LightGBM, RF, GBDT, and TPOT were chosen to investigate risk factors associated with ADEs and the algorithm with the best performance was selected to establish the ADE prediction model. The evaluating metrics for model performance are as follows (Powers and Ailab, 2011):

$$\text{Precision} = \frac{TP}{TP + FP},$$

$$\text{Recall} = \frac{TP}{TP + FN},$$

$$\text{F1} = \frac{2 \times Precision \times Recall}{Precision + Recall}.$$

TP, true positive, indicating the positive class is predicted as the number of positive classes; TN, true negative, indicating the negative class is predicted as the number of negative classes; FP, false positive, indicating the negative class is predicted as the number of positive classes; FN, false negative, indicating the positive class is predicted as the number of negative classes.

F1 is used to measure the merits and defects of the model, a larger F1 value indicating better model performance.

RESULTS

Study Population

A total of 1,800 patients (cases) were enrolled in this study, while 54 patients were excluded, 28 of whom had no drug exposure and 26 of whom were diagnosed with cancer. The whole dataset was divided into derivation and test cohorts at the ratio of 8:2, which were 1,396 and 350 cases, respectively. According to **Table 1**, there is no significant difference between derivation and test cohorts ($p > 0.05$), except that gender and treatment with sedative analgesics have a slightly lower p-value ($p = 0.02$). In the final dataset of 1,746 cases, children were of the average age of 3.84 years, ranging from 0.08 to 17.75 years, females accounted for 35% (611 cases) and males 65% (1,135 cases), and the average body mass index (BMI) was 16.45 kg/cm^2. The mean length of hospital stay was 7.83 days (ranging between 1 and 63 days), the average number of using drugs was 14 (1–64) per patient, and the average doses were 114 doses (1–1,206 doses) per patient. A total of 221 patients had ADEs, of which 32.6% were females, 77.4% were children with natural delivery, and proportions of children treated with antibacterial, sedative analgesic, and anesthetic drugs were 66.1, 43.0, and 52.5%, respectively. The relationships of these factors with the occurrence of ADEs need further screening in the following sections.

ADEs and Risk Factors

A total of 247 ADEs were identified in 221 patients, with an incidence rate of 12.7%. In **Table 2**, we summarize the classification of the drugs leading to the 247 ADEs. Anti-infective drugs including antibacterials, antivirals, and anti-tuberculosis drugs were the most common drugs causing ADEs in pediatric inpatients (35.9%). The importance scores of risk factors were calculated and ranked using seven algorithms. Since the GBDT model was ultimately proven to be the optimal one, **Figure 1** only displays the importance score ranking in the GBDT model, the top 10 of which includes the number of trigger true [triggers were found to occur, TT (+)], number of doses, BMI, number of drugs, number of admission, height, length of hospital stay, weight, age, and number of diagnoses in a descending order. Among them, the number of TT (+) has the highest score of 0.2911, followed by the number of doses (0.1589) and BMI (0.1179), demonstrating their importance in predicting pediatric ADEs.

As depicted in **Figure 2**, for risk factors including the number of TT (+), number of doses, number of drugs, number of admission, number of diagnoses, and height, the dot color is redder when SHAP value gets larger and the color is bluer when SHAP value gets smaller, thus showing positive impacts of these factors on the risk of ADEs. Their SHAP values also show the same indications, which are 0.009, 0.082, 0.086, 0.011, 0.004, and 0.008 for the number of TT (+), number of doses, number of drugs, number of admission, number of diagnoses, and height, correspondingly. On the contrary, risk factors including age,

TABLE 1 | Characteristics of patients with and without ADEs.

Variable	Derivation cohort (N = 1,396)	Test cohort (N = 350)	*p*-value	Total (n = 1,746)	Patients with ADEs (n = 221)	Patients with no ADEs (n = 1,525)
Demographics						
Female (%)	33.6%	40.6%	0.02	35.0%	32.6%	35.3%
Age (y)	3.8 ± 3.89	3.72 ± 3.89	0.35	3.84 ± 3.89	3.72 ± 4.12	3.86 ± 3.85
Weight (kg)	16.30 ± 11.66	15.54 ± 10.72	0.39	16.15 ± 11.48	15.37 ± 11.51	16.26 ± 11.47
Height (cm)	95.01 ± 29.37	93.46 ± 29.41	0.36	94.70 ± 29.38	91.97 ± 31.40	95.10 ± 29.06
BMI (kg/cm^2)	16.49 ± 3.63	16.27 ± 3.13	0.84	16.45 ± 3.53	16.17 ± 2.85	16.49 ± 3.62
Developmental and nutritional status						
Fine	513 (36.7%)	126 (36.00%)	0.41	639 (36.6%)	70 (31.7%)	569 (37.3%)
Medium	757 (54.2%)	187 (53.43%)		944 (54.1%)	123 (55.7%)	821 (53.8%)
Lower middle	99 (7.1%)	25 (7.14%)		124 (7.1%)	19 (8.6%)	105 (6.9%)
Others	27 (1.9%)	12 (3.43%)		39 (2.2%)	9 (4.1%)	26 (2.0%)
Status at birth						
Natural delivery	382 (27.4%)	84 (24%)	0.22	1,280 (73.3%)	171 (77.4%)	1,110 (72.7%)
Cesarean	1,014 (72.6%)	266 (76%)		466 (26.7%)	50 (22.6%)	416 (27.3%)
Premature birth	63 (4.5%)	16 (4.57%)	0.92	79 (4.5%)	14 (6.3%)	65 (4.3%)
Weight at birth	3.22 ± 0.50	3.22 ± 0.51	0.83	3.22 ± 0.50	3.18 ± 0.49	3.22 ± 0.51
Admission						
Length of stay (d)	7.90 ± 5.51	7.58 ± 4.32	0.42	7.83 ± 5.29	10.23 ± 8.03	7.48 ± 4.66
Number of medical diagnoses	2.94 ± 1.89	3.11 ± 2.02	0.92	2.97 ± 1.89	2.92 ± 1.98	2.83 ± 1.71
Number of admissions	1.80 ± 1.43	1.88 ± 1.39	0.67	1.81 ± 1.42	2.07 ± 1.60	1.77 ± 1.39
Number of admissions in the previous 1 year	0.47 ± 1.02	0.59 ± 1.12	0.26	0.49 ± 1.04	0.61 ± 1.01	0.47 ± 1.04
Treatment						
Surgical operation	422 (30.2%)	90 (25.7%)	0.11	506 (29.0%)	64 (30.3%)	442 (28.8%)
Number of drugs	14.14 ± 6.82	14.31 ± 6.53	0.84	14.18 ± 6.77	18.82 ± 9.02	13.51 ± 6.01
Number of doses	114.24 ± 109.94	114.10 ± 87.77	0.83	113.94 ± 104.97	189.94 ± 187.00	102.92 ± 83.30
Antibacterial use	720 (51.6%)	194 (55.43%)	0.22	914 (52.3%)	146 (66.1%)	768 (50.4%)
Sedative analgesic use	587 (42.0%)	122 (34.86%)	0.02	709 (40.6%)	95 (43.0%)	614 (40.3%)
Anesthetic use	798 (57.2%)	199 (56.86%)	0.97	997 (57.1%)	117 (52.5%)	880 (57.7%)
Other						
Number of TT (+)	1.42 ± 1.49	1.56 ± 1.62	0.88	1.45 ± 1.51	2.95 ± 2.02	1.23 ± 1.29
ADEs	177 (79.1%)	44 (19.9%)	0.99	221 (12.7%)	221 (100%)	0

Abbreviations: BMI, body mass index; TT, trigger true; ADEs, adverse drug events

Notes: Data for variables are presented as mean ± variance, excluding those presented as cases and percentage (%). p-value is calculated for comparing the difference between derivation and test cohorts, $p < 0.05$ *is considered significant.*

BMI, and weight display negative impacts on the risk of ADEs, and their SHAP values are −0.003, −0.005, and −0.008, respectively. The length of hospital stay shows unclear direction of influence (SHAP = 0.001). Some display evident influencing directions, and others are relatively indistinct. With a larger sample size, the direction would be clear.

Model Establishment and Comparison

In **Table 3**, the metrics of seven models are compared in terms of precision, recall, and F1 value. Among the seven models, TPOT has the highest precision (75%) but moderate values of recall (13.64%) and F1 (23.08%), while GBDT has the highest values of recall (25%) and F1 (31.88%) with a moderate precision (44%). In addition, the visual comparisons of the seven models are displayed in **Figure 3**, including the precision-recall curve and the ROC curve, where the GBDT model achieves the highest AUC of 0.809. It can be seen that the GBDT model outperforms other models in the aspects of recall, F1, and AUC, demonstrating a good ability of model classification and prediction. After overall consideration of the predicting performance, we chose the model using the GBDT algorithm over the others to predict the occurrence of ADEs. Compared with the PPV of 13.3% in the study by Ji et al., the GBDT model has a precision of 44%, which surpassed their outcome (Marcum et al., 2013).

DISCUSSION

Prediction based on important risk factors is necessary for the prevention of ADEs in pediatric patients; nevertheless, it is difficult to achieve a precise prediction due to complex body status and dosing regimens of children. In the present study, we attempted to apply machine learning methods to deeply explore the risk factors associated with ADEs, since in the real-world studies, variables are not always independent of each other, and they are closely related in the nonlinear way. The normally used multivariate analysis methods cannot capture the complex relationships of variables, which machine learning methods are skilled in, especially GBDT that we used is able to divide and reaggregate variables to achieve the minimum prediction error when growing sub-trees. In this way, the nonlinear relationship between variables can be well captured. In addition, they all have the ability to learn from data with missing values directly, which can better adapt to the data situation in the real world. In the

TABLE 2 | Classification of drugs leading to occurrence of ADEs.

