BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902023e21077

Article

A retrospective analysis to estimate trough concentrations of teicoplanin in patients with suspected or documented Gram-positive infections

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Teicoplanin is a glycopeptide antibiotic commonly used to treat Gram-positive bacterial infections in the clinic. The aim of this study was to provide a therapeutic reference for the clinical application and dosage regimen adjustment of teicoplanin by identifying factors associated with its plasma trough concentration (C_{trough}). A retrospective study was performed on patients with suspected or documented Gram-positive infections who were hospitalized from November 2017 to January 2020 and treated with teicoplanin while undergoing routine therapeutic drug monitoring (TDM). A total of 112 C_{trough} trough measurements were obtained from 72 patients were included in this study. SPSS software was used for correlation analysis and receiver operator characteristic curve (ROC) analysis. The C_{trough} for teicoplanin showed statistically significant relationships (P<0.05) with PLT, S_{cr}, CL_{cr}, eGFR, BUN and Cys-C. ROC curve analysis revealed that CL_{cr} and eGFR were more sensitive and specific for C_{trough} compared to the other factors. These findings should be considered in the clinical application of teicoplanin and for its dosage adjustment.

Keywords: Teicoplanin. HPLC. Therapeutic drug monitoring. Trough concentration. Creatinine clearance. Estimated glomerular filtration rate.

INTRODUCTION

Teicoplanin is a glycopeptide antibiotic developed after the discovery of vancomycin and is composed of structurally similar compounds (Marcone *et al.*, 2018). It has similar antibacterial activity and mechanism of action to vancomycin, mainly by blocking the biosynthesis of cell walls. Teicoplanin is recommended for the treatment of infections caused by Gram-positive bacteria such as *Staphylococcus epidermidis* (MRSE), *Streptococcus*, *Enterococcus* and the majority of anerobic positive bacteria (Tascini *et al.*, 2012; Sader *et al.*, 2019).

Teicoplanin, cannot be absorbed orally and, is thus usually administered by intramuscular or intravenous injection. It binds strongly to plasma proteins and has a binding rate of approximately 90%. It also has good tissue permeability and is distributed mainly in the lung, myocardium and bone tissues, but has poor penetrateion into the cerebrospinal fluid (CSF). Teicoplanin has a long plasma half-life and its non-metabolic form is excreted mainly through the kidneys. Compared to vancomycin, teicoplanin needs a longer time period to achieve the steady-state concentration (Takechi *et al.*, 2017; Electronic Medicines Compendium, 2017).

Glycopeptide antibiotics are time-dependent and have long post-antibiotic effects (PAE). The ratio of the area under the drug concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) is refered

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to as the pharmacokinetic-pharmacodynamic (PK/PD) parameter, and is correlated with antibacterial efficacy and clinical outcomes (Craig, 2003; Ramos-Martín *et al.*, 2017). The PK/PD parameter for teicoplanin is the AUC during 24 h (AUC_{24}/MIC). Clinical targets for the treatment of general and severe infections are AUC_{24}/MIC ≥125 and AUC_{24}/MIC ≥345, respectively (Ahn *et al.*, 2011; Matsumoto *et al.*, 2016). For clinical treatment, the plasma trough concentrations (C_{trough}) for teicoplanin as measured by high-performance liquid chromatography (HPLC) is >10 mg/L for most Gram-positive bacterial infections and 15-30 mg/L for severe infections such as endocarditis or bloodstream infection. When measured by fluorescence polarization immunoassay (FPIA), the C_{trough} is >15 mg/L for most infections, >20 mg/L for bone or prosthetic infections, and 30-40 mg/L for endocarditis (Roberts *et al.*, 2012; Ueda *et al.*, 2012; Kato *et al.*, 2016; Electronic Medicines Compendium, 2017).

The aim of this study was therefore to evaluate the relationship between various physiological factors and the C_{trough} for teicoplanin.

MATERIALS AND METHODS

Patient enrollment

Patients, suspected or documented Gram-positive infections enrolled in this study were admitted to the First Hospital of China Medical University between November 2017 and January 2020. They received intravenous teicoplanin treatment and TDM was performed at least 24 h afterwards, with at least more than one C_{trough} measurement obtained from each patient.

Exclusion criteria: were (1) patients who were younger than 18 years old; (2) patients undergoing renal replacement therapy; and (3) patients for which clinical data was unavailable.

