

Therapeutic Drug Monitoring and Nephrotoxicity of Teicoplanin Therapy in Chinese Children: A Retrospective Study

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Purpose: This study aims to 1) describe the distribution characteristics of teicoplanin trough concentration (C_{\min}) and explore the related influencing factors and 2) evaluate the nephrotoxicity of teicoplanin in children.

Patients and Methods: A cohort of children who were treated with teicoplanin intravenously were included in this retrospective study. Regression analysis was performed to explore the factors associated with the fluctuations of teicoplanin C_{\min} and the development of nephrotoxicity. Classification and regression tree analysis was used to identify the population at high risk for teicoplanin nephrotoxicity.

Results: A total of 269 plasma samples from 186 children were collected. Underexposure ($C_{\min} < 10$ mg/L) was documented in 52.7% of cases. The C_{\min} /dose after administering the loading dose was strongly associated with age ($P = 0.008$), weight ($P = 0.039$), and serum creatinine ($P = 0.022$). The C_{\min} /dose after administering the maintenance dose was strongly associated with gender ($P = 0.014$) and serum creatinine ($P = 0.006$). C_{\min} ($P = 0.012$) and the concomitant treatment with amphotericin B ($P = 0.001$) were the independent risk factors for teicoplanin-related nephrotoxicity. Children who were concomitantly treated by amphotericin B with teicoplanin $C_{\min} > 9.81$ mg/L or patients with teicoplanin $C_{\min} > 21.94$ mg/L were at high risk for nephrotoxicity.

Conclusion: The fluctuations of teicoplanin C_{\min} could be affected by age, weight, gender, and serum creatinine. C_{\min} and concomitant treatment with amphotericin B were the independent risk factors for nephrotoxicity. We suggested that the therapeutic drug monitoring of teicoplanin should be performed in children.

Keywords: teicoplanin, trough concentration, children, nephrotoxicity, factor

Introduction

Gram-positive bacterial infections remain a significant health concern in pediatric patients.^{1,2} Teicoplanin is a glycopeptide antibiotic exhibiting high antibacterial activities against the majority of gram-positive bacteria. It is widely used for the treatment of skin and soft tissue infections, bone and joint infections, pneumonia, urinary tract infections and infective endocarditis in pediatrics worldwide,³ as the superior tissue penetration, slower rate of elimination and fewer adverse reactions compared with vancomycin.⁴

Previous studies showed that teicoplanin trough concentration (C_{\min}) was significantly associated with improved clinical response, and a C_{\min} of > 60 mg/L would increase the likelihood of nephrotoxicity.⁵⁻⁷ Generally, it is recommended

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that, for most gram-positive infections, teicoplanin C_{\min} should be maintained at least 10 mg/L (measured by high performance liquid chromatography, HPLC) or 15 mg/L (measured by fluorescence polarization immunoassay, FPIA) in clinical practice.^{8,9} In addition, large inter-individual and intra-individual variation of teicoplanin C_{\min} have been observed in both adult and pediatric patients,^{10–16} and it has been reported that drug under-exposure was documented in more than half of the cases.³ Weight, serum creatinine and other clinical factors were found to be significantly correlated with the C_{\min} of teicoplanin.^{3,17–19}

Clinical data focused on therapeutic drug monitoring (TDM) of teicoplanin in pediatric patients, especially in children, is very limited. And factors influencing teicoplanin C_{\min} have not been fully elucidated. Yamada et al evaluated the C_{\min} of teicoplanin after the recommended loading dose in 36 children and found that age and renal function were significantly associated with teicoplanin C_{\min} .¹⁷ Another large-scale retrospective TDM study (280 pediatric patients) conducted by Strenger et al indicated that age and gender contributed to the variation of teicoplanin concentration.¹⁹ However, more researches are needed to further explore the influencing factors of teicoplanin C_{\min} due to the limited data.