Classification of medicines	Types of medicines	Number of cases	Percentage (%)
Anti-infective drugs	Antibacterials	86	35.9
	Antivirals	3	
	Anti-tuberculosis drugs	1	
Nervous system drugs	Anti-epileptics	12	27.1
	Anti-anxiety drugs	1	
	Sedatives	55	
Digestive system drugs	Acid inhibitors	7	4.8
	Antidiarrheal drugs	5	
Hormonal and endocrine system drugs	Glucocorticoids	6	4.4
	Insulin	5	
Drugs to regulate water, electrolyte, and acid–base balance	Potassium chloride, glucose	10	4.0
Urological system drugs	Diuretics	4	2.0
	Dehydrating agent	1	
Antipyretic, analgesic, and anti-inflammatory drugs	Antipyretics	4	1.6
Cardiovascular medicines	Anti–heart failure drugs	1	1.2
	Anti-hypertensives	1	
	Anti-shock drugs	1	
Vitamins, minerals, amino acids, etc.	Minerals, amino acids	3	1.2
Hematology and hematopoietic system drugs	Anticoagulants	3	1.2
Anti-allergic reaction drugs	Anti-allergy drugs	2	0.8
Others	Immunomodulators	14	15.9
	Chinese herbal medicine/Chinese medicine injections	6	
	Mistake intake of paraquat, acetochlor, cocklebur	6	
	Blood products	5	
	Anesthetics	2	
	Medical tapes	1	
	Unspecified	6	

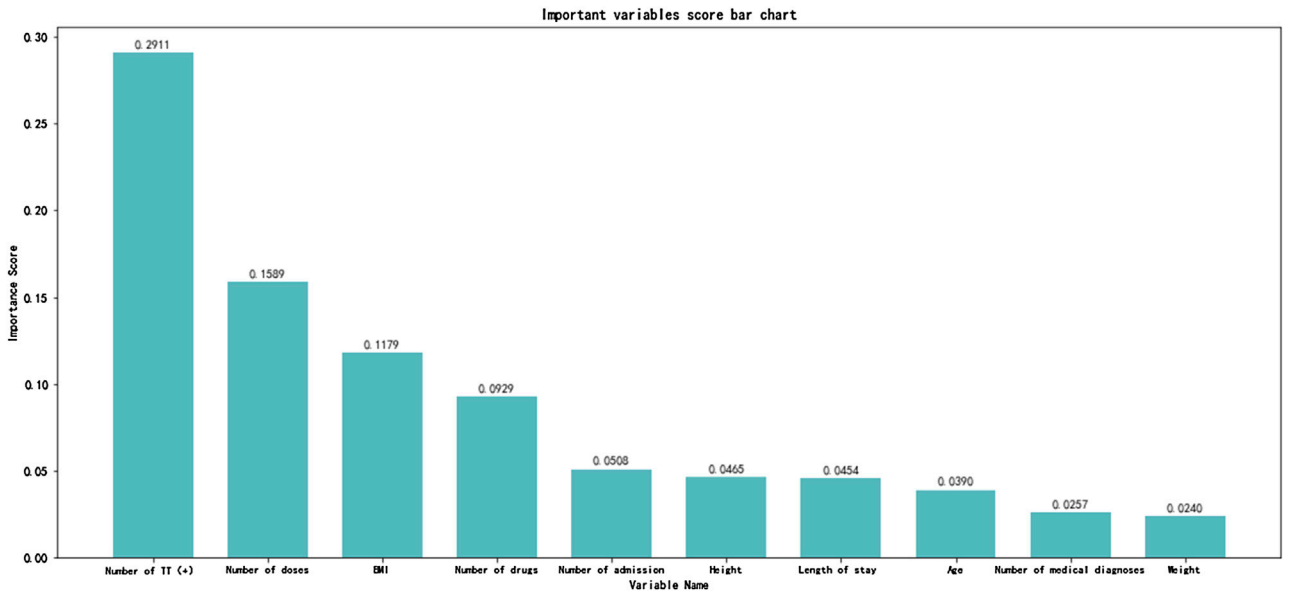

FIGURE 1 | Importance score ranking for risk factors.

study by Ji et al., they found that an overall PPV of using trigger tools for ADE prediction was 13.3% at the Children's Hospital of Chongqing Medical University, within the range of other trigger tools in pediatric care centers from 3.7 to 38% (Kirkendall et al., 2012; Marcum et al., 2013; Chapman et al., 2014; Unbeck et al., 2014; Solevag and Nakstad, 2014; Hibbert et al., 2015; Stockwell et al., 2015). In our study, the precision/PPV of the selected GBDT model was 44%, which outperforms the results of the study by Ji et al. and the majority of similar studies using trigger tools for ADE prediction.

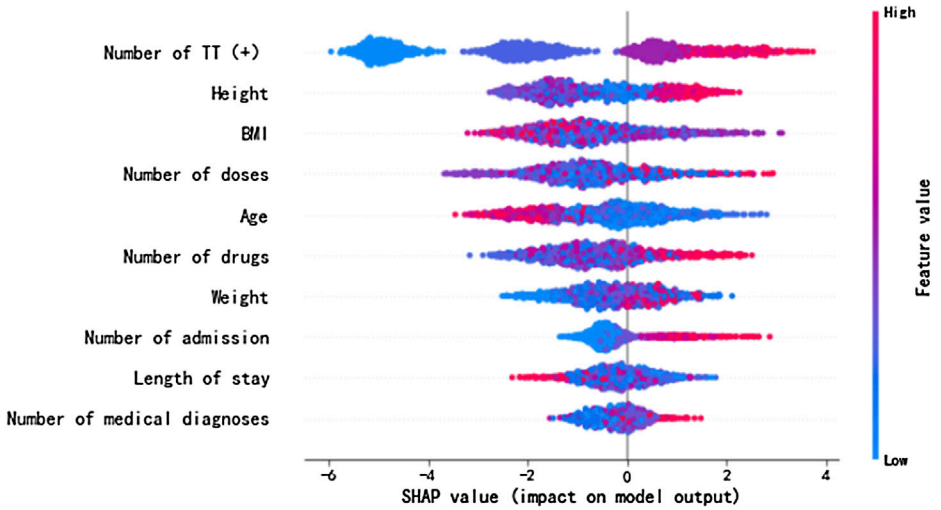

FIGURE 2 | SHAP values of the important risk factors. The dot color is redder when the feature value gets higher and bluer when the feature value gets lower. When the SHAP value gets higher, the impact of the variable on model output is larger.

TABLE 3 | Model performance using seven algorithms.

Model	Precision	Recall	F1
GBDT	44.00	25.00	31.88
LightGBM	27.27	6.82	10.91
AdaBoost	41.18	15.91	22.95
RF	23.08	13.64	17.14
CatBoost	46.15	13.64	21.05
TPOT	75.00	13.64	23.08
XGBoost	34.62	20.45	25.71

Ji et al. found the significant risk factors for ADEs including the number of drugs, the number of doses, and the number of admissions (Marcum et al., 2013). Compared with their findings, our study identified the number of TT (+), BMI, height, weight, age, length of hospital stay, and number of drugs, doses, admission, and diagnoses, as the top 10 significant risk factors, which should be paid more attention on their measurement and take corresponding prevention in clinical. The trigger tools have proven their utility in multiple studies worldwide, some of which used IHI GTT (such as in the study by Ji et al., PPV 13.3%) and some of which developed other trigger tools, such as the U.S. pediatric-focused trigger tool (PPV 3.7%), the British National Health Service Pediatric Trigger Tool (PPV 19.8%), and the U.K. Pediatric Trigger Tool (Kirkendall et al., 2012; Marcum et al., 2013; Chapman et al., 2014; Solevag and Nakstad, 2014; Unbeck et al., 2014; Hibbert et al., 2015; Stockwell et al., 2015). Trigger tools show their practical ability in pediatric patients; however, the PPV of trigger tools was generally low and varied greatly among different populations and health care centers. We found that the number of TT (+) has a positive relationship with ADEs, which is also the most important

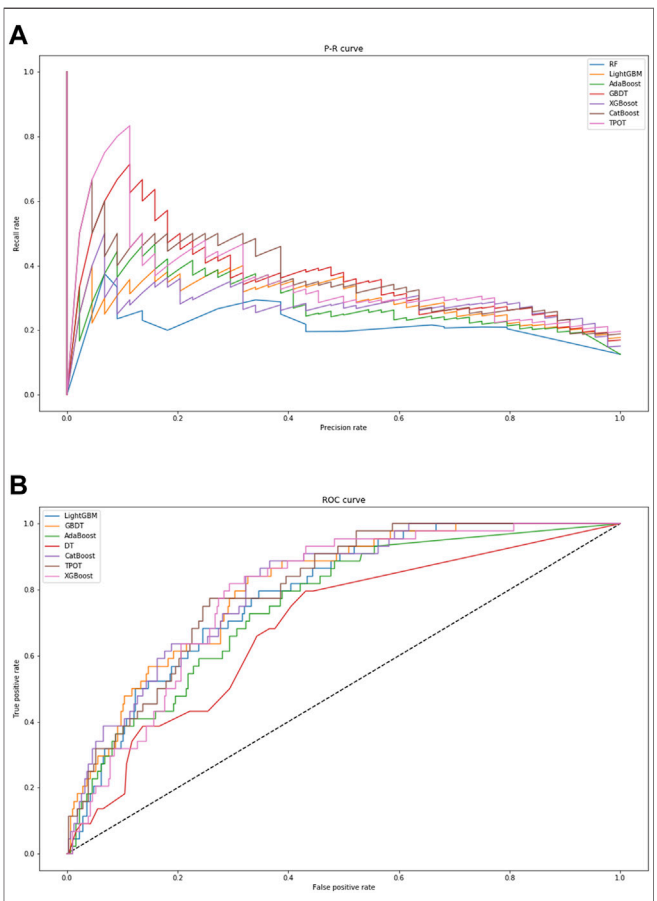

FIGURE 3 | Visual presentation of model performance based on seven algorithms. **(A)** displays the precision–recall curve. **(B)** displays the ROC curve. When the area under curve is closer to "1," the performance of model classification and prediction is better. Abbreviations: RF, Random Forest; GBDT, Gradient Boosting Decision Tree; XGBoost, eXtreme Gradient Boosting.

risk factor, demonstrating that ADEs could be better predicted with more occurred triggers. Hence, it is highly recommended to increase the number of triggers and take them into consideration with other important risk factors together, in order to predict ADEs more accurately.