Chromatography conditions

An Agilent 1100 HPLC system (Agilent Technologies, Japan) was adopted for sample analysis. An ODS Hypersil column (250 mm×4.6 mm, 5μm) was used for separation and the temperature was maintained at 40 ºC. The mobile phase consisted of 10 mM sodium dihydrogen phosphate buffer (pH=2.3): acetonitrile at 75:25 (v/v) with a flow rate of 1.2 ml/min. Ultraviolet measurements were carried out at 215 nm. The linear range of the calibration standard curve was 3.125-100 mg/L and the intra- and inter- coefficients of variation were all < 11.0%. This method was suitable for the clinical TDM of teicoplanin.

Sample preperation

Blood samples were collected into EDTA tubes just before the next teicoplanin administration. Plasma samples were obtained after centrifuging at 4,500 rpm for 10 min. Aliquots of 50 μl of internal standard (piperacillin sodium) and 400 μl of plasma were placed into a 2.0 ml microtube and 600 μl of acetonitrile was then added. After vortex-mixing for 30 s and centrifugation at 13,000 rpm for 5 min, 900 μl of the supernatant was placed into another microtube. Dichloromethane (400 μl) was then added, the mixture was vortexed for 30 s and then centrifuged at 13,000 rpm for 5 min again. The supernatant was carefully collected and a volume of 20 μl was injected for HPLC analysis.

Data collection and groups

Demographic and clinical data were collected from each patient's individual medical records. Demographic information included gender, age, height and weight. Laboratory information included routine blood, hepatic and renal function markers such as lymphocyte (LY), neutrophil (NE), ratio of neutrophil (NE%), hemoglobin (HGB), platelet (PLT), total protein (TP), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), serum creatinine concentration (S_{cr}), creatinine clearance (CL_{cr}), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN) and cystatin C (Cys-C). Clinical information included TDM results, the type of infectious organisms and the concomitant antibacterials used. Patients were divided into two groups based on

C_{trough} as follows: Group A had a C_{trough} <10 mg/L (n=28) and Group B had a C_{trough} ≥10 mg/L (n=84). CL_{cr} and eGFR were calculated using the Cockroft - Gault formula (Cockcroft, Gault, 1976) and the abbreviated MDRD formula (Foundation, 2002) respectively:

CL_{cr}=(140-age(years))×weight(kg)/
(0.818×S_{cr}(μmol/L)) Males
CL_{cr}=0.85×(140-age(years))×weight/(kg)/
(0.818×S_{cr}(μmol/L)) Females

eGFR(ml/min/1.73m^2)=186×(S_{cr}(mg/dL))$^{-1.154}$×(age(years))$^{-0.203}$ Males
eGFR(ml/min/1.73m^2)=0.742×186×(S_{cr}(mg/dL))$^{-1.154}$×(age(years))$^{-0.203}$ Females

Statistical analysis

Continuous variables were expressed as the mean±standard deviation (SD) or as the median and interquartile (IQR) range. The Spearman method was used for correlation analysis. A *P* value of <0.05 was considered to represent statistical significance. Regression analysis was performed to evaluate the relationship between C_{trough} and defferent variables.

RESULTS AND DISCUSSION

The demographic and clinical data of patients in this study are shown in Table I. A total number of 72 patients (44 males and 28 females) with an age range of 19-92 years (63±15 years) and weight range of 42-100 kg (65±11 kg) were enrolled. The main types of infections during hospitalization were abdominal infections (27.8%), bloodstream infections (27.8%) and pneumonia infections (16.7%), while the responsible organisms were *Enterococcus* (19/61), *Staphyloccocus* (16/61), *Acinetobacter baumannii* (7/61), *Pseudomonas aeruginosa* (6/61), *Klebsiella pneumonia* (4/61) and *Cornebacterium striatum* (3/61).

