

# Retrospective analysis of relationships among the dose regimen, trough concentration, efficacy, and safety of teicoplanin in Chinese patients with moderate–severe Gram-positive infections

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**Objectives:** Teicoplanin, an antibiotic, has poor clinical efficacy when using the current drug label's recommended regimen, which is approved by the China Food and Drug Administration. This study explores the appropriate loading and maintenance doses of teicoplanin and evaluates the therapeutic target of teicoplanin trough concentration (minimum concentration [ $C_{\min}$ ]).

**Subjects and methods:** All patients treated with teicoplanin from February 2015 to August 2016 at Zhengzhou Central Hospital were screened for enrollment. A total of 113 subjects were included and then divided into four groups: A (received three to six doses at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 400 mg/day), B (received three doses at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 400 mg/day), C (received two doses at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 200 mg/day), and D (received one to three doses at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 200 mg/day).  $C_{\min}$  values of teicoplanin were detected with high-performance liquid chromatography on day 4, 30 minutes before maintenance-dose administration. Teicoplanin  $C_{\min}$ , efficacy, and safety were compared among the four groups.

**Results:** Mean  $C_{\min}$  differed significantly among the four groups (A,  $18.11 \pm 6.37$  mg/L; B,  $15.91 \pm 4.94$  mg/L; C,  $17.06 \pm 5.66$  mg/L; D,  $11.97 \pm 3.76$  mg/L) ( $P < 0.001$ ), with creatinine clearance of 89.62 (53.72–162.48), 49.66 (40.69–59.64), 27.17 (9.7–39.45), and 96.6 (17.63–394.73) mL/min, respectively. The ratio of loading dose for 3 days to creatinine clearance and serum  $C_{\min}$  were significantly correlated ( $R = 0.59$ ,  $P < 0.001$ ). The correlation between the estimated probability of success and teicoplanin  $C_{\min}$  was assessed using binary logistic regression (OR 2.049,  $P < 0.001$ ). Hepatotoxicity- and nephrotoxicity-incidence rates did not significantly differ among the four groups ( $P = 0.859$  and  $P = 0.949$ , respectively).

**Conclusion:** A loading dose of 400 mg at 12-hour intervals three to six times is needed to achieve the early target range (15–20 mg/L) and improve the clinical efficacy rate for normal-renal-function patients. It is urgently necessary to amend the drug label for the recommended regimen.

**Keywords:** teicoplanin, loading dose, serum trough concentration, efficacy, safety, Chinese drug label

## Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen in health care-associated infections, leading to high morbidity and mortality.<sup>1–5</sup> As per current guidelines, teicoplanin and vancomycin are the first-line antibiotics for clinical infections caused by Gram-positive bacteria, especially MRSA.<sup>3,6–10</sup> Teicoplanin is a

semisynthetic glycopeptide antibiotic that kills Gram-positive bacteria by inhibiting the synthesis of cell-wall peptidoglycans. Meta-analysis has indicated that teicoplanin is equally effective as vancomycin, with less risk of nephrotoxicity and red man syndrome.<sup>7,11–14</sup> Teicoplanin has a long elimination half-life of 30–180 hours, due to its high plasma protein-binding rate (over 90%); therefore, teicoplanin is slow to reach a steady-state concentration. To achieve target serum trough concentration (minimum concentration [ $C_{\min}$ ]), a sufficient loading dose must be administered.<sup>15–17</sup>

Recent research found that teicoplanin  $C_{\min}$  was strongly influenced by loading dosage and creatinine clearance ( $Cl_{cr}$ ) rate.<sup>16,18–20</sup> A teicoplanin  $C_{\min}$  range of 10–30 mg/L was identified as the therapeutic target with optimal clinical efficacy and safety.<sup>15–20</sup> An individualized initial loading dose followed by therapeutic drug monitoring was recommended to achieve the target  $C_{\min}$ . The  $C_{\min}$  must be maintained at a minimum of 10–20 mg/L for moderate Gram-positive infections and 20–60 mg/L for all severe staphylococcal infections, including endocarditis. Optimal  $C_{\min}$  has been associated with treatment success. Several reports have indicated that teicoplanin  $C_{\min}$  correlates with loading dose and clinical efficacy.<sup>7,14–22</sup>