We also confirmed the importance of the number of drugs, doses, and admissions, which was consistent with the study by Ji et al. and previous research. The potential reason for the number of drugs as a risk factor could be the rising accumulated risks of multiple drug treatment, interactions between different drugs, and medication errors (Marcum et al., 2013). A similar reason can explain the number of doses being a risk factor, in that patients faced more risks of ADRs and the occurrence of overdose and drug abuse. As for the number of admissions, pediatric patients who were admitted frequently were commonly diagnosed with diseases requiring high-risk drugs, such as antiepileptic drugs for epilepsy, antibacterial drugs for recurrent infection, and some drugs for chronic diseases including corticosteroids, immunosuppressive agents, and analgesics (Rashed et al., 2012; Marcum et al., 2013). With regards to the number of diagnoses, a newly confirmed risk factor positively associated with ADEs in our study, generally, more drugs are used if the patient is diagnosed with more diseases. It can be explained by the increasing opportunities of drug–drug interactions, use of high-risk drugs, and occurrence of ADRs as well.

In terms of the hospital stay length, our result shows that it has an impact on the occurrence of ADEs. However, the length of hospital stay is commonly influenced by a couple of other factors, such as patient status, nursing care, and drug regimens (including the number of drugs and doses). Therefore, we did not consider the length of hospital stay as an independent risk factor for ADEs. In addition, some research believed that ADEs lead to prolonged length of hospital stay, which shows an inverse causal relationship (Rashed et al., 2012; Munoz-Torrero et al., 2010; Amelung et al., 2017). The causal relationship between length of hospital stay and ADEs is still a controversial topic currently, which needs further research in the future.

Of note, BMI, height, and weight were identified as remarkable risk factors. It is possibly because children have substantial variation in terms of weight and height, with their weights varying from 400 g to 120 kg (Takata et al., 2008). Moreover, most drugs need dosing calculation based on children's weight, which may lead to a potential of 300-fold dosing errors (Takata et al., 2008). This is a noteworthy factor that needs careful records and strict reference of weight and height in order to predict pediatric ADEs in clinical practice. According to our findings, BMI and weight are negatively correlated to ADEs, indicating that children with low weight/BMI may experience more ADEs, possibly due to patient vulnerability as a result of low nutritional status.

Different from the findings of Ji et al., we found that age is a risk factor for the occurrence of ADEs, which was inconsistent with previous studies (Munoz-Torrero et al., 2010; Rashed et al., 2012). One indicated that age was not an independent risk factor of ADEs, as older patients showed more possibilities of having ADEs, which they believed was associated with more opportunities of using high-risk drugs (Rashed et al., 2012). In our viewpoint, younger children may be more vulnerable to ADEs because of the immature developmental and nutritional status and the susceptibility to drug reactions.

In conclusion, to our knowledge, this is a novel study to establish a prediction model for ADEs using machine learning in Chinese pediatric inpatients. The risk factors identified in this study could be incorporated into routine screen systems to improve inpatient safety in clinical practice. One drawback is the limited sample size, which needs to include more pediatric patient data in the future from different health care centers. Furthermore, the prediction model using GBDT should also be further validated in more pediatric inpatients including those in the hematology, oncology, PICU, and neonatal units.

DATA AVAILABILITY STATEMENT

The data are available on request from the corresponding author.

ETHICS STATEMENT

This study was exempted from ethical review by the Institutional Review of the Children's Hospital of Chongqing Medical University. It complies with the Ministry of Health's 2007 Chinese Regulation on Ethical Review of Biomedical Research Involving Human Subjects. The study methods were carried out in accordance with the relevant guidelines and regulations.

AUTHOR CONTRIBUTIONS

All the authors were involved in the study. ZY, HJ, LS, JX, FG, and YJ designed the study. TT, HJ, and PW did sampling and record review. HJ, JZ, QQ, and YJ analyzed and interpreted the data. ZY, HJ, and XH wrote the manuscript. All authors read and approved the final manuscript for publishing.

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frontiers in Pharmacology

REVIEW
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Model Based Evaluation of Hypersensitivity Adverse Drug Reactions to Antimicrobial Agents in Children

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Drug use in children is–in most cases–supported by extrapolation of data generated from clinical trials in adult populations. This puts children at higher risk of developing adverse drug reactions (ADRs) due to "off-label" use of drugs and dosing issues. Major types of ADRs are drug hypersensitivity reactions, an idiosyncratic type of ADRs that are largely unpredictable and can cause high morbidity and mortality in a hard-to-identify specific population of patients. Lack of a complete understanding of the pathophysiology of DHRs and their unpredictive nature make them problematic in clinical practice and in drug development. In addition, ethical and legal obstacles hinder conducting large clinical trials in children, which in turn make children a "therapeutic orphan" where clear clinical guidelines are lacking, and practice is based largely on the personal experience of the clinician, hence making modeling desirable. This brief review summarizes the current knowledge of model-based evaluation of diagnosis and management of drug hypersensitivity reactions (DHRs) to antimicrobial drugs in the pediatric population. Ethical and legal aspects of drug research in children and the effect of different stages of child development and other factors on the risk of DHRs are discussed. The role of animal models, *in vitro* models and oral provocation test in management of DHRs are examined in the context of the current understanding of the pathophysiology of DHRs. Finally, recent changes in drug development legislations have been put forward to encourage drug developers to conduct trials in children clearly indicate the urgent need for evidence to support drug safety in children and for modeling to guide these clinical trials.

Keywords: children, adverse drug reactions, modeling, antimicrobacterial, drug safety

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INTRODUCTION

An adverse drug reaction (ADR) is defined as any noxious and unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or modification of physiological function. A conservative estimate of the rate of ADRs in the general population is 5% per course of treatment, however; it can be as high as 50%, for example, in the case of cancer chemotherapy (Elzagallaai et al., 2017). ADRs are a leading cause of morbidly and mortality in patients from all age groups (Lombardi et al., 2018; Lombardi et al., 2019; Lombardi et al., 2020;

Pagani et al., 2021). Serious ADRs occur at a rate of 6.7% in hospitalized patients and 0.32% of them are fatal. A review of 17 prospective studies of incidence rate of ADRs in pediatric in- and out-patients estimated the incidence to be 9.5% (95% CI 6.81, 12.26) in in-patients and 1.5% (95% CI 0.7, 3.03) in out-patients (Impicciatore et al., 2001). Accurate estimation of the incidence of ADRs in children is hindered by under-reporting, lack of clear definition of age groups and causality issues (Smyth et al., 2012). It is well known that subtle age differences during infancy and childhood–which extends from birth to the onset of puberty–are associated with significant changes in pharmacokinetics and pharmacodynamics of medications, notably in the first several years of life. Body weight doubles by 5 months and triples by 1 year. Major maturation of body systems occur during the first few years of life and body water and fat compositions changes dramatically (Kauffman, 2019). All these factors put children at risk of developing ADRs as typically drugs are not studied in children during the process of drug development and approval and, hence safety data in this age group is almost always missing.

Drug Hypersensitivity reactions (DHRs) including true "drug allergy" represent up to one third of all ADRs and can be severe and life-threatening requiring prolonged hospitalization and associated healthcare costs (Demoly et al., 2007; Sousa-Pinto et al., 2020). DHRs are classified, according to their onset and the immune mechanism involved, into immediate-type DHR (IDHRs) or delayed-type DHRs (DDHRs). IDHRs occur within an hour of drug exposure and are mediated by IgE antibodies generated against the drug or metabolite(s). On the other hand, DDHRs occur days or weeks after drug exposure and are IgG or T-cell-mediated (Rieder, 2018). Antibiotics are the most commonly prescribed drugs in children (Stam et al., 2012; Holstiege and Garbe, 2013; Youngster et al., 2017) and they are the second leading cause of ADRs resulting in emergency department visit and/or hospital admission in children (18%) after cancer chemotherapy (Langerova et al., 2014; Lombardi et al., 2018; Lombardi et al., 2019; Lombardi et al., 2020; Pagani et al., 2021). DHRs represent a major clinical problem because of their potential seriousness and high morbidity. In addition, labeling a child with antibiotic allergy without confirmation has its consequences to both the patient and public health (Tanno et al., 2018). Approximately 10% of children are reported by their parents to have antibiotic allergy and 75% of them are diagnosed before their third birthday (Vyles et al., 2017b). Unfortunately, this is frequently incorrect and over-Labeling of antibiotic allergy has been demonstrated to have a negative health impact both on the patient and the health care system (Charneski et al., 2011). Unconfirmed childhood allergy labeling most often extends to the rest of the patients' life leading to unnecessarily depriving them from useful and safe drugs and exposing them to less safe and more expensive alternatives. In fact, studies have shown that when labeled children are challenged with the culprit drug, over 90% are able to tolerate the drug (Rebelo Gomes et al., 2008; Vezir et al., 2014; Vyles et al., 2017a). Current data shows that up to 10% of children are reported to have beta-lactam allergy and are the most common trigger of anaphylactic reactions in children (Gomes et al., 2016; Regateiro et al., 2020). The risk of fatal anaphylaxis due to penicillin use has been estimated at 0.0015–0.002% of treated patients (International Collaborative Study of Severe Anaphylaxis, 2003). Up to 75% of fatal drug-induced anaphylaxis in the United States are caused by penicillins, which corresponds to 500–1,000 annual fatality (Neugut et al., 2001).

Prescribing medicines to children is challenging due to the lack of reliable safety data as a result of the limited number of clinical trials in the pediatric population. One example is dose. Dose calculation for pediatric patients based on weight and body surface area (BSA) can be both inaccurate and prone to errors. Children are not merely little adults; they have their own unique pharmacokinetics and pharmacodynamics and these parameters change dramatically especially during the first few years of life (Elzagallaai et al., 2021). Dose estimation from adult studies can be extrapolated with allometric scaling but this may not always result in an optimal or safe dose due to the variability imposed by ontogeny.