Besides, compared to vancomycin, teicoplanin lead to a lower risk of nephrotoxicity.^{20,21} However, nephrotoxicity is associated with greater hospital costs and longer length of stay in non-critically ill children.²² To date, only Yamada et al reported that the incidence of nephrotoxicity in children was 2.3%, and no significant difference in renal impairment was found between the groups with $C_{\min} > 20$ mg/L and $C_{\min} < 20$ mg/L (measured by FPIA).¹⁷ However, the risk factors of teicoplanin-related nephrotoxicity have not been fully explored in children.

In this regard, this study aimed to conduct a retrospective study to 1) describe the distribution characteristics of teicoplanin C_{\min} and explore the related influencing factors associated with C_{\min} ; 2) analyze and evaluate the incidence of teicoplanin-related nephrotoxicity and its risk factors in children.

Patients and Methods

Study Population

In this retrospective study, we included a cohort of children who were treated with teicoplanin intravenously at the First Affiliated Hospital of Xi'an Jiaotong University

and Xi'an Children's Hospital between March 2017 and December 2018. Inclusion criteria were: 1) patients aged from 2 months to 18 years old; 2) patients who were clinically diagnosed or suspected with gram-positive bacterial infections, such as respiratory infections, bloodstream infections, bone and joint infections, skin and soft tissue infections and so on, and then were treated with teicoplanin (for children aged 2 months to 12 years, loading dose: one single dose of 10 mg/kg body weight administered intravenously every 12 hours, repeated 3 times; maintenance dose: one single dose of 6–10 mg/kg body weight administered intravenously once a day. For children aged >12 years, loading dose: 6 mg/kg body weight every 12 hours for 3 intravenous or intramuscular administrations; maintenance dose: 6 mg/kg body weight intravenous or intramuscular once a day). The specific prescription of each patient was determined by physicians; 3) patients who underwent TDM of teicoplanin. Exclusion criteria were: 1) patients who underwent continuous renal replacement therapy or peritoneal dialysis; 2) patients who received teicoplanin for less than 48 hours. This study protocol was approved by the Ethics Committee of the two hospitals.

Data Collection

The patient's clinical data were extracted through the hospital's electronic medical record system and the nursing system. The main information was as follows: 1) demographic data, such as gender, age, and weight; 2) underlying diseases and diagnosis of infection; 3) dosage regimen of teicoplanin and the concomitant medication (defined as the other drugs were given at or almost at the same day with teicoplanin before performing TDM for more than one day); 4) laboratory test results, such as creatinine, transaminase (aspartate aminotransferase and alanine transaminase) and platelet count; 5) adverse reactions information, such as nephrotoxicity.

Blood Sample Collection and Concentration Measurement

At least 3 days after the first dose of teicoplanin, plasma samples were taken from patients 30 minutes before the next dose. A validated HPLC method established by our research group was used to quantify the plasma concentrations of teicoplanin. The linear range was 5.63–125.00 mg/L ($r = 0.9995$). The minimum limit of quantitation was 5.63 mg/L. The average relative standard deviations of

intra-day and inter-day were 3.2% and 6.8%, respectively, and the mean relative error of intra-day and inter-day were 0.12% and 0.10%, respectively.²³

Definitions

Teicoplanin C_{\min} were divided into two groups: C_{\min} in the first group were the plasma concentrations measured on day 3 or 4 after the first dose of teicoplanin. C_{\min} in another group were the plasma concentrations measured at steady state (the teicoplanin dosage was not changed for ≥ 72 h).²⁴ Underexposure was defined as the C_{\min} of teicoplanin was less than 10 mg/L.