The drug label approved by the China Food and Drug Administration recommends a load dosage of 200 mg or 400 mg one to three times at 12-hour intervals, followed by maintenance dosing of 200 mg or 400 mg/day; however, this treatment regimen results in poor clinical efficacy.<sup>23</sup> In clinical practice, doctors must increase the loading dose to achieve the desired effect, but this is illegal in the view of the drug administration. Therefore, it is urgently necessary to determine the optimal load and maintenance doses to ensure clinical efficacy and safety in Chinese patients. We will push to revise the drug label and clinical guidelines by collecting sufficient data and clinical evidence. In the present work, we conducted a retrospective study to analyze the relationship between the revised regimen (an increased load and maintenance dose), teicoplanin  $C_{\min}$ , and clinical efficacy and safety (adverse events, nephrotoxicity, and hepatotoxicity) in Chinese patients with Gram-positive infections.

## Subjects and methods

### Patients and protocol

This was a retrospective study of all teicoplanin-treated adult patients with Gram-positive infections admitted to Zhengzhou Central Hospital, affiliated with Zhengzhou University, from February 2015 to August 2016. Hospitalized patients who met the following criteria were included: age  $\geq 18$  years; met the criteria of community-acquired

pneumonia, confirmed by bacterial culture of drug-resistant Gram-positive bacterial infections;<sup>1,24</sup> duration of teicoplanin therapy  $\geq 5$  days, received teicoplanin as initial therapy for  $\geq 3$  days, with maintenance therapy  $\geq 2$  days; during teicoplanin therapy, therapeutic drug-monitoring data were accurate, complete, and available; efficacy and safety data were accurate, complete, and available; and written informed consent to participate in the study had been provided. Exclusion criteria were patients allergic to teicoplanin, pregnant patients, patients with abnormal hematopoietic function, and those for whom efficacy and safety could not be evaluated. A standardized case-report form was designed to collect enrolled patients' demographic, clinical, and routine laboratory data. Laboratory data from serum or blood collected 24 hours before and/or after the hospital stay included levels of albumin, CRP, creatinine, ALT, hemoglobin, leukocytes, and platelets. The end point was the clinical response evaluated at the end of the teicoplanin therapy. This study was conducted in accordance with the Declaration of Helsinki, approved by the institutional review boards at Zhengzhou Central Hospital, and registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT03229135).

### Treatment regimen and groups

As per the decision issued by the European Medicines Agency on September 12, 2013 ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Targocid\\_30/WC500143827.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Targocid_30/WC500143827.pdf)) and the teicoplanin drug label approved by the China Food and Drug Administration in 2009, all enrolled patients were categorized into four groups. Group A ( $Cl_{cr} \geq 60$  mL/min) received teicoplanin intravenously three to six times for moderate–severe infections at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 400 mg/day. Group B (40–60 mL/min) received teicoplanin intravenously three times at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 400 mg/day. Group C ( $Cl_{cr} < 40$  mL/min) received teicoplanin intravenously twice at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 200 mg/day. Group D (standard regimen, according to the drug label approved by the China Food and Drug Administration) received teicoplanin intravenously one to three times at a loading dose of 400 mg at 12-hour intervals, followed by maintenance dosing of 200 mg/day. Maintenance doses were adjusted as per drug level ( $C_{\min}$ ) on day 4. The target  $C_{\min}$  was set to 15–30 mg/L.<sup>15,18</sup>  $Cl_{cr}$  values for males and females were calculated as follows:

$$([140 - \text{age \{years\}}] \times \text{body weight [kg]}) / (0.818 \times \text{serum creatinine [S}_{cr}; \mu\text{mol/L]}) \text{ (male)}$$

$$([140 - \text{age \{years\}}] \times \text{body weight [kg]}) / (0.818 \times S_{\text{cr}} [\mu\text{mol/L}]) \times 0.85 \text{ (female)}$$

Renal function was assessed by  $Cl_{\text{cr}}$  levels as normal ( $> 60$  mL/min), mildly impaired (40–60 mL/min), or impaired ( $< 40$  mL/min).