The term "off-label" use refers to the use of a drug for an indication that is not listed in the drug license and monograph (Frattarelli et al., 2014). Off-label use is very common in children, which has been demonstrated to be an independent risk factor for ADRs (Neubert et al., 2004). Off-label use of medications in children ranges from 11 to 80% and a higher rate of use has been described in younger children and in hospital setting as opposed to ambulatory care. This number increases to up to 90% in neonates in Neonatal Intensive Care Units (Conroy et al., 1999; Langerova et al., 2014). It still unclear why off-label use of drugs in children increases risk for ADRs and larger studies in this field and further research are needed (Mason et al., 2012). Hence children have been historically considered to be "therapeutic orphans" because of the lack of robust data on the safety and efficacy of drug use in children (Shirkey, 1999; Shirkey, 2006).

Historically, children have been the preferred subjects to conduct drug development research–especially vaccine research–as they were considered easy to control and previously unexposed to immune-modulating infections. For example, Edward Jenner first tested the smallpox vaccine on his own children. Jenner's vaccine was later tested in Philadelphia in 1802 on 48 children (Burns, 2003). However, this changed dramatically after events such as Elixir of Sulfanilamide Tragedy and the Thalidomide Disaster (Shirkey, 1999). Changes in drug regulation resulted in the unintended but very real consequence of children being excluded from most drug research, resulting in the 'therapeutic orphan' status described above (Wilson, 1999). Over the past 2 decades this has been increasingly recognized as a problem and legislative and policy changes have addressed this. Currently, drug approval regulations and ethical principles have facilitated the enrollment of children in many trials of new drugs (NICHD, 2020). However as noted above this does not apply to older drugs, which are the most commonly prescribed to children. This review discusses the current knowledge of model-based evaluation of safety of antimicrobials in children highlighting the available models to expand our knowledge and capability to predict and mange ADRs in children.

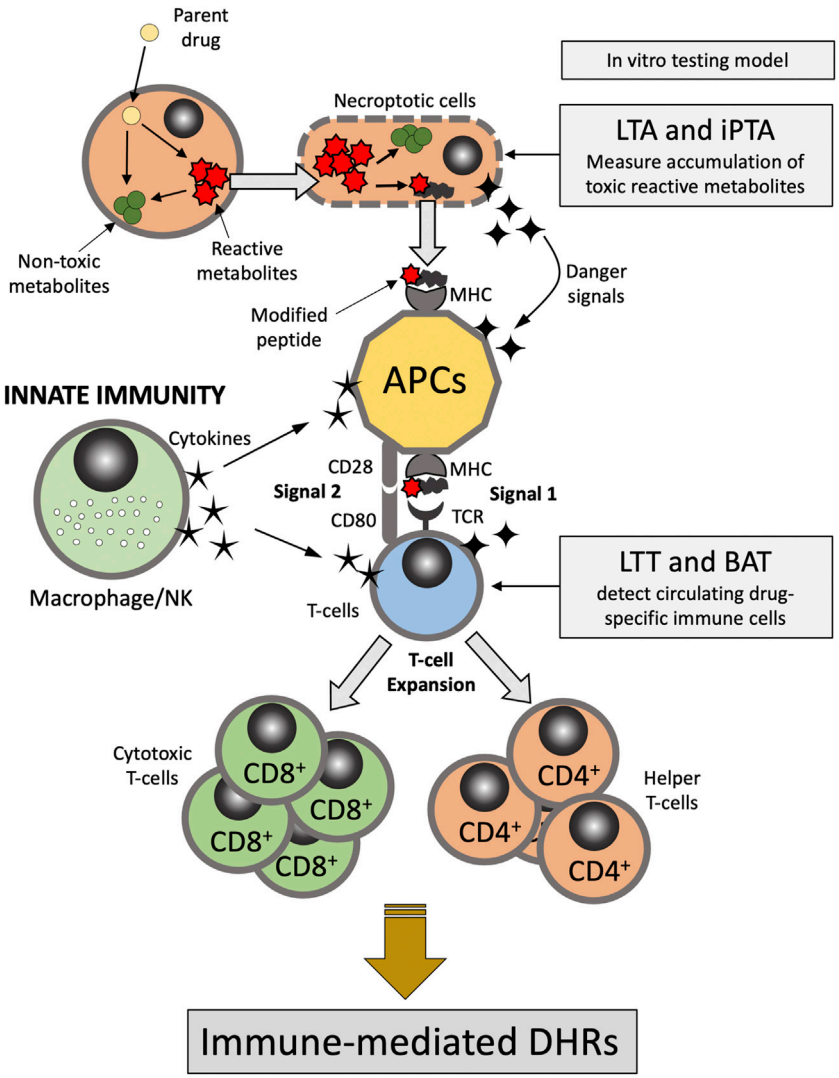

FIGURE 1 | Pathophysiology of delayed-type DHRs. APC, antigen presenting cells; BAT, basophil activation test; DHRs, drug hypercreativity reactions; iPTA, *in vitro* platelet toxicity assay; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test; MHC, Major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

PATHOPHYSIOLOGY AND ETIOLOGY OF DRUG HYPERSENSITIVITY REACTIONS

There are multiple hypotheses exist that attempt at exploring the metabolic and immune mechanisms underlying DHRs. The "hapten hypothesis" proposes that drugs (or their metabolites) form covalent adducts with endogenous macromolecules (e.g., proteins), which then can be recognized by the immune system as a "non-self" antigen (Roujeau, 2006). The "danger hypothesis" assumes that in order for a full immune system response to be mounted, immune cells have to be primed by mediators released from apoptotic or necroptotic cells (dead or dying cells) (Pirmohamed et al., 2002). The "reactive metabolite hypothesis" proposes that accumulation of reactive metabolites (RMs) due to imbalance between the generation and detoxification/elimination of these RMs is the first step in the cascade of events leading to the development of the DHRs (**Figure 1**). In addition, "the pharmacological interaction of drugs with the immune system (p-i) hypothesis" postulates that drugs or their metabolites can directly and non-covalently interact and activate immune cells causing DHRs (Chen et al., 2018; Pichler, 2019). Evidence also exist that supports the concept of drug-induced alteration in the self-peptide repertoire presented in the context of the major histocompatibility complex (MHC) molecules by antigen presenting cells to T-cells. This has provided explanation as to the role of human leukocyte antigen (HLA) genetic variation in the pathophysiology of DHRs (e.g., abacavir-induced DHRs) (Illing et al., 2012; Ostrov et al., 2012). Understanding DHRs pathophysiology is crucial to the development and interpretation of *in vitro* tests for drug hypersensitivity as discussed further below.

EVALUATION AND MANAGEMENT OF DRUG HYPERSENSITIVITY REACTIONS TO ANTIMICROBIALS

Drug hypersensitivity always represents a major challenge to clinicians as the predicament of "to discontinue or not to discontinue" the suspected drug is often a difficult decision especially if no alternative drug is available or if alternative therapy is considered inferior in respect to outcome. Current clinical practice include detailed review of medical history; however, identifying the culprit drug may be complicated by polypharmacy. Careful physical examination and investigation of signs and symptoms including type of skin rash (e.g., urticarial, maculopapular, purpuric, bullous or eczematous) may aid differentiating drug-induced reactions from other disease conditions such as viral or bacterial infections. One method to exclude drugs is to find out whether the patient has tolerated the drug in the past, although this is not absolutely true in all cases as patients may develop reaction to drugs after taking them for years, notably in the case of Type I allergic reactions (Roberts et al., 2020).

Over the recent years several international guidelines have been released summarizing recommendations and protocols for diagnosis and management of drug allergy and hypersensitivity reactions (Gomes et al., 2016; UK NCGC, 2014; Aberer et al., 2003; Brockow et al., 2015; Cardona et al., 2020; Doña et al., 2021; Doña et al., 2018; Gupta et al., 2017; Romano et al., 2020). Other algorithms and causality assessment tools have been developed to aid identifying the causative drugs such as the Naranjo scale (Naranjo et al., 1981). Algorithms to guide management of DHRs are available and always include careful medical history, skin testing, *in vitro* testing and DPT (Ariza et al., 2020). However, the clinical presentation of DHRs is always variable and complicated by polypharmacy, concomitant infection and other diseases. In the setting of infections, diagnosis of allergy is problematic. Blood tests such as measuring serum levels of the serine protease tryptase can be helpful for diagnosis of acute type-I allergic reactions, which are immediate and IgE-mediated including anaphylactic reactions (Schwartz et al., 1989). Elevation in serum tryptase is an indicator of mast cells degranulation but the test cannot differentiate between IgE-mediated and direct mast cell degranulation and may be elevated in both anaphylactic and anaphylactoid reactions (Schwartz, 2004). Serum tryptase peaks within 1–2 h of the acute reaction, so blood samples should be obtained within this time frame, although high serum tryptase levels may last for several hours and test may still of value. In addition, the test cannot identify the culprit drug (Mirakian et al., 2009). IgE specific assays such as the RAST may be useful but are very antigen specific. In addition, there is only limited number of antigens for which RAST assays are available.

There are certain classes of antimicrobial drugs that are most associated with eliciting DHRs. These include beta-lactam antibiotics, quinolone antibiotics, sulfonamides, dapsone, vancomycin, tetracyclines, aminoglycosides, clindamycin and metronidazole (Araujo and Demoly, 2008; Elzagallaai et al., 2011a; Sanchez-Borges et al., 2013; Kuyucu et al., 2014; Grinlington et al., 2020), however, theoretically, any antimicrobial drug can cause DHRs. Clinicians must be very suspicious if one of these classes of drugs appears on the patient medical history list when untoward events occur during therapy.