TABLE I - Demographic and clinical data of patients

Characteristics	Values
Demographic characteristics (mean±SD (range))	
Number of patients	72
Gender (males/female, *n*)	44/28
Age (years)	63±15 (19-92)
Height (m)	1.67± 0.08 (1.50-1.90)
Weight (kg)	65 ±11 (40-100)
BMI (kg/m^2)	23.33±3.37 (16.53-32.39)
Type of infection, n(%)	
Abdominal	20 (27.8)
Bloodstream	20 (27.8)
Pneumonia	12 (16.7)
Endocarditis	4 (5.5)
Skin and soft tissue	8 (11.1)
Other[a]	8 (11.1)
Clinical characteristics (median (IQR))	
WBC (10^9/L)	8.22 (5.76-13.39)
LY (10^9/L)	0.91 (0.65-1.51)
NE (10^9/L)	6.30 (3.95-11.42)
NE% (%)	79.2 (67.8-85.9)
HGB (g/L)	103 (88-106)
PLT (10^9/L)	234 (143-360)
TP (g/L)	56.4 (50.7-63.8)
ALB (g/L)	27.8 (24.4-32.3)
ALT (U/L)[b]	27 (12-52)
AST (U/L)[c]	24 (19-42)
TBIL (μmol/L)	11.2 (7.4-16.6)
S_{cr} (μmol/L)	60 (44-79)
CL_{cr} (ml/min)[d]	100.4 (63.6-126.2)
eGFR (ml/min/1.73m^2)[e]	117.5 (89.6-148.0)
BUN (mmol/L)	4.8 (3.3-7.6)
Cys-C (mg/L)[f]	1.26 (0.90-1.80)
Infectious organisms[g]	
Acinetobacter baumannii	7
Cornebacterium striatum	3
Enterococcus	19
Klebsiella pneumonia	4
Pseudomonas aeruginosa	6
Staphyloccocus	16
Other	6
Concomitant antibacterials[h]	
Cefoperazone and Sulbactam	15
Piperacillin and Tazobactam	8
Meropenem	15
Ertapenem	10

TABLE I - Demographic and clinical data of patients

Characteristics	Values
Imipenem and Cilastatin	16
Moxifloxacin	6
Other[i]	5

[a]included pelvic, urinary tract, joint and catheter-related infection;[b]ALT (n=71); [c]AST (n=58); [d]CL_{cr} was calculated by Cockroft & Gault formula; [e]eGFR was calculated by MDRD formula; [f]Cys-C (n=59); [g]Pathogenic bacteria from 43 patients was isolated and some patients were infected by several pathogenic bacteria; [h]some patients administered more than one antibacterial agent; [i] included Cefminox, Ceftriaxone, Ciprofloxacin, Cefotaxime Sodium and Sulbactam Sodium and Cefazolin Sodium. BMI=body mass index; WBC=white blood cell; LY= lymphocyte; NE=neutrophil; NE%=ratio of neutrophil; HGB=hemoglobin; PLT=platelet; TP=total protein; ALB=serum albumin; ALT=alanine aminotransferase; AST=aspartate aminotransferase; TBIL=total bilirubin; S_{cr}=serum creatinine concentration; CL_{cr}=creatinine clearance; eGFR=estimated glomerular filtration rate; BUN=blood urea nitrogen; Cys-C=cystatin C.

In total, 112 Ctrough measurements were obtained. There were 46, 38 and 28 concentrations that were collected on days 2 to 4, days 5 to 10 and days >10 of therapy, the mean±SD of the C_{trough} were 15.46±7.90, 14.63±6.97 and 15.94±4.66 respectely (Figure 1). There was no statistical significance of C_{trough} among different sampled days of therapy.