## Serum teicoplanin trough concentrations

Serum teicoplanin  $C_{\text{min}}$  of enrolled patients was monitored on day 4, 30 minutes before maintenance-dose administration. As per the technical standard of the hospital, blood samples (2–3 mL per subject) were collected in blood-collection tubes without any additives and centrifuged at 3,500 rpm for 10 minutes. Serum teicoplanin  $C_{\text{min}}$  was determined by high-performance liquid chromatography, as previously described.<sup>16,21</sup> Therapeutic drug monitoring was implemented at the Translational Medicine Center of Zhengzhou Central Hospital.

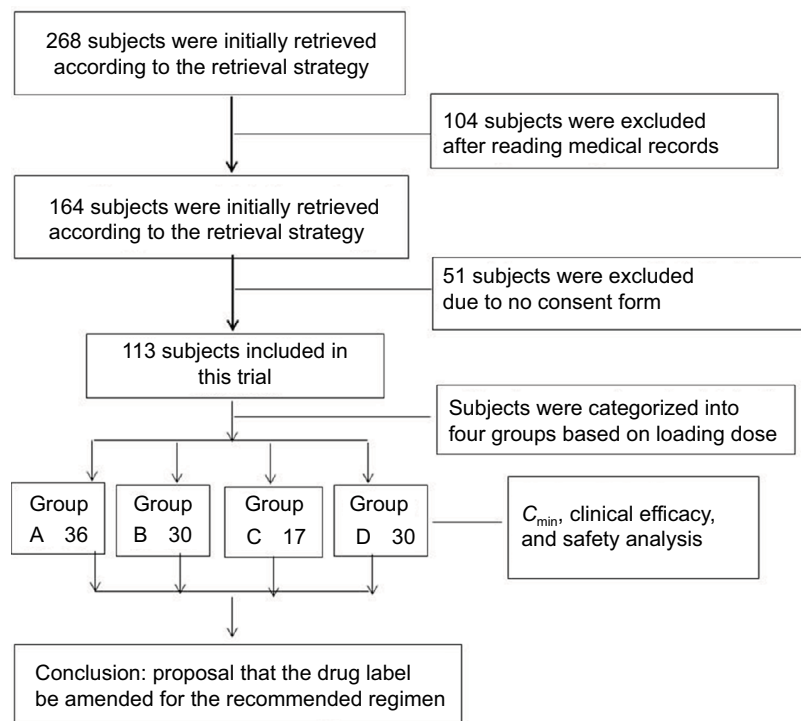
## Data collection

The hospital medical records of all patients treated with teicoplanin from February 2015 to August 2016 at Zhengzhou Central Hospital were screened, reviewed, and analyzed by trained reviewers (Figure 1). Clinical data were collected: demographics, comorbidities, concomitant medications, source of infection, clinical information regarding teicoplanin

dosing, duration of teicoplanin therapy, patients' symptoms, body temperature, chest X-rays, and adverse events. Laboratory data included routine blood work, bacteriology, liver function, renal function, and a blood coagulation index. This included white blood cell counts, CRP, AST, ALT, ALP, total bilirubin, albumin,  $S_{\text{cr}}$ , platelet counts, and  $Cl_{\text{cr}}$ .

## Efficacy assessment of teicoplanin

Efficacy was assessed as per the guidance for clinical trials of antibacterial drugs published by the Centre for Drug Evaluation of the China Food and Drug Administration.<sup>25</sup> Clinical response to teicoplanin was evaluated based on patients' clinical symptoms, laboratory data, and bacteriological findings on the day after the last dose of maintenance administration. The final clinical response to teicoplanin was evaluated and confirmed based on patients' clinical symptoms, laboratory data, and bacteriological findings on days 5–7 after the last dose. The final confirmed response was classified as clinical cure or clinical failure. A clinical cure was defined as the disappearance of clinical symptoms, obvious improved laboratory data, and eradicated bacteria. A clinical failure was defined as no disappearance or worsening of clinical symptoms and/or laboratory data, requiring other antibacterial therapy. In other words, patients without clinical cure were included as clinical failures.