Many pharmacogenetic markers have been found to associate with antimicrobial-induced DHRs. Variants in genes such as NAT2 (Wolkenstein et al., 1995; Zielinska et al., 1998; Pirmohamed et al., 2000), HLA (Lonjou et al., 2008; Kongpan et al., 2015; Wong et al., 2020), and GCLC (Wang et al., 2012) have been reported to associate with sulfonamides-induced DHRs. Other genotypes and haplotypes have been found to associate with beta-lactam-induced DHRs (Yang et al., 2006; Daly et al., 2009; Lucena et al., 2011; Gueant et al., 2015; Rutkowski et al., 2017). Specific genetic variants have also been found to put patients at higher risk of developing DHRs to cephalosporins, quinolones, macrolides, and vancomycin (Kim et al., 2009; Barbaud et al., 2014). Pharmacogenetics of DHRs to drugs including antimicrobials have been recently reviewed elsewhere (Pavlos et al., 2012; Piccorossi et al., 2020; Stocco et al., 2020).

MODELING IN DRUG THERAPY

Many drug regulatory agencies around the world have recently issued mandates to promote drug development for children use that is evidence-based (Turner et al., 2014). However, conducting a large-scale detailed pharmacokinetics/pharmacodynamics (PK/PD) trials in children is a huge undertake even for major pharmaceutical companies and might not be feasible. In the United States, The Best Pharmaceutical for Children Act (BPCA), which became a law in 2002, has been put forward to encourage the pharmaceutical industry to perform studies to improve evidence-based pediatric drug therapy (NICHD, 2020). Model-based studies and application of simulation and pharmacometrics for pediatric therapy has gained momentum in recent years (Vinks et al., 2015). Pharmacometrics applies quantitative mathematical models of physiology, pharmacology and pathology to predict pharmacokinetics (PK) and pharmacodynamics (PD) parameters for the purpose of assessing drug efficacy and safety (Barrett et al., 2008). This recent concept has been applied in pediatrics to evaluate the influence of growth and development on drug disposition and toxicity (Anderson et al., 2006). However, data supporting model-based evaluation of antimicrobial-induced hypersensitivity reactions has been scarce and current guidelines do highlight this problem (Doña et al., 2018; Mirakian et al., 2009; Joint Task Force on Practice Parameters et al., 2010; Mirakian et al., 2015; Muraro et al., 2017).

Application of pharmacometrics methods in clinical practice give the ability to analyze pharmacokinetics profile and define the optimal doses of drugs in special populations such as children, in whom drugs are not usually studied during clinical trials (Sutherland et al., 2019). It is also possible to quantify dose-response relationships in these populations (Lala, 2012). Pharmacometrics methods are also more cost effective than clinical trials to generate information used in optimization of drug therapy (Gobburu, 2020). This is what makes pharmacometrics methods very attractive alternative to clinical trials especially in the pediatric populations. However, accuracy of model prediction is largely dependent on the quality of the original data used during modeling (Liu and Ward, 2019).

The selection of a model is driven by the pathophysiology believed to be responsible for the ADR. For instance, in the case of

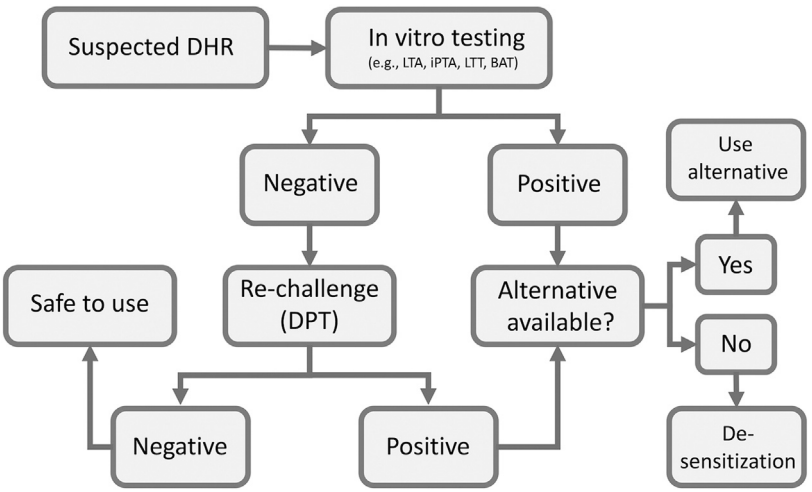

FIGURE 2 | Flow chart of clinical assessment of suspected DHRs. BAT, basophil activation test; DPT, drug provocation test; iPTA, *in vitro* platelet toxicity assay; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test.

DHRs there are several distinctly different immune mediated pathways producing adverse events. As eluted to in previous section, immediate events such as penicillin-induced anaphylaxis is typically mediated by IgE (Gell and Coombs Type I Hypersensitivity) (**Table 1**). In contrast, delayed onset DHR such as Stevens-Johnson Syndrome and Serum Sickness Like Reactions appear to be mediated by specific T cell subsets. Thus, the model system employed should be tailored around the putative pathogenesis of the ADR of interest (**Figure 1**). The principle of the lymphocyte toxicity assay (LTA) and the *in vitro* platelet toxicity assay (*i*PTA) tests is based on the hypothesis that DHRs are developed as a result of accumulation of toxic reactive metabolites (RMs) resulting in induction of necroptosis and release of intracellular "danger signals", and haptenation of endogenous peptides that can be recognized by the immune system (Matzinger, 2002; Pirmohamed et al., 2002). The LTT and BAT tests detect circulating drug-specific immune cells (lymphocytes and basophil, respectively), which are thought to mediate the immune reaction (Nyfeler and Pichler, 1997; Pichler and Tilch, 2004; Hausmann et al., 2009; Marraccini et al., 2018). Role of the *in vitro* testing model is discussed further below.

DRUG PROVOCATION TEST

Drug provocation test (DPT) or drug re-challenge is the controlled administration of the suspected drug under close medical observation for the purpose of diagnosing DHRs. DPT is considered by many guidelines in the field as the "gold standard" for DHRs diagnosis (Aberer et al., 2003). However, the main limitation of the test is possibility of provoking a full reaction, which makes it contraindicated in cases of severe life-threatening DHRs. Therefore, it is only performed if other *in vitro* tests are negative or cannot confirm diagnosis (**Figure 2**). The test is also contraindicated for pregnant patients and patients with severe comorbidities that put them at high risk. Co-medication with drugs that may interfere with emergency treatments (e.g., adrenergic beta-blockers), mask symptoms of positive response (e.g., H_1 antihistamines, corticosteroids, ipratropium bromide, leukotriene modifiers and long acting theophylline) or aggravate the reaction (e.g., ACE inhibitors) is contraindicated during DPT (Messaad et al., 2004). Prior to deciding to perform the test a careful medical history of the patient is crucial to determine the nature of previous exposure

TABLE 1 | Classification of immune-mediated DHRs.

Type	Mechanism	Example	Drugs most commonly involved with DHRs
I	IgE-mediated	Anaphylaxis, urticaria, bronchospasm, and rhinitis	Beta-lactam antibiotics, ACE inhibitors, NMBAs, radiocontrast media, NSAIDs, and opioids
II	IgG-mediated	Blood cell dyscrasia	Penicillins, sulfonamides, aromatic anticonvulsants, quinine, heparin, thiazides, and gold salts
III	IgG/ M-mediated	SSLR, vasculitis	Cephalosporins (e.g., cefaclor), infliximab, allopurinol, and bupropion
IV	T-cell-mediated	DRESS, SJS, TEN, AGEP, ME, and FDE	Sulfonamides, nevirapine, aromatic anticonvulsants, NSAIDs, dapsone, allopurinol, abacavir, and minocycline

ACE, angiotensin converting enzyme; AGEP, acute generalized exanthematic pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; FDE, fixed drug eruption; ME, maculopapular exanthema; NMBAs, neuromuscular blocking agents; NSAIDs, non-steroidal anti-inflammatory drugs; SJS, Steven's Johnson syndrome; SSLR, serum sickness-like reactions; TEN, toxic epidermal necrolysis.

TABLE 2 | *In vitro* test used for DHRs and their advantages and limitations.

Test	Advantages	Limitations
Lymphocyte toxicity assay (LTA)	• Can be performed before, during or after the reaction (i.e., used for prediction and diagnosis of DHRs) • It detects the genetic predisposition of the patient to develop DHRs • Several drugs can be tested at the same time • Can be used to identify the culprit drug among multiple drugs	• Complicated procedure that is both labor intensive and costly • Mainly confined to well-equipped research centers • Its predictive value largely depends on the suspected drug • Has been validated for only a small number of drug classes
In vitro platelet toxicity assay (*i*PTA)	• Can be performed before, during or after the reaction (i.e., used for prediction and diagnosis of DHRs) • Has simpler and less expensive procedure than the LTA. • Its predictive value seems enhanced compared to the LTA. • It detects the genetic predisposition of the patient to develop DHRs • Can be used to identify the culprit drug among multiple drugs	• Recently developed and therefore, lacks inter-lab validation
Lymphocyte transformation test (LTT)	• Can be used for both immediate-and delayed-type DHRs • Several drugs can be tested at the same time • New readout systems (flow cytometry) have eliminated the need to use radioactive reagents	• Special technical skills and equipment are required making the test available in only few research centers • Low sensitivity • It can only be used after the reaction has occurred after recovery, therefore; cannot be used to screen vulnerable patients • Sensitivity and specificity depend on the drug involved and type of reaction
Basophil activation test (BAT)	• Very useful for diagnosis of suspected immediate-type DHRs • Recent flow cytometry applications have enhanced the test sensitivity • Commercial kits are now available • Has been used successfully for penicillins, NMBAs, NSAIDs, fluoroquinolones and RCMs	• Its procedure has not been standardized and inter-lab variabilities exist • Positive tests decrease over time post-reaction

and reaction type. For patients on multiple drugs, identifying the most likely causative drug can be aided by determining the temporal relationship between the time of the drug administration and the start of the reaction. Also, knowledge of the drugs that are most commonly associated with DHRs and clinical experience with the clinical presentation of the disease is very helpful in zeroing on the culprit drug. Some scoring algorithms are available that may help identifying drugs that are most likely be the cause of the reactions (Naranjo et al., 1981) and a standardized questionnaire has been published (Demoly et al., 1999). The drug should, if possible, be given using the same route of administration that was originally used (i.e., oral, parenteral, topical), and should be started at low dose especially in case of severe reactions and stopped once the first signs of positivity appear (Bousquet et al., 2008).