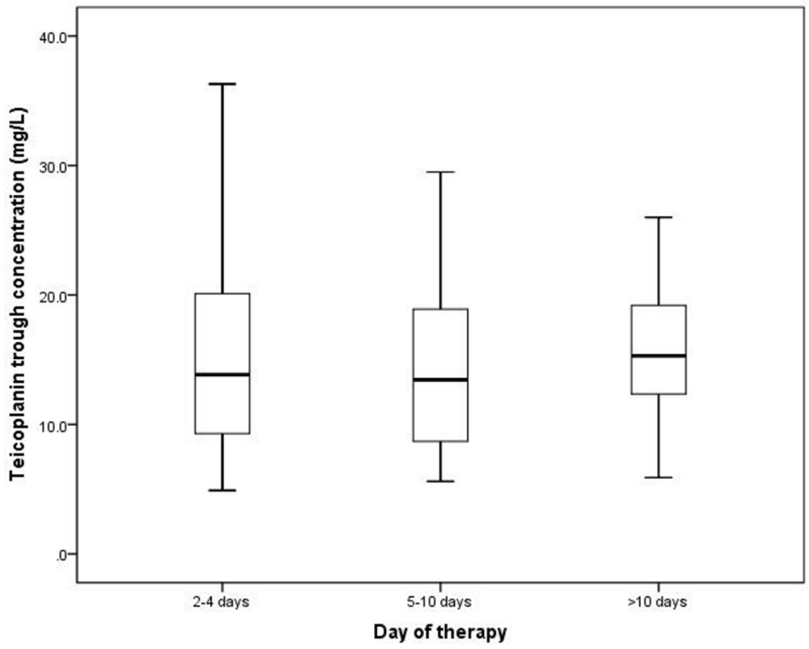

FIGURE 1 - Trough concentration of teicoplanin of patients measured on days 2 to 4, days 5 to 10 and days >10 of therapy.

The heatmap shown in Figure 2 clearly displays the correlation matrix for the different variables. As listed in Table II, C_{trough} had a significant positive correlation with S_{cr}, BUN and Cys-C, but a negative correlation with PLT, CL_{cr} and eGFR. Higher C_{trough} was collected with higher values of S_{cr}, BUN and Cys-C, but with lower values of PLT, eGFR and CL_{cr}. Only CL_{cr} and eGFR were significantly different between

the two groups (P<0.05) as shown in Table III. ROC analysis curves (Figure 3) revealed that the area under the curve (AUC) of CL_{cr} and eGFR for C_{trough} were 0.678 [95% confidence interval (CI), 0.555-0.802] and 0.705 [95% confidence interval (CI), 0.577-0.832], with cut-offs of 123.8 ml/min and 161.55 ml/min/1.73m^2 respectively. The AUC of all other factors were all less than < 0.50.

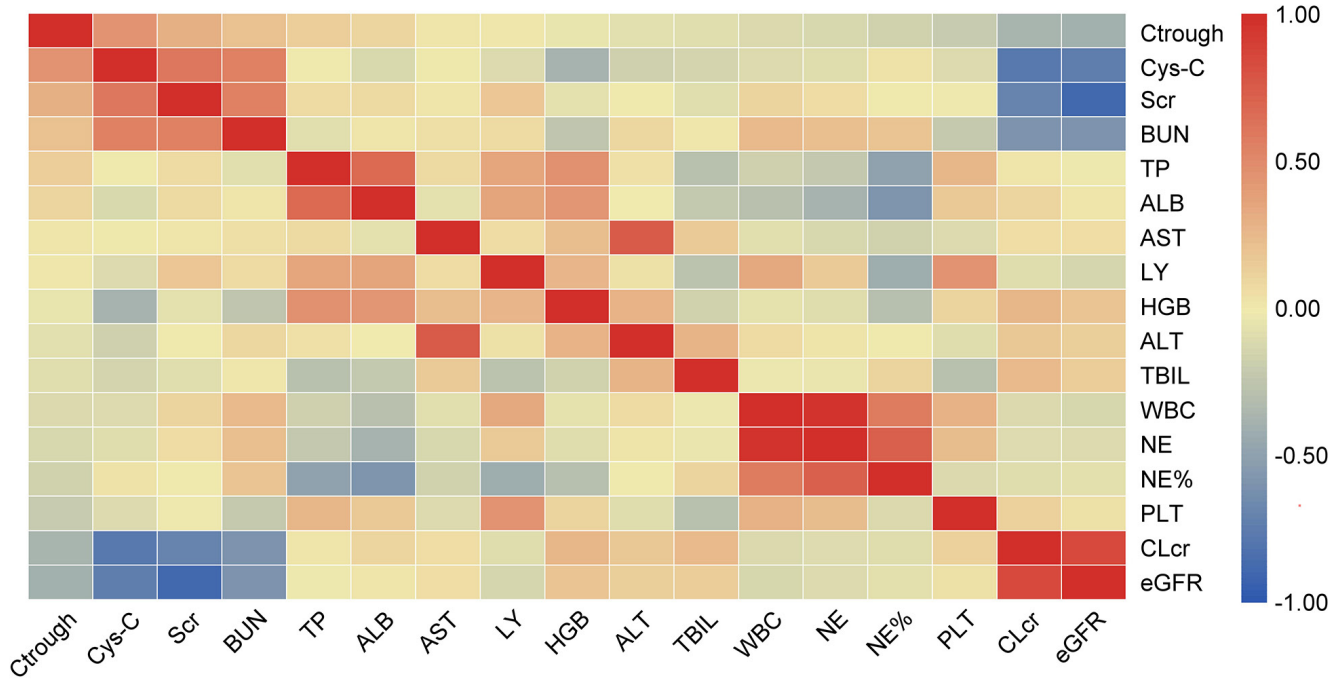

FIGURE 2 - Heatmap of the correlation matrix for variables.