**Figure 1** Research process flowchart.

**Abbreviation:**  $C_{\text{min}}$ , minimum concentration.

## Safety assessment

Nephrotoxicity was defined as increased  $S_{cr}$  of 0.5 mg/dL or 50% increase from the pretreatment value.<sup>3,12,25–27</sup> Hepatotoxicity was defined as ALT or AST more than three times the upper limit of the institution's normal reference ranges (AST 13–33 U/L, ALT 6–30 U/L). For patients with abnormal values at baseline, hepatotoxicity was defined as ALT or AST more than three times the baseline value. All teicoplanin-related adverse events were recorded throughout teicoplanin treatment.

## Statistical analysis

All statistical analyses were conducted using SPSS statistics for Windows, version 17.0. Data are described as number (percentage) for categorical variables and mean  $\pm$  SD, and median values (range/IQR) for continuous variables. Fisher's exact or  $\chi^2$  tests was used to compare groups for categorical variables. Comparisons were conducted using Student's *t*-test or Mann–Whitney *U* test for continuous variables and one-way analysis of variance or Kruskal–Wallis test for continuous variables. Relationships among the teicoplanin loading-regimen ratio and  $Cl_{cr}$  and  $C_{min}$  were analyzed using Pearson's correlation analysis. Relationships between clinical response and  $C_{min}$  and between safety assessment and  $C_{min}$  were analyzed using binary logistic regression.  $P < 0.05$  was considered statistically significant.

## Results

### Patient demographic data

Demographic data and clinical characteristics for all included patients are displayed in Table 1. No differences were found for age, sex, body weight, serum albumin, ALT, or AST among the four groups. No significant differences were found in the ratio of coadministered antibiotics ( $\beta$ -lactams, carbapenems, quinolones, or aminoglycosides) with teicoplanin or in the basic diseases (hypertension, diabetes, coronary heart disease, cerebral infarction, hyperlipidemia, or bone disease) among the four groups (all  $P > 0.05$ ; data not shown). Teicoplanin-therapy duration differed significantly among the four groups ( $F = 3.415$ ,  $P = 0.02$ ), but did not differ significantly between groups A, B, and C (A vs B,  $P = 0.805$ ; B vs C,  $P = 0.749$ ; A vs C,  $P = 0.903$ ).

### Teicoplanin trough concentration

Teicoplanin  $C_{min}$  values in the four groups are shown in Table 2 and Figure 2.  $C_{min}$  was 18.11  $\pm$  6.37 mg/L, 15.91  $\pm$  4.94 mg/L, 17.06  $\pm$  5.66 mg/L, and 11.97  $\pm$  3.76 mg/L in groups A, B, C, and D, respectively. The proportion of patients achieving the target range (15–30 mg/L) was 69.44% (25 of 36), 66.67% (20 of 30), 70.59% (12 of 17), and 23.33% (seven of 30) in groups A, B, C, and D ( $\chi^2 = 18.529$ ,  $P < 0.001$ ) on day 4, respectively. Compared with group D,  $C_{min}$  was higher in groups A, B, and C (11.97 vs 18.11, 15.91, and 17.06).