The positivity of DPT for suspected antimicrobials and NSAIDs-induced DHRs is surprisingly low. In a single center study Vezir *et al.*(Vezir et al., 2014) reported a positivity rate of 6.8% indicating that medical history and clinical presentation are not reliable for diagnosis of DHRs and that DPT can be very useful to rule out suspected drugs.

IN VITRO TESTING MODEL

In vitro testing for DHRs has the advantage of carrying no potential harm to patients (Elzagallaai et al., 2009; Elzagallaai et al., 2011a). The selection of an *in vitro* diagnostic test for DHRs depends on the type of reaction (i.e., immediate vs delayed). Immediate IgE-mediated reactions are mediated by a specific IgE against the culprit drug and, therefore, quantification of those antibodies has been used to diagnose this type of reactions. Radioallergosorbent test (RAST), cellular fluorescent assay-IgE (CAP-IgE) and enzyme-linked immunosorbent assay (ELSA) have a good predictive value (Edwards et al., 1982). A radioactive technique is no longer used but, "RAST" has become generic name for IgE quantification. These tests tend to have an excellent specificity but very poor sensitivity and have been validated only for a few very specific drug-induced reactions (i.e., classical allergy or Gell and Coombs Type I Hypersensitivity) and only for a few drugs (Elzagallaai et al., 2011a). The basophil activation test (BAT) has been found useful in diagnosing immediate-type reactions to muscle relaxants, beta-lactam antibiotics and NSAIDs (Abuaf et al., 1999; Torres et al., 2004; Sanz et al., 2005; De Weck et al., 2009). The lymphocyte transformation test (LTT) measures drug specific T-cells in the circulation and it has been found to useful to aid diagnosis of delayed-type hypersensitivity reactions. However, due to its complected and expensive procedure, its clinical utility has been limited to highly sophisticated research center (Elzagallaai et al., 2011a). The lymphocyte toxicity assay (LTA) and the *in vitro* platelet toxicity assay (iPTA) are both very useful for delayed-type reactions and have been validated for DHRs due to multiple drug classes (Elzagallaai et al., 2010; Elzagallaai et al., 2011b; Elzagallaai et al., 2013). Both tests measures accumulation of toxic reactive drug metabolites (RMs) in peripheral blood monocytes (PBMCs) isolated from the patient and a healthy control. Cells that accumulate higher concentrations of RMs and lack defense against oxidative stress generated by these RMs undergo cell death (necroptosis), which can be measured using different techniques and expressed as percentage of control (vehicle

without the drug) (Elzagallaai et al., 2009). A cut-off value of 20% increase in cell death is used to identify positive tests. It is not well characterized how accumulation of RMs lead to eliciting immune-mediated ADR, but it seems to be the first trigger in the cascade of events leading to the reaction manifestations (Cho and Uetrecht, 2017).

The available *in vitro* tests tend to have good specificities and positive predictive values, but their sensitivities and negative predictive values are much affected by the test procedure and the readout systems (Elzagallaai et al., 2009; Elzagallaai et al., 2011a). Other factors that may affect the performance of *in vitro* testing include the time of testing in relation to the beginning of the reaction, the severity of the reaction and type of drug involved (Elzagallaai et al., 2009). Our experience with the recently developed iPTA supports its enhanced sensitivity but more work is needed to define its role in the diagnosis of DHRs (Elzagallaai et al., 2011b; Elzagallaai et al., 2013). These *in vitro* models may serve as logical first step in the management of DHRs (**Figure 2**). Their main limitation if their technical complexity, availability and cost, which make them confined to well-equipped sophisticated research centers with adequate expertize to perform and interpret the tests. We have been using the *in vitro* toxicity assays (the LTA and later the iPTA) for over 25 years and found them very useful and practical with reasonable turnaround time. In our experience with some care blood samples can be packaged and shipped internationally with good stability and minimal cost. **(Table 2)**

ANIMAL MODELS

Use of animal models to evaluate age-specific risk of toxicity is practical and may guide dosing in human children. In addition, the shorter life span of laboratory animals permits detection of long-term effects of toxicities that is normally appears after decades in human subjects. The pitfalls of using animal models to predict drug safety in human children include variability in systems development among animals species and lack of validated animal models for many drug classes (Berde and Cairns, 2000). DHRs are idiosyncratic in nature, which makes them unpredictable. Animal models to predict DHRs would be a very attractive tool for drug developers and health care providers, however, finding a suitable animal model for DHRs has so far proven to be illusive. Animals do develop hypersensitivity reactions to drugs and other xenobiotics but with the same unpredictability as in people (Bloom, 2006; Voie et al., 2012). The pathophysiology underlying DHRs is not fully understood and multiple metabolic and immunologic factors are thought to contribute to the development of these types of reactions.

Attempts at validating animal models to study or predict DHRs have not been very successful (Uetrecht, 2006). One exception to that is the female Brown Norway rats which has been demonstrated to be a model for nevirapine-induced skin rash model (Shenton et al., 2003). In this model Shenton *et al.* (Shenton et al., 2003) were able to induce skin rash in 32/32 (100%) of female Brown Norway rats with nevirapine at dose of 150 mg/kg/day. Interestingly, lower doses of 40–75 mg/kg/day did not lead to skin rash development and protected treated rats from nevirapine-induced skin rash when treated afterward with 150 mg/kg/day (Shenton et al., 2003). Further studies on this model demonstrated that a hydroxy metabolite of nevirapine (12-OH-neverapine) is responsible for the skin rash reaction (Sharma et al., 2013).

The usefulness of an animal model to study a disease depends on how closely the model resembles the actual condition (Scarpelli, 1997). In case of DHRs the clinical presentation of the disease is poorly defined making designing an animal model for the condition an unreachable task without more phenotypic clarity. An additional factor is that patients may develop DHRs to multiple drugs and a reaction to the same drug may present in different ways in different people and, sometimes, in the same patient (Perez-Ezquerra et al., 2006; Pichler et al., 2017). All these factors have hampered any progress in developing animal models to investigate or predict DHRs. This has been a major impediment in research in this area.

MODEL-BASED EVALUATION

Figure 1 summarizes a scheme for evaluation and management of DHRs. Medical history, blood work, allergy work up and scoring algorithms are all utilized early on to assess the probability of a DHR. *In vitro* tests are the first choice giving their safety to the patient. *In vitro* tests often have high specificity and positive result exclude DPT. However, after considering the contraindications, DPT can be performed if the *in vitro* test used is negative. Negative DPT indicates that the drug is safe to use. Positive *in vitro* test or DPT mandate that an alternative drug must be considered. If no alternative drug is available, desensitization procedure should be attempted, a process that depends on the clinician judgment on case-by-case basis.

CONCLUSION

In terms of drug development, use of modeling for assessment of drug safety for antimicrobials has been hampered by both a lack of suitable animal models and by a lack of understanding of the putative pathophysiology of DHRs. As our understanding of the fundamental biology of DHRs expands and our ability to develop humanized animal increases it is hoped that this will enable better modeling of DHRs to antimicrobial therapy in children. This review summarizes the current state-of-the-art knowledge of model-based evaluation of DHRs to antimicrobials in children. Several key issues in the field have been highlighted, which include lack of animal model to study the molecular pathophysiology of DHRs and limited validated *in vitro* tests with good predictive values. We believe that further understanding of the exact pathophysiology underlying DHRs will allow the development of more predictive models to optimize the management of these ADRs.

AUTHOR CONTRIBUTIONS

MR conceived of the idea, jointly wrote the first outline with AE and edited subsequent drafts. AE jointly wrote the first draft with MR, edited subsequent drafts and submitted the final manuscript.

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Latamoxef for Neonates With Early-Onset Neonatal Sepsis: A Study Protocol for a Randomized Controlled Trial

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Early-onset neonatal sepsis (EONS), a bacterial infection that occurs within 72 h after birth, is associated with high likelihood of neonatal mortality. Latamoxef, a semi-synthetic oxacephem antibiotic developed in 1980s, has been brought back into empirical EONS treatment in recent years. In the preliminary work, we established a population pharmacokinetics (PPK) model for latamoxef in Chinese neonates. Moreover, in order to better guide clinical treatment, we conducted dose simulation and found that ascending administration frequency could improve the target rate of 70% of patients having a free antimicrobial drug concentration exceeding the MIC during 70% of the dosing interval (70% fT > MIC). Accordingly, this study is aimed to compare the 70% fT > MIC, efficacy and safety between conventional regimen and PPK model regimen for rational use of latamoxef in EONS treatment. A single-blind, multicenter randomized controlled trial (RCT) for latamoxef will be conducted in Chinese EONS patients. Neonates (≤3 days of age, expected number = 114) admitted to the hospital with the diagnosis of EONS and fulfilling inclusion and exclusion criteria will be randomized (ratio of 1:1) to either a conventional regimen (30 mg/kg q12h) or model regimen (20 mg/kg q8h) latamoxef treatment group for at least 3 days. Primary outcome measure will be 70% fT > MIC and secondary outcome indicators will be the latamoxef treatment failure, duration of antibiotic therapy, changes of white blood cell count (WBC), C-reactive protein (CRP) and procalcitonin (PCT), blood culture results during administration and incidence of adverse event (AE)s. Assessments will be made at baseline, initial stage of latamoxef treatment (18–72 h) and before the end of latamoxef treatment. Ethical approval of our clinical trial has

been granted by the ethics committee of the Beijing Children's Hospital (ID: 2020-13-1). Written informed consent will be obtained from the parents of the participants. This trial is registered in the Chinese Clinical Trial Registry (ChiCTR 2000040064).It is hoped that our study will provide a clinical basis for the rational clinical use of latamoxef in EONS treatment.