To explore factors affecting the fluctuation of teicoplanin C_{\min} , we performed an analysis to investigate the relationship between different factors and the value of C_{\min} /Dose (C/D). C/D were divided into two groups: one was $C_{\min}^{3/4}/D_{\text{CLD}}$ (the ratio between C_{\min} on day 3 or day 4 after teicoplanin administration and the cumulative loading dose), and the other was $C_{\min}^{\text{SS}}/D_{\text{MD}}$ (the ratio between the teicoplanin C_{\min} at steady state and the maintenance dose). Nephrotoxicity was defined as a serum creatinine (SCr) increase at least 1.5 times that of the baseline.²⁵

Statistical Analysis

Statistical analyses were performed using SPSS 19.0. The mean \pm standard deviation (SD) or median (interquartile range, IQR) was used to describe continuous variables depending on the normality of distribution, whereas percent or count was used to describe categorical variables. Univariate and multivariate linear regression analysis was applied to determine potential factors affecting the teicoplanin C/D. Univariate and multivariate logistic regression analyses were applied to explore the potential risk factors for nephrotoxicity. Variables with $P < 0.1$ in the univariate analysis were combined in the multivariate analysis. Logistic regression and classification and regression tree (CART) analysis were performed to identify the patient population with a greater or less likelihood of developing nephrotoxicity. In this study, variables with $P < 0.1$ in a multivariate logistic regression analysis were included in the CART analysis.

Results

Baseline Patient Characteristics

One hundred and eighty-six children were included in this study. Patients were typically male (56.5%), with a median

age of 3.82 years (IQR 1.53–6.27 years). The median weight was 15.3 kg (IQR 11.0–21.0 kg). The main reason for teicoplanin therapy was respiratory infections (58.1%) and malignancy was the most common comorbid condition (46.2%). Only 25.8% of patients were proven to be infected with gram-positive bacterial. Median albumin and SCr were 35.0 g/L and 26 $\mu\text{mol/L}$, respectively (Table 1).

Distribution of Teicoplanin Trough Concentrations

The distribution of teicoplanin C_{\min} was shown in Figure 1. A total of 269 teicoplanin C_{\min} were included in this study. The median of C_{\min} was 9.49 mg/L (IQR 5.97–15.35 mg/L)

Table 1 Patients' Characteristics

Characteristics	Value
Number of patients, n	186
Gender, males/female, n (%)	105/81 (56.5%/43.5%)
Age (year), median (IQR)	3.82 (1.53, 6.27)
Weight (kg), median (IQR)	15.3 (11.0, 21.0)
Teicoplanin loading dose (mg/kg), median (IQR)	10.0 (9.7, 10.00)
Teicoplanin maintenance dose (mg/kg), median (IQR)	10.00 (9.7, 10.00)
Duration of teicoplanin therapy (days), median (IQR)	12 (9, 16)
Type of infection, n (%)	
Skin and soft tissue infection	14 (7.5%)
Respiratory infection	108 (58.1%)
Bloodstream infection	45 (24.2%)
Bone and joint infections	17 (9.1%)
Other infections	2 (1.1%)
Isolated gram-positive organisms, n (%)	
Staphylococcus	18 (9.7%)
Enterococcus	9 (4.8%)
Streptococcus	9 (4.8%)
Others	12 (6.5%)
Comorbid conditions, n (%)	
Malignancy	86 (46.2%)
Congenital heart disease	21 (11.3%)
Hypoalbuminemia	32 (17.2%)
Baseline WBC ($10^9/\text{L}$), median (IQR)	5.24 (1.20, 11.23)
Baseline NEUT%, median (IQR)	52.1 (28.9, 69.7)
Baseline albumin (g/L), median (IQR)	35.0 (30.7, 39.6)
Baseline ALT (U/L), median (IQR)	20.0 (12.0, 42.0)
Baseline AST (U/L), median (IQR)	27.5 (20.0, 43.0)
Baseline SCr ($\mu\text{mol/L}$), median (IQR)	26 (20, 33)
Baseline Ccr (mL/min) ^a , median (IQR)	95.2 (66.9, 127.2)

Note: ^aEstimated by Cockcroft-Gault.

Abbreviations: IQR, interquartile range; C_{\min} , trough concentration; WBC, white blood cell; NEUT%, neutrophil percentage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCr, serum creatinine; Ccr, creatinine clearance.

