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

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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 (Cmin) of 10 mg/L and pharmacokinetic/pharmacodynamic (PK/PD, [AUC24/MIC]) of 125 for moderate infection. For severe infection, the optimal dosing regimens were defined as achieving the target 15 mg/L and AUC24/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 severe infection. With standard maintenance doses, both patients with moderate and severe infection failed to achieve the target Cmin. 12 and 16 mg/kg/day were required to achieve a Cmin ≥ 10 and 15 mg/L, respectively. However, standard maintenance dose was adequate to achieve AUC24/MIC ≥ 125 for moderate infection, and 12 mg/kg/day was needed to achieve AUC24/MIC ≥ 345 for severe infection. Lower weight and serum creatinine were associated with higher dose.

Conclusion: Optimal doses based on the target Cmin were higher than that based on the PK/PD target. To achieve the Cmin 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 hydrophobic 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 (Cmin) 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), Cmin 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 Cmin were 48–89% (Sanchez et al., 1999; Strenger et al., 2013; Zhao et al., 2015). The mean Cmin 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 Cmin <10 mg/L (Strenger et al., 2013), and the overall mean Cmin 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 (AUC24/MIC) (Ramos-Martin et al., 2017a). AUC24/MIC goals of ≥250 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 regimen 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 and stored 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 a population approach 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, \( \chi^2 \) 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, \( \chi^2 \) 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).

\[
\text{PE} = \frac{\text{Model predicted concentration} - \text{Observed concentration}}{\text{Observed concentration}} \times 100\%
\]

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

**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 \( C_{\text{min}} \) were predicted by the day 3 of therapy. \( C_{\text{min}} \) at steady state was predicted for maintenance dosing (by the day 5). A dosage regimen was defined as optimal if mean \( C_{\text{min}} \) 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 AUC24/MIC target of 125 and 345. AUC24 was calculated in this study by the formula: AUC24 = 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 were 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:

\[
CL (L/h) = 0.0694 \times \left( 1 + \theta_1 \times \frac{WT}{16.71} \right) \times \theta_2^{(SCr/29.07)} \times e^{\eta_1}
\]

\[
V_d (L) = 1.39 \times \theta_3^{(WT/16.71)} \times e^{\eta_2}
\]

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%
and 52.4% of the variability of CL and Vd in the data, respectively. The shrinkage were 26.9% and 19.8% for CL and Vd, 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 $\pm 20\%$ for $C_{\text{min}} < 10\, \text{mg/L}$ was $94.8\%$ (55/58), and within $\pm 15\%$ for $C_{\text{min}} \geq 10\, \text{mg/L}$ 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 $\mu\text{mol/L}$) 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 $C_{\text{min}}$ achieved with different loading dose regimens. A standard loading dose of 10 mg/kg achieved a mean $C_{\text{min}}$ 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 $C_{\text{min}}$ 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 $C_{\text{min}}$ 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 $C_{\text{min}}$ 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 AUC24/MIC $\geq 125$. However, with an AUC24/MIC $\geq 345$, only CFR of 68.7–85.7% were obtained. A higher maintenance dose of 12 mg/kg/day achieved a CFR $\geq 90\%$ 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, %)3 | —      | —          |
| 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) | 8.8 ± 12.1 (10.3, 2.6–82.3) | 9.6 ± 5.6 (8.6, 2.5–29.5) |

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

aCreatinine clearance was calculated by the Cockcroft formula.

bThe number of patients co-medicated with at least one other anti-bacterial drug were summarized.

3Administered for three doses at the start of teicoplanin therapy.

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). 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 PKP 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).
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 Vd (1.85 L/kg) was showed compared with our and other studies (0.2–1.02 L/kg). The estimate of Vd 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 $C_{\text{min}}$ of only 12 mg/L achieved in this study. Sanchez reported that the mean

![Image of Figure 2](image-url)
same dose administered once daily, illuminating the 14 days when different loading doses were followed by the treatment. However, the difference appeared to vanish after loading dose could provide higher drug exposure at the start of loading doses of 10
\[ \theta \]

Residual variability (%)
IIV (%)

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Parameters Final model Estimates based on 1,000 bootstrap replicates*

| Parameters | Estimate values | Relative standard deviation (%) | Mean | 95% confidence interval |
|------------|-----------------|---------------------------------|------|------------------------|
| CL (L/h)   | 0.0694          | 11.3                            | 0.0718 | 0.0453–0.0983         |
| Vd (L)     | 1.39            | 11.0                            | 1.77 | 1.34–2.20             |
| \( \theta \) on CL | 2.82        | 20.6                            | 3.62 | 1.21–6.03             |
| \( \theta \) on CL | 0.882      | 5.0                             | 0.794 | 0.688–0.9             |
| \( \theta \) on Vd | 1.75        | 6.3                             | 1.76 | 1.29–2.23             |
| IV (%)     |                |                                 | 64.1 | 57.3–71.9             |
| CV-CL      | 65.9            | 17.6                            | 69.6 | 43.8–90.5             |
| CV-Vd      | 61.0            | 42.5                            |      |                        |
| Residual variability (%) |                |                                 | 8.5  | 5.1–11.9               |