TABLE II - Correlation analysis of the relationship of variables with C_{trough}

Variable	Correlation Coefficient	*P*
PLT (10^9/L)	-0.205	0.030
S_{cr} (μmol/L)	0.305	0.001
CL_{cr} (ml/min) [a]	-0.365	0.000
eGFR (ml/min/1.73m^2) [b]	-0.376	0.000
BUN (mmol/L)	0.216	0.023
Cys-C (mg/L)	0.460	0.000

[a]CL_{cr} was calculated by Cockroft - Gault formula; [b]eGFR was calculated by abbreviated MDRD formula;PLT=platelet; S_{cr}=serum creatinine concentration; CL_{cr}=creatinine clearance; eGFR=estimated glomerular filtration rate; BUN=blood urea nitrogen; Cys-C=cystatin C.

TABLE III - Characteristics of patients in groups

Item	Median (IQR)		*P*
	Group A (n=28)	Group B (n=84)	
C_{trough} (mg/L)	8.05 (6.6-8.7)	16.4 (13.1-21.2)	0.000
PLT (10^9/L)	262 (180-421)	253 (168-351)	0.355
S_{cr} (μmol/L)	45 (39-63)	58 (50-71)[d]	0.712
CL_{cr} (ml/min)[a]	129.2 (102.1-186.0)	105.6 (73.3-134.2)[d]	0.008
eGFR (ml/min/1.73m^2)[b]	160.4 (116.8-206.8)	129.0 (98.3-149.7)[d]	0.004
BUN (mmol/L)	3.5 (2.9-5.7)	5.0 (3.4-6.8)[d]	0.900
Cys-C (mg/L)[f]	0.88 (0.76-1.51)[c]	1.17 (0.97-1.42)[e]	0.621

[a]CL_{cr} was calculated by Cockroft - Gault formula; [b]eGFR was calculated by abbreviated MDRD formula;PLT=platelet; S_{cr}=serum creatinine concentration; CL_{cr}=creatinine clearance; eGFR=estimated glomerular filtration rate; BUN=blood urea nitrogen; Cys-C=cystatin C; [c]n=23; [d]n=83; [e]n=77.

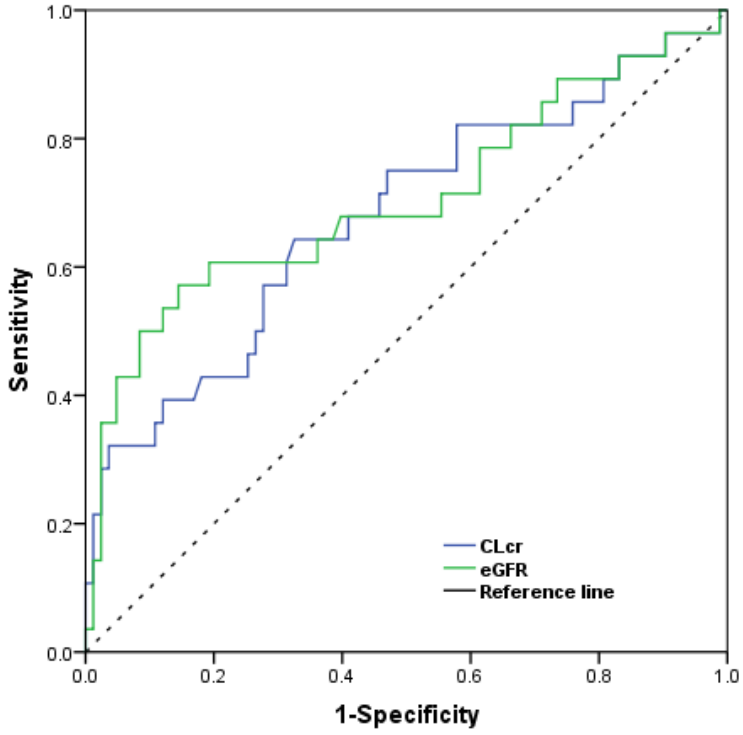

FIGURE 3 - ROC plot of CL_{cr} and eGFR (the diagonal is the indifference line).