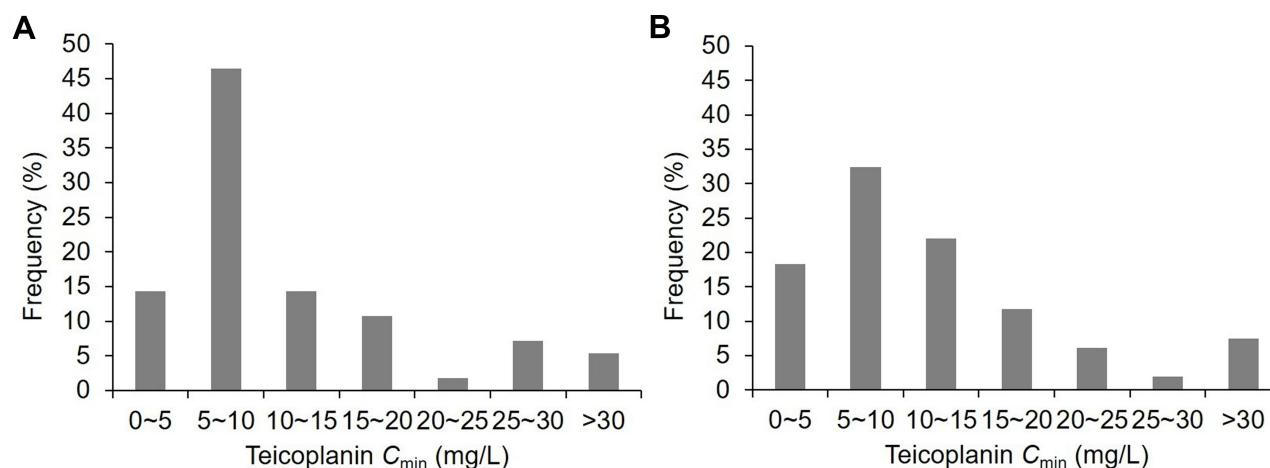


Figure 1 Distribution of teicoplanin trough concentrations. Panel (A) shows the distribution of C_{min} on day 3 or day 4 after teicoplanin administration. Panel (B) shows the distribution of teicoplanin C_{min} at steady state.

and 52.7% of C_{min} is less than 10 mg/L. Among the 269 teicoplanin C_{min} , 56 C_{min} were obtained on day 3 or 4 after the initial teicoplanin administration, the median was 8.43 mg/L (IQR 6.41–15.02 mg/L) (Figure 1, panel A). The median of the remaining 213 teicoplanin C_{min} obtained at steady state was 9.77 mg/L (IQR 5.89–15.60 mg/L) (Figure 1, panel B). Compared with the steady state C_{min} , those obtained on day 3 or day 4 were more likely to be < 10 mg/L.

Factors Influencing Teicoplanin C/D

Factors Influencing Teicoplanin $C^{3/4}_{min}/D_{CLD}$

As shown in Table 2, gender, age, weight, concomitant use of carbapenems, and SCr were allowed to be included in the multivariate analyses due to those factors had the P value < 0.1. Finally, it was found that teicoplanin $C^{3/4}_{min}/D_{CLD}$ was significantly affected by age ($P = 0.008$), weight ($P = 0.039$), and SCr ($P = 0.022$).

Factors Influencing Teicoplanin C^{SS}_{min}/D_{MD}

Accordingly, Table 3 shows the factors that influencing the teicoplanin C^{SS}_{min}/D_{MD} . Although univariate analyses indicated that gender, weight, and SCr had the P value < 0.1, no significant correlation was found between weight and teicoplanin C^{SS}_{min}/D_{MD} in the multivariate analyses. Gender and SCr were found to be independently associated with teicoplanin C^{SS}_{min}/D_{MD} ($P = 0.014$, $P = 0.006$, respectively).