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

C\( \text{min} \) 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\( \text{min} \) 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\( \text{min} \) of 5.6–9.4 mg/L, which are in agreement with the C\( \text{min} \) 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\( \text{min} \) 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\( \text{min} \) above 10 mg/L and all patients attain C\( \text{min} \) > 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\( \text{min} \) 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\( \text{min} \) 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\( \text{min} \) of > 15 mg/L. The reasons are as follows: 1) The maintenance dose based on the C\( \text{min} \) targets are higher than that based PK/PD targets. In other words, maintenance dose based on the C\( \text{min} \) targets could achieve both microorganism-nonspecific and microorganism-specific targets simultaneously. It is worthy to be noticed that the two evaluation criteria, mean C\( \text{min} \) of 10 (15) mg/L and AUC\( _{24} \)/MIC \( \geq \) 125 (345), are not in correspondence. It
would be more reasonable to define a dose achieving 90% of patients with a $C_{\text{min}}$ 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 $C_{\text{min}}$ target attainment rates in such situation. Gao et al. reported dosing regimens for Chinese pediatrics to achieve the $C_{\text{min}}$ 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

### TABLE 3 | Optimal dosing regimens achieving target teicoplanin $C_{\text{min}}$ at 48 h for loading dose regimens and at day 5 for maintenance dose regimens, and AUC24/MIC for moderate and severe infection$^a$.

| Subgroup | Moderate infection | Severe infection |
|----------|--------------------|-----------------|
|          | $C_{\text{min}} \geq 10$ mg/L | AUC24/MIC $\geq 125$ | $C_{\text{min}} \geq 15$ mg/L | AUC24/MIC $\geq 345$ |
|          | Loading dose | Maintenance dose | Maintenance dose | Loading dose | Maintenance dose | Maintenance dose |
| WT < 10  | 10 mg/kg q12h x 3 | 14 mg/kg q24h | 6 mg/kg q24h | 15 mg/kg q12h x 3 | 20 mg/kg q24h | 16 mg/kg q24h |
| SCr < 44 |           |                |                |           |                |                |
| 10 $\leq$ WT $< 20$ | 10 mg/kg q12h x 3 | 12 mg/kg q24h | 6 mg/kg q24h | 14 mg/kg q12h x 3 | 18 mg/kg q24h | 12 mg/kg q24h |
|          |           |                |                |           |                |                |
| 20 $\leq$ WT $< 30$ | 10 mg/kg q12h x 3 | 8 mg/kg q24h | 6 mg/kg q24h | 10 mg/kg q12h x 3 | 14 mg/kg q24h | 12 mg/kg q24h |
|          |           |                |                |           |                |                |
| WT $\geq 30$ | 10 mg/kg q12h x 3 | 6 mg/kg q24h | 6 mg/kg q24h | 10 mg/kg q12h x 3 | 12 mg/kg q24h | 10 mg/kg q24h |
|          |           |                |                |           |                |                |
| Overall  | 10 mg/kg q12h x 3 | 12 mg/kg q24h | 6 mg/kg q24h | 10 mg/kg q12h x 3 | 16 mg/kg q24h | 12 mg/kg q24h |

Abbreviations: $C_{\text{min}}$, trough concentration; WT, weight (kg); SCr, serum creatinine ($\mu$mol/L); AUC24/MIC, the ratio of the 24-h area under the curve to the minimum inhibitory concentration.

$^a$Cmin $\geq 10$ mg/L and AUC24/MIC $\geq 125$ were defined as the target values for moderate infection; Cmin $\geq 15$ mg/L and AUC24/MIC $\geq 345$ were defined as the target values for severe infection.
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 $C_{\text{min}}$ correlates with AUC$_{24}$ strongly (Cazaubon et al., 2017; Zhao et al., 2015), which make it possible for $C_{\text{min}}$ as a surrogate of AUC$_{24}$. In the present study, the mean $C_{\text{min}}$ 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 5](image1.png) Mean teicoplanin $C_{\text{min}}$ 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 $C_{\text{min}}$ was simulated by day 3 (48 h). The dashed red line and blue line indicate the target $C_{\text{min}}$ of 10 mg/L (moderate infection) and 15 mg/L (severe infection), respectively.

![FIGURE 6](image2.png) Mean teicoplanin $C_{\text{min}}$ 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 $C_{\text{min}}$ was simulated by day 5 (96 h). The dashed red line and blue line indicate the target $C_{\text{min}}$ of 10 mg/L (moderate infection) and 15 mg/L (severe infection), respectively.
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 \( C_{\text{min}} \) target attainment rate (Tobin et al., 2010). 3) Children have demonstrated a higher \( \text{CL} \) of teicoplanin than adults (Rowland, 1990; Tarral et al., 1988).

In the adults study published previously, seven out of ten of the teicoplanin \( \text{CL} \) 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 \( C_{\text{min}} \geq 60 \text{ mg/L} \) 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 \( C_{\text{min}} \) 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 \( C_{\text{min}} \) 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 \( \geq 125 \) 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 \( C_{\text{min}} \) with efficacy, 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 \( C_{\text{min}} \) 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 \( C_{\text{min}} \) 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 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.

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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.

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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