Keywords: latamoxef, early-onset neonatal sepsis, neonate, randomized controlled trial, study protocol

INTRODUCTION

Neonatal sepsis, a leading cause of mortality in neonates worldwide, is divided into early-onset (EONS) and late-onset neonatal sepsis (LONS) (Polin, 2012; Shane et al., 2017). EONS occurs within 72 h after birth and the mortality rate of EONS was reported as high as 30% in high-income countries and up to 60% in low-income countries (Thaver and Zaidi, 2009; Stoll et al., 2011). Accordingly, rational anti-infective treatment of EONS plays a crucial role in preventing neonatal mortality and protecting the health of neonates. However, antibiotic resistance, off-label use and adverse reactions plague EONS treatment. Because the prevalence of antibiotic-resistant bacterial strains has increased dramatically, recently there has been a renewed interest in historical antibiotics for EONS treatment (Thaver and Zaidi, 2009; Stoll et al., 2011), such as latamoxef. Latamoxef, a second-generation semi-synthetic oxacephem antibiotic, developed in 1980s, is mainly used to treat infections, caused by Gram-positive and -negative aerobic, as well as anaerobic bacteria (Carmine et al., 1983). Although latamoxef has been used for the anti-infective treatment of neonates since 1980s, limited neonatal pharmacokinetics (PK) data and off-label use remain a vexing problem for this drug being used in the field of EONS treatment.

To assess the PK features of latamoxef in neonates, we performed a population pharmacokinetics (PPK) study of latamoxef in Chinese neonates and established a PPK model for them (Carmine et al., 1983). Current body weight, birth weight, and postnatal age have been identified as significant covariates influencing latamoxef clearance (Qi et al., 2019). Moreover, to develop a rational dosing regimen for latamoxef, we conducted dose simulation and found that ascending administration frequency could improve the target rate of 70% of patients having a free antimicrobial drug concentration exceeding the MIC during 70% of the dosing interval (70% fT > MIC) (Qi et al., 2019). Based these findings, to provide more pharmacodynamics (PD) data for generalizing this PPK model-based regimen, we plan to conduct a single-blind, multicenter randomized controlled trial (RCT) and compare the 70%fT > MIC, efficacy and safety between conventional regimen and PPK model regimen for latamoxef in EONS treatment for the first time.

METHODS AND DESIGN

Trial Design

The proposed clinical trial will be a randomized, single-blind and multicenter intervention study for latamoxef in EONS treatment. This trial is registered in the Chinese Clinical Trial Registry (ChiCTR 2000040064) and is in full adherence to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. This trial will be conducted at three hospitals in China (**Table 1**), and 114 EONS patients will be randomly enrolled to two regimen groups with a ratio of 1:1 from November 2020 to December 2021. The schematic diagram of study design is shown in **Figure 1**.

Ethics and Dissemination

Our research group will protect the rights and safety of participants by full compliance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Ethical approval of this trial has been granted by the ethics committee of the Beijing Children's Hospital (ID: 2020-13-1). Written informed consent will be obtained from the parents of the participants. Adequate measures will be taken to ensure confidentiality of data collected in this trial. Results of this trial will be disseminated to the public through relevant academic and professional journals, academic conferences and workshops.

Diagnostic Criteria of Early-Onset Neonatal Sepsis

The diagnostic criteria of EONS will refer to expert Consensus on the Diagnosis and Management of Neonatal sepsis (version 2019) (The Subspecialty Group of Neonatology, 2019).

1) The suspected diagnosis of postnatal age in days (PNA) ≤3 contains any of the following: abnormal clinical manifestations, the mother has chorioamnionitis and premature rupture of membranes (PROM) ≥18 h. Sepsis can be ruled out if there are no abnormal clinical manifestations, including negative blood culture, and less than two consecutive non-specific blood tests (white blood cell count, immature neutrophil count, platelet count, C-reactive protein (CRP) and procalcitonin (PCT), etc.) at 24 h intervals.

TABLE 1 | Hospitals participating in this RCT.

Code	Participating hospitals
1	Beijing friendship hospital
2	Beijing obstetrics and gynecology hospital
3	Children's hospital, Capital institute of pediatrics

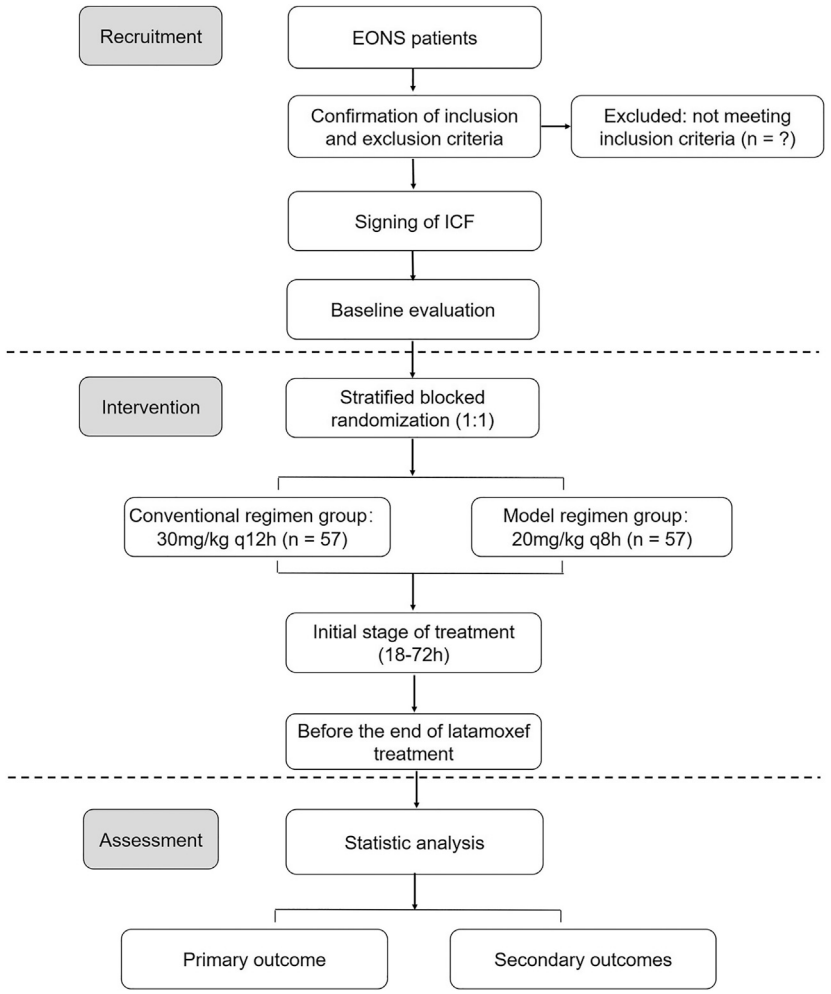

FIGURE 1 | The schematic diagram of the trial design.

TABLE 2 | Clinical manifestations of neonatal sepsis.

System	Clinical manifestations
Whole body	Fever, hypothermia, poor response, poor feeding, edema, low apgar score
Digestive system	Jaundice, abdominal distension, vomiting or gastric retention, diarrhea and hepatosplenomegaly
Respiratory system	Dyspnea, apnea, cyanosisetc.
Circulatory system	Pale face, cold limbs, bradycardia, tachycardia, marbled skin, hypotension or capillary filling time >3 s
Urinary system	Oliguria and renal failure
Blood system	Bleeding and purpura

2) The patient has been clinically diagnosed with clinical abnormalities (**Table 2**) and met any of the following conditions at the same time: the blood non-specific tests ≥2 positive, the cerebrospinal fluid (CSF) test suppurative meningitis change, the pathogenic DNA detected in the blood.
3) When the patient has clinical manifestations (**Table 2**), blood culture or CSF (or other sterile cavity fluid) culture positive, and the diagnosis confirmed.

Inclusion Criteria

Patients will be recruited for this study if they meet all of the following criteria:

1) PNA ≤ 3;
2) Term infants and preterm infants with gestational age (GA) ≥ 32 weeks;
3) The EONS diagnostic criteria;

TABLE 3 | Study schedule of latamoxef RCT in EONS treatment.

Items	Study phases (The beginning of latamoxef treatment is set as 0 h)		
	Baseline (−3–−1 day)	Initial stage of treatment (18–72 h)	Before the end of latamoxef treatment
Informed consent form (ICF)	X		
Demographic information	X		
Medical history	X		
Diagnosis and determination of the treatment regimen	X		
Inclusion/exclusion criteria	X		
Get the random number	X		
Comorbid drug use	X	X	X
Weight	X	X	X
Vital signs[a] and physical examination	X	X	X
Blood routine[b]	X	X	X
Blood culture	X	X	X
CRP and PCT	X	X	X
Liver and kidney function[cd]	X	X	X
Cerebrospinal fluid (CSF) examination (optional)[e]	X	X	X
Dose, frequency and time point of latamoxef administration		X	X
Detection of plasma latamoxef concentration		Random sampling point	
Sampling time of plasma samples		X	
Efficacy assessment			X
Adverse event assessment		X	X
Case report form (CRF)	X	X	X

[a]*Vital signs include the temperature, blood pressure and oxygen saturation (SaO_2).*
[b]*Blood routine tests include red blood cells, hemoglobin, white blood cells, and platelets.*
[c]*Liver function tests include alanine and aspartate aminotransferases, alkaline phosphatase level, total bilirubin, and gamma-glutamyl transferase.*
[d]*Kidney function tests include creatinine and blood urea nitrogen.*
[e]*CSF examination include CSF routine (characters, cells and Pandy's test) and culture. This examination can be used when neonatologists suspect a patient has a neurological infection.*

4) Suitable for latamoxef treatment;
5) Written informed consent signed by the parent or legal guardian of the neonates.