Nephrotoxicity Analysis

One hundred and eighty-two children were eligible for nephrotoxicity analysis. Nine of one hundred and

eighty-two (4.9%) patients occurred nephrotoxicity. As shown in Table 4, both univariable and multivariable logistic analysis indicated that teicoplanin C_{min} and the concomitant use of amphotericin B were the risk factors for the incidence of nephrotoxicity related to teicoplanin ($P = 0.012$, $P = 0.001$, respectively). Further CART model showed that children with concomitant treatment with amphotericin B had teicoplanin $C_{min} > 9.81$ mg/L or patients with teicoplanin $C_{min} > 21.94$ mg/L were at high risk for nephrotoxicity (Figure 2). Inversely, patients who were concomitantly treated by amphotericin B with teicoplanin $C_{min} < 9.81$ mg/L or those with teicoplanin $C_{min} < 21.94$ mg/L were at low risk of nephrotoxicity.

Discussion

In this retrospective study, we described the distribution characteristics of teicoplanin C_{min} and investigated the potential factors affecting the concentration of teicoplanin based on 269 TDM data from 186 patients. In addition, we explored the risk factors related to the nephrotoxicity of teicoplanin and identified patients with high-risk of nephrotoxicity.

Teicoplanin C_{min} of 9.49 mg/L (IQR 5.97, 15.35 mg/L) was observed in this study. When $C_{min} > 10$ mg/L was defined as the therapeutic target of teicoplanin, more than half of the teicoplanin C_{min} (52.7%) did not achieve the therapeutic target, which was similar to previous studies.^{16,26} Zhao et al reported the teicoplanin C_{min} was 11.8 mg/L (IQR 3.0, 49.6 mg/L), and 48% of children had sub-therapeutic steady-state C_{min} .¹⁶ Yamada et al reported

Table 2 Univariate and Multivariate Analyses of the Variables Tested for Potential Association with $C_{\min}^{3/4}/D_{\text{CLD}}$

Variables	Univariate Analysis		Multivariate Analysis	
	R ²	P value	P value	β (95% CI)
Gender (Male)	0.082	0.032	–	
Age (year)	0.209	0.001	0.008	0.69 (0.019–0.119)
Weight (kg)	0.064	0.061	0.039	–0.015 (–0.029–0.001)
Concomitant medication	–	–	–	
Antibacterial drugs	–	–	–	
Cephalosporins	0.023	0.270	–	
Carbapenems	0.065	0.058	0.080	–0.194 (–0.413–0.024)
Antifungal drug	0.001	0.856	–	
Antiviral drugs	0.001	0.918	–	
Others	0.035	0.138	–	
Comorbid conditions	–	–	–	
Malignancy	0.044	0.121	–	
Congenital heart disease	0.002	0.771	–	
Hypoalbuminemia	0.010	0.453	–	
WBC (10 ⁹ /L)	0.004	0.636	–	
ALT (U/L)	0.004	0.648	–	
AST (U/L)	0.000	0.915	–	
Albumin (g/L)	0.023	0.268	–	
SCr (μmol/L)	0.279	0.001	0.022	0.007 (0.001–0.013)
Ccr (mL/min) ^a	0.048	0.106	–	

Note: ^aEstimated by Cockcroft-Gault.

Abbreviations: $C_{\min}^{3/4}/D_{\text{CLD}}$, the ratio between C_{\min} on day 3 or day 4 after teicoplanin administration and the cumulative loading dose; CI: confidence interval; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCr, serum creatinine; Ccr, creatinine clearance.

that the median C_{\min} of teicoplanin was 16.3 (3.6, 25.9) mg/L in children (measured by FPIA), and 46.2% of patients did not achieve a trough value ≥ 15 mg/L was in the recommended dose regimen group.¹⁷ Given those findings, it seems that teicoplanin C_{\min} existed inadequate exposure in most patients. We suggest that the dose increase of teicoplanin and the exploration of C_{\min} -related influencing factors should be conducted in children to achieve better clinical responses.