This retrospective analysis was carried out on patients who were suspected or documented as having with Gram-positive infections and who received treatment with teicoplanin. Correlation analysis revealed that PLT, S_{cr}, CL_{cr}, eGFR, BUN and Cys-C were the main factors associated with teicoplanin C_{trough}. Several previous studies have also analyzed factors that may influence teicoplanin C_{trough}. Wang *et al.* (2015) reported that dosage (mg/kg) and CL_{cr} were significant factors in their study.

Pea *et al.* (2003) found that teicoplanin C_{trough} was correlated with dose/kg on the second or third day of therapy, and with dose/kg, age and CL_{cr} on the fourth day of therapy.

In their study, the mean C_{trough} was 15.3 mg/L and the range was 4.9-36.3 mg/L. In the present study, 28/112 (25%) of the teicoplanin C_{trough} measurements were <10 mg/L. Moreover, all C_{trough} values were > 10 mg/L when the loading dose was 800 mg, even 24 h after the first administration, while the time to reach target C_{trough} was longer in patients with a 400 mg loading dose. The teicoplanin C_{trough} is associated with efficacy and antibacterial response, hence trough levels of > 10 mg/L are required for general or severe infections. Higher loading doses and longer therapy durations are also needed.

The present results also showed that higher C_{trough} was associated with lower PLT. Previous studies also reported that teicoplanin treatment might cause thrombocytopenia (Hsiao *et al.*, 2012; Wang *et al.*, 2013), and specifically immune thrombocytopenia. The proposed mechanism is that drug-dependent anti-platelet antibodies produced by the body which can recognize and react with the platelet membrane glycoprotein complexes IIb/IIa or Ib/IX/V (Kroll, Sun, Santoso, 2000; Garner *et al.*, 2005). The adverse reactions of teicoplanin involving thrombocytopenia are reported as being low probability. However, routine blood tests are still recommended during teicoplanin treatment.

Teicoplanin has antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Streptococcus* and *Enterococcus*. Because some of the patients in this study were infected with two or more pathogenic organisms, combined antibacterial treatments with penicillin/cephalosporin+enzyme inhibitor, carbapenem or quinolone antibiotics were combined used.

Several studies on the comparative efficacy and safety of teicoplanin versus vancomycin have been conducted since the 1990s. Most showed that teicoplanin had similar efficacy, less adverse reactions and less serious adverse events compared to vancomycin. Some researchers have suggested that teicoplanin could be used as an alternative to vancomycin to treat infections caused by MRSA or other resistant gram-positive organisms (Wood, 1996; Wood, 2000; Svetitsky, Leibovici, Paul, 2009; Yoon *et al.*, 2014). Both teicoplanin and vancomycin are mainly excreted through the kidney and hence their elimination half-life is prolonged in patients with renal failure (Li *et al.*, 2017; Ponce *et al.*, 2018). Considering that the maintenance dose of teicoplanin is onceper day and that it has a lower rate of dose-related nephrotoxicity, teicoplanin is likely to be superior to vancomycin for clinical antibacterial application (Svetitsky, Leibovici, Paul, 2009; Shime *et al.*, 2018).

Several limitations of this study should be considered. First, this was a retrospective analysis conducted at a single center, with some missing data. Second, CL_{cr} and eGFR were calculated using Cockroft - Gault formula and abbreviated MDRD formula, which may be inconsistent with the measured value. Third, comparisons of teicoplanin C_{trough} between different gender and age groups were not performed due to the limited data, and will require investigation in lager patient cohorts.

CONCLUSIONS

Clinical TDM can help monitor teicoplanin concentrations in order to maintain effective concentrations and thus ensure clinical efficacy. The trough concentrations of teicoplanin were mainly related to markers of renal function, especially eGFR and CL_{cr}, and were usually associated with lower PLT during therapy. These findings should be considered during the clinical application and dosage adjustment of teicoplanin.

ACKNOWLEDGEMENTS

Sincerely thank all investigators for their participation and help.

FUNDING

This work was supported by Liaoning Province Natural Science Foundation of China (Grant No. 2020-BS-106).

ETHICAL APPROVAL AND CONSENT TO

PARTICIPATE

The present study was approved by the First Hospital of China Medical University (approval no. [2020]244; Shenyang, China).

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Received for publication on 11th February 2021
Accepted for publication on 08th June 2021