Exclusion Criteria

Patients with any of the following exclusion criteria shall not be admitted to this study:

1) Expected survival time shorter than the duration of the treatment cycle;
2) Severe congenital malformations;
3) Having the high risk of serious bleeding, such as disseminated intravascular coagulation (DIC) and Vitamin K deficiency bleeding (VKDB) (Rajagopal et al., 2017; Araki and Shirahata, 2020):
   A. Decreased platelet count ($\leq 150 \times 10^9$/L);
   B. Significantly prolonged prothrombin time (PT, especially PT is more than twice over upper limit of the normal range);
   C. Prolonged activated partial thromboplastin time (APTT, is more than the upper limit of the normal range);
   D. INR ≥4 or a value >4 times the normal values in the presence of normal platelet count and fibrinogen level;
4) Undergoing surgery within the first week of birth;
5) Receiving other trial drug treatment;
6) Having other factors that researchers believe are not suitable for inclusion.

Recruitment Strategies

Inpatient neonates will be enrolled from Beijing Friendship Hospital, Beijing Obstetrics and Gynecology Hospital, and Children's Hospital, Capital Institute of Pediatrics (**Table 1**). We'll use advertisements for recruitment on social media, such as WeChat, QQ, etc. Associate chief physicians in the neonatal units of these three hospitals will be in charge of EONS patient recruitment.

Randomization and Blinding

To minimize selective bias, Beijing Six Yuan Space Information Technology Co., Ltd (Six Yuan) has been entrusted to conduct a stratified blocked randomization by using a computer random number generator in the system of Six Yuan. Participants will be randomly divided into the conventional treatment group and the model treatment group with a ratio of 1:1. The randomized code of the trial, derived from the random system of Six Yuan, will be the unique identification code of participants. After assignment of the randomization code, researchers are un-blinded to the treatment regimen of latamoxef. Considering that the drug concentration detection and data analysis will significantly affect the conclusion of this trial, all the research assistants in charge of drug concentration detection and statisticians will be blinded to treatment assignment until the trial is completed.

Intervention

After inclusion in the study, participants will be randomized into a conventional treatment group and a model treatment group. They will receive the following interventions at least 3 days. Conventional treatment group: latamoxef, 30 mg/kg q12h; model treatment group: latamoxef, 20 mg/kg, q8h. As steady-state plasma concentration of latamoxef will be reached after 18 h

of dosing, the opportunistic blood sampling method will be used to collect samples for testing plasma drug concentration at initial stage of the treatment (18–72 h) (**Table 3**).

Outcome Measures

Primary Outcome

The primary outcome will be 70% fT > MIC, which is the target rate of 70% of patients having a free antimicrobial drug concentration exceeding the MIC during 70% of the dosing interval. 70% fT > MIC is appropriate to evaluate therapeutic efficacy of time dependent antibiotics in neonates (Craig, 1995; Wu et al., 2020). Based on PPK model of latamoxef, 70% fT > MIC will be calculated after testing plasma drug concentration at the initial stage of treatment (**Table 3**).

Secondary Outcomes

This trial has five secondary outcomes:

1) Rate of latamoxef treatment failure: the symptoms and laboratory indicators of infection persist or worsen after latamoxef treatment. Neonatologists have to increase of the dose of latamoxef, or add other antibiotics to the treatment with latamoxef, or stop latamoxef treatment and switch to other antibiotics.
2) Duration of antibiotic therapy: the length of antibiotic therapy for EONS;
3) Changes of white blood cell count (WBC), CRP and PCT: comparison of the changes of WBC, CRP and PCT at baseline, initial stage of treatment (18–72 h) and before the end of treatment (**Table 3**);
4) Blood culture results during administration: comparison of blood culture results at baseline, initial stage of treatment (18–72 h) and before the end of treatment (**Table 3**);
5) Incidence of adverse events (AE)s: monitoring and recording AEs during latamoxef therapy (**Table 3**).

Safety and AE Monitoring

In this trial, safety will be monitored, including AEs, serious AEs, and withdrawals due to AEs. The safety indexes are mainly composed of the routine blood, liver function, kidney function, coagulation function and vital signs. AEs of latamoxef mainly include anaphylaxis (such as rashes, urticaria, and itching), gastrointestinal reactions (such as vomiting, diarrhea and abdominal pain), and other latamoxef associated AE (such as anaphylactic shock, elevated levels of aminotransferases and serious bleeding).

Sample Size Estimates

According to our preliminary PPK study and dose simulation for latamoxef in neonates (Qi et al., 2019), 60.2% of neonates using conventional treatment regimen (30 mg/kg q12 h) reached 70% fT > MIC and 80.1% of neonates using model treatment regimen (20 mg/kg q8h) reached 70% fT > MIC with MIC of 2 mg/L, respectively. We conducted sample size estimation for superiority design by using PASS 15.0 (NCSS, Kaysville, Utah, United States). To achieve a statistical power of 80% (one-sided type 1 error of 5%), the calculated sample size of each treatment group was 57 patients per treatment group (114 in total) with the ratio of 1:1. Taking into account a 10% dropout rate, 64 patients per treatment group (128 in total) will be required.

Study Data and Statistical Analysis Plan

The procedures and contents of data collection for this trial are detailed in **Table 2**. Demographic information, diagnosis, clinical data and laboratory data at baseline will be recorded on electronic case report form (eCRF) platform provided by Six Yuan (**Table 2**). In addition, clinical data, laboratory data and AEs at every planed time point after initiation of treatment will also be recorded in this eCRF platform (**Table 2**). According to the data collection methods and standards formulated by project director and researchers, all data of eCRF platform will be recorded in a true, detailed and careful manner to ensure the authenticity of the data.

Statisticians, independent of all the other processes, will conduct the statistical analyses by using SPSS version 15.0 for Windows (Chicago, IL, United States). The statisticians will calculate the mean, standard deviation, median, minimum, maximum, lower quartile (Q1), upper quartile (Q3) for quantitative data and describe numbers and percentages for qualitative data (Wang et al., 2020). Comparisons between two groups will be conducted as following: t-tests or Wilcoxon rank-sum for normal or nonnormal ability distributions for quantitative data; chi-square test or Fisher's exact test for qualitative data (Wang et al., 2020). Analysis for missing data performed on the intention-to-treat principle. For all analysis, p value < 0.05 will be considered statistically significant.

Quality Control

In order to ensure the quality of the trial, project director and researchers from each hospital have formulated detailed project implementation protocol and emergency plan at the beginning of this trial. During the clinical trial, researchers participating in this experiment shall undergo unified training to clarify and unify the recording methods and standards for data collection on the eCRF platform. Moreover, the clinical inspector, designated by the director, will make an inspection tour to each hospital periodically to ensure that the researchers strictly adhere to the clinical trial protocol and fill in the information correctly.

DISCUSSION

In our proposed study, based on our preliminary PPK-PD analysis of latamoxef in neonates, we are aimed to conduct a single-blind, multicenter RCT and compare the 70%fT > MIC, efficacy and safety between conventional regimen and PPK model regimen for latamoxef in EONS treatment for the first time. Our study will provide PD data for optimizing latamoxef usage in EONS treatment.

EONS, a serious threat for health of neonates, is mainly caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery (Hornik et al., 2012). The organisms involved in EONS are not identical in different countries and regions. In the developed countries, *Group B*

Streptococcus (*GBS*) and *Escherichia coli* (*E. coli*) are most frequently bacteria; in China, *E. coli* and *Coagulase-negative staphylococcus* (*CONS*) were the leading pathogenic bacteria (Jiang et al., 2019), followed by *Achromobacter xylosoxidans* (*A. xylosoxidans*) and *Klebsiella pneumoniae* (*K. pneumoniae*). Therefore, broad-spectrum cephalosporins are often used as an important anti-infective drug in the Chinese EONS treatment, such as latamoxef. However, due to the limited PK and PD neonatal data, the dosing guidelines and optimal treatment regimen of latamoxef cannot be applied in EONS treatment.

To ensure that the finding of this trial can comprehensively reflect PD characteristics of latamoxef in EONS treatment, 70% fT > MIC will be used as the primary outcome indicator, and efficacy and safety indexes will be employed as the secondary outcome indicators. Because there's no clinical evaluation of latamoxef in EONS treatment, the trial design is derived from other clinical trials about cephalosporin treatment or therapeutic decision conducted in children or neonates (Stocker et al., 2017; Wu et al., 2020). Rate of treatment failure, duration of antibiotic therapy, changes of inflammatory indicators, results of blood culture and incidence of AEs are commonly used indicators in efficacy and safety evaluation for anti-infective agents (Molyneux et al., 2011; Stocker et al., 2017). Since latamoxef is an oxacephem antibiotic that imparts time-dependent bactericidal effects, fT > MIC as a PD parameter is essential for efficacy evaluation of latamoxef. Although 40–50% fT > MIC is usually used in adult antimicrobial treatment, a goal of 70% fT > MIC is considered as a more conservative endpoint for avoiding treatment failure in immunologically immature neonates (Craig, 1995; Craig, 2001).

According to the bacterial susceptibility data of latamoxef in relation to the bacteria commonly observed in Chinese EONS patients, the MIC90 values of *E. coli* and *K. pneumoniae* were 1 mg/L and 2 mg/L (Cui Lan-Qing, 2016). Thus, 70% fT > MIC targets in two treatment regimens with MIC of 2 mg/L were applied as parameters in sample size calculation.

Our study had some limitations. First, since EONS patients often improve or recover at hospital discharge, follow-up is not designed in this trial. Hence our efficacy evaluation may miss some relapse situation after hospital discharge. Second, due to the few positive culture results and antimicrobial susceptibility results of bacteria in neonatal clinical practice, we chose 70% fT > MIC target with MIC of 2 mg/L in sample size calculation based on epidemiological microbiology data instead of individual microbiology. Finally, our study data are only from Chinese EONS patients in Beijing, limiting the generalizability to other populations and areas with different epidemiological microbiology data.

We hoped that our study can provide reliable data to support rational use of latamoxef in EONS treatment.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Beijing Children's Hospital (ID: 2020-13-1). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AS and WZ conceived and designed this study. HQ and YW wrote the manuscript with contributions from all authors. YL, CK, ZW, XP, LC, HC, YW, and JL refined the protocol. All authors contributed to the article and approved the submitted version.

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