In this study, age, weight, and SCr were found to be the factors that exerted a significant effect on teicoplanin $C_{\min}^{3/4}/D_{\text{CLD}}$. Our results were partially similar with a previous study with a relatively small sample size (36 children) which reported that teicoplanin C_{\min} would be influenced by age, SCr and estimated glomerular filtration when giving a fixed-dose.¹⁷ Since teicoplanin is

Table 3 Univariate and Multivariate Analyses of the Variables Tested for Potential Association with $C_{\min}^{\text{SS}}/D_{\text{MD}}$

Variables	Univariate Analysis		Multivariate Analysis	
	R ²	P value	P value	β (95% CI)
Gender (Male)	0.034	0.007	0.014	0.395 (0.080–0.709)
Age (year)	0.003	0.402	–	
Weight (kg)	0.025	0.021	–	
Concomitant medication	–	–	–	
Antibacterial drugs	–	–	–	
Penicillins	0.004	0.346	–	
Cephalosporins	0.008	0.190	–	
Carbapenems	0.001	0.966	–	
Antifungal drug	0.002	0.512	–	
Antiviral drugs	0.001	0.650	–	
Others	0.012	0.118	–	
Cumulative loading dose (mg/kg)	0.008	0.182	–	
Comorbid conditions	–	–	–	
Malignancy	0.010	0.153	–	
Congenital heart disease	0.012	0.115	–	
Hypoalbuminemia	0.003	0.432	–	
WBC (10 ⁹ /L)	0.001	0.727	–	
ALT (U/L)	0.001	0.965	–	
AST (U/L)	0.001	0.977	–	
Albumin (g/L)	0.001	0.891	–	
SCr (μmol/L)	0.041	0.003	0.006	0.014 (0.004–0.025)
Ccr (mL/min) ^a	0.004	0.352	–	

Note: ^aEstimated by Cockcroft-Gault.

Abbreviations: $C_{\min}^{\text{SS}}/D_{\text{MD}}$, the ratio between the teicoplanin C_{\min} at steady state and the maintenance dose; CI: confidence interval; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCr, serum creatinine; Ccr, creatinine clearance.

mainly excreted by the kidneys,²⁷ impaired renal function usually causes a decrease of teicoplanin clearance.²⁸ In addition, drug clearance and volume of distribution in children also changed with the increase of age and weight, further affecting the drug exposure. Strenger et al found that compared with school-age children, young children had significantly lower initial teicoplanin C_{\min} .¹⁹ Besides, several studies have also indicated that weight could significantly influence the pharmacokinetics of teicoplanin in children.^{3,16,29} Therefore, it is necessary to consider age, weight and serum creatinine to achieve the therapeutic target of teicoplanin in children as soon as possible.

For the $C_{\min}^{\text{SS}}/D_{\text{MD}}$, in addition to SCr, gender was also found to be significantly related to teicoplanin $C_{\min}^{\text{SS}}/D_{\text{MD}}$. Similar to the recent results concluded

Table 4 Univariable and Multivariable Analysis of Risk Factors for Nephrotoxicity in Patients Receiving Teicoplanin

Variables	Univariate Analysis		Multivariate Analysis	
	Wald χ^2	P value	P value	OR (95% CI)
Gender (Male)	0.816	0.217	–	0.285 (0.183–0.388)
Age (year)	0.003	0.956	–	
Weight (kg)	0.013	0.908	–	
Concomitant nephrotoxic drugs	–	–	–	
Aminoglycosides	0.001	0.999	–	
Loop diuretics	1.731	0.188	–	
Acyclovir	0.001	0.999	–	
Amphotericin B	15.509	0.001	0.001	
Cis-platinum	0.001	0.999	–	
Comorbid conditions	–	–	–	
Malignancy	0.373	0.541	–	0.005 (0.001–0.008)
Congenital heart disease	1.005	0.316	–	
Hypoalbuminemia	0.179	0.672	–	
Teicoplanin C_{\min} (mg/L)	5.511	0.019	0.012	
Baseline SCr ($\mu\text{mol/L}$)	0.078	0.780	–	
Baseline Ccr (mL/min) ^a	0.034	0.853	–	

Note: ^aEstimated by Cockcroft-Gault.

Abbreviations: OR, odds ratio; CI, confidence interval; C_{\min} , trough concentration; SCr, serum creatinine; Ccr, creatinine clearance.

from Cai et al, which demonstrated that there were gender-related differences in teicoplanin C_{\min} .²⁹ Another study found that adolescent girls had significantly higher initial and follow-up teicoplanin C_{\min} than adolescent boys, and the authors suggested that gender-related differences in protein binding, tissue distribution or renal excretion of teicoplanin may explain this difference.¹⁹ More prospective studies are expected in the future to explore the causes of this phenomenon.

In the field of TDM, studies rarely focused on the nephrotoxicity of teicoplanin in children. The incidence of nephrotoxicity was 4.9% according to the current study. A retrospective study found that the overall incidence of nephrotoxicity in children was 2.3%.¹⁷ We found that teicoplanin C_{\min} and concomitant treatment with amphotericin B were independent risk factors for nephrotoxicity of teicoplanin in children. Moreover, there was an increased risk of nephrotoxicity when the C_{\min} of teicoplanin exceed 21.94 mg/L in children or the C_{\min} exceed 9.81 mg/L in children with concomitant use of amphotericin B. To our knowledge, this is the first study to report

the risk factors of teicoplanin-related nephrotoxicity and the high-risk population in children. Previous studies reported that a C_{\min} of > 60 mg/L increased the likelihood of nephrotoxicity of teicoplanin.⁶ Similarly, Wilson reported that adult patients with teicoplanin C_{\min} > 60 mg/L had a higher incidence of nephrotoxicity compared to patients with teicoplanin C_{\min} of 20–40 mg/L.³⁰ However, another study drew a contradictory conclusion that there was no significant correlation between the C_{\min} and the occurrence of nephrotoxicity in adults.⁵ The most common adverse reaction of amphotericin B is nephrotoxicity. A previous study showed that amphotericin B combined with vancomycin was associated with impaired renal function.³¹ In this study, 4 of 9 patients developing nephrotoxicity were received concomitant treatment with amphotericin B. The nephrotoxicity threshold of teicoplanin was decreased from 21.94 mg/L to 9.81 mg/L when combining amphotericin B and teicoplanin, it may be caused by the synergy between the two drugs. This result suggested that the concomitant use of amphotericin B could aggravate the nephrotoxicity possibility of teicoplanin. Therefore, more attention should be paid to the children who received concomitant treatment with amphotericin B and teicoplanin in the future, even when the C_{\min} does not reach the therapeutic target.

There are several limitations in our study. Firstly, this study was a retrospective study, neither the number of TDM samples nor the timing of TDM for each patient was consistent. Secondly, the relationship between drug exposure and clinical efficacy was not explored because there are few microbiologically documented gram-positive bacterial infections in this study. Larger-scale, multicenter and prospective studies are expected to further validate the results of teicoplanin TDM in children.

Conclusion

This is a retrospective study of teicoplanin in a larger sample size of children patients. The current dose regimen of teicoplanin may result in inadequate drug exposure in children. Age, weight, gender and SCr are important factors that can significantly influence the fluctuation of teicoplanin C_{\min} . Teicoplanin C_{\min} and concomitant treatment with amphotericin B were independent risk factors for nephrotoxicity. It is recommended to perform TDM in children to ensure the efficacy and safety of teicoplanin.

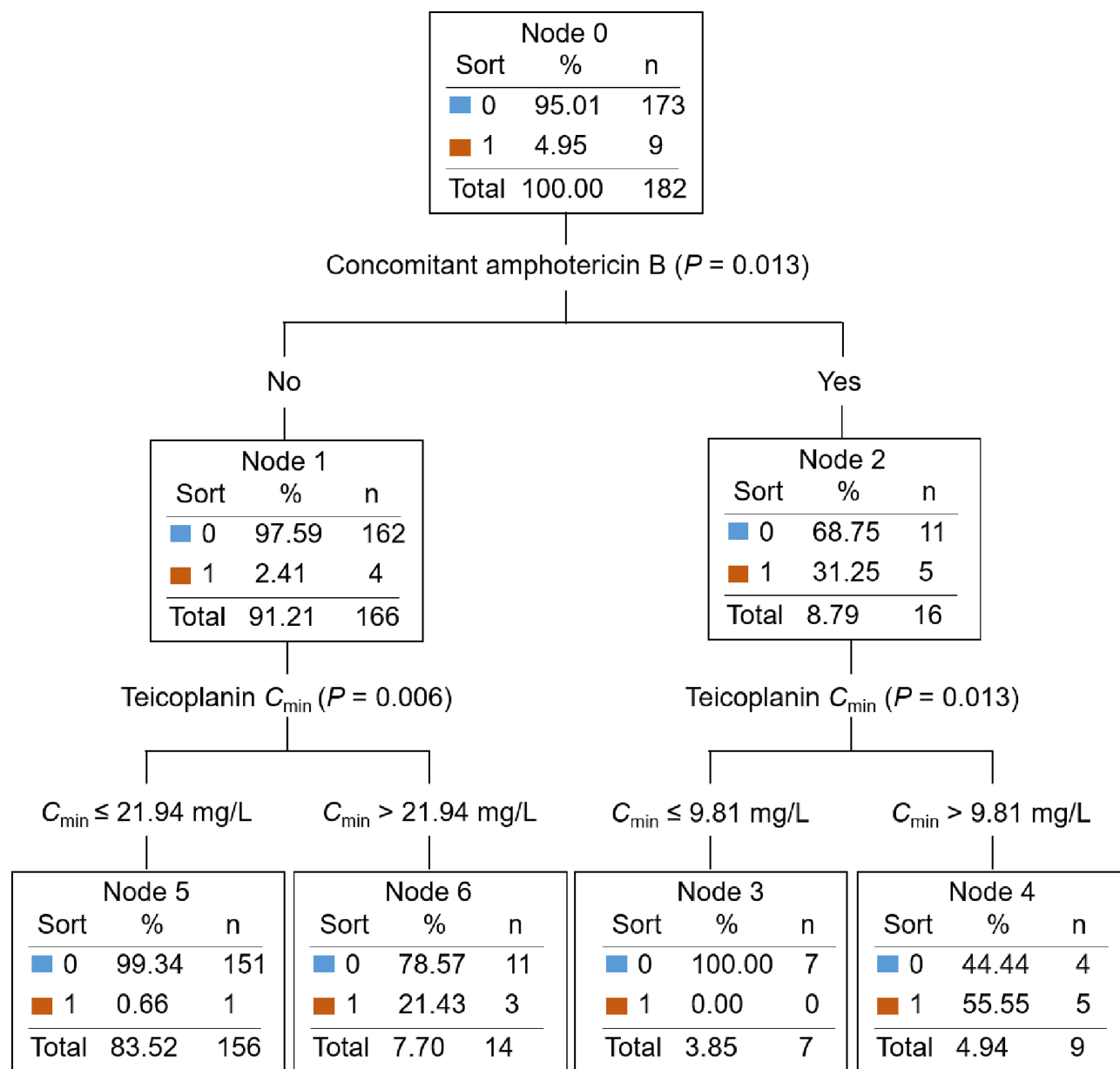


Figure 2 Classification and regression tree model for the nephrotoxicity of teicoplanin therapy. A value of 0 indicated that no nephrotoxicity was observed and a value of 1 indicated that nephrotoxicity was observed.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and the Ethics Committee of Xi'an Children's Hospital, respectively. Waiving of informed consent was given due to the retrospective, non-interventional study design. All patient data were collected anonymously. This study was performed in accordance with the Declaration of Helsinki. Patients were ensured about the confidentiality of their information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dan Sun and Tao Zhang are co-first authors for this study. The authors declare that they have no conflicts of interest.

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