**Table 1** Demographic data and clinical characteristics of subjects

	Group A, n=36	Group B, n=30	Group C, n=17	Group D, n=30	P
Sex (male/female), n	26/10	21/9	13/4	19/11	0.788
Age (years)	78.17 $\pm$ 14.28	82.53 $\pm$ 6.91	81.82 $\pm$ 13.06	76.37 $\pm$ 13.78	0.2
Body weight (kg) <sup>a</sup>	67.51 $\pm$ 8.98	69.93 $\pm$ 6.32	65.35 $\pm$ 9.76	65.67 $\pm$ 8.3	0.168
Albumin (g/L) <sup>a</sup>	29.11 $\pm$ 3.71	29.48 $\pm$ 3.61	28.82 $\pm$ 4.76	29.43 $\pm$ 4.59	0.945
Loading dose for 3 days (mg)	2,000–2,400	2,000	1,200	1,200–1,600	
AST (U/L) <sup>a</sup>	27.24 $\pm$ 11.1	29.77 $\pm$ 12.26	27.06 $\pm$ 10.78	24.47 $\pm$ 10.71	0.35
ALT (U/L) <sup>a</sup>	23.81 $\pm$ 14.51	20.57 $\pm$ 10.51	20.06 $\pm$ 10.89	19.7 $\pm$ 10.97	0.504
$Cl_{cr}$ (mL/min) <sup>a</sup>	89.62 (53.72–162.48)	49.66 (40.69–59.64)	27.17 (9.7–39.45)	96.6 (17.63–394.73)	<0.001
Duration of teicoplanin therapy (days)	7.09 $\pm$ 2.93	6.70 $\pm$ 2.64	7 $\pm$ 2.67	8.27 $\pm$ 3.64	0.02
Maintenance dose (mg/day)	402.47 $\pm$ 88.23	358.3 $\pm$ 74.39	236.65 $\pm$ 51.74	344.63 $\pm$ 86.7	0.036

**Notes:** <sup>a</sup>Day 1 of teicoplanin therapy. Data presented as mean  $\pm$  SD or medians (range/IQR) for continuous variables. For sex, comparison with  $\chi^2$  test; for age, body weight, albumin, dose, duration of therapy, ALT, and AST, comparison with one-way analysis of variance; for  $Cl_{cr}$ , comparison with Kruskal–Wallis test.

**Abbreviation:**  $Cl_{cr}$ , creatinine clearance.

**Table 2** Teicoplanin trough concentration

	Group A, n=36	Group B, n=30	Group C, n=17	Group D, n=30	$F/\chi^2$	P
$C_{min}$	18.11 $\pm$ 6.37	15.91 $\pm$ 4.94	17.06 $\pm$ 5.66	11.97 $\pm$ 3.76	7.849 <sup>a</sup>	<0.001
10–30 mg/L	32 (88.89%)	26 (86.67%)	15 (88.23%)	21 (70%)	5.136 <sup>a</sup>	>0.05
15–30 mg/L	25 (69.44%)	20 (66.67%)	12 (70.59%)	7 (23.33%)	18.529 <sup>a</sup>	<0.001

**Notes:** Data presented as mean  $\pm$  SD and n (%). <sup>a</sup>One-way analysis of variance; <sup>b</sup> $\chi^2$  test for categorical variables.

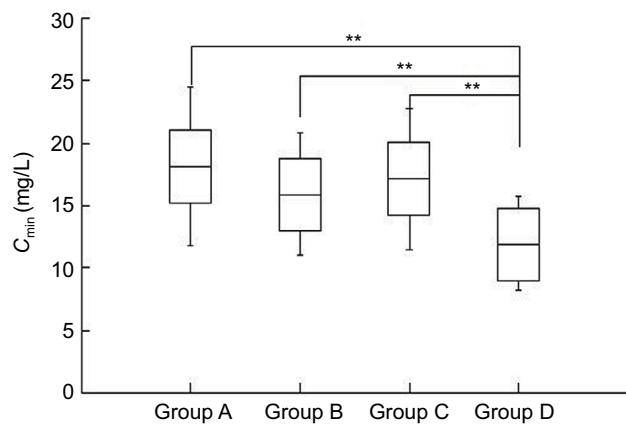
**Abbreviation:**  $C_{min}$ , minimum concentration.

The proportion of  $C_{min}$  15–30 mg/L and 20–30 mg/L was higher in groups A, B, and C than in group D (Figure 3). As shown in Figure 4, there was a significant correlation between the  $C_{min}$  and the ratio of loading dose for the 3 days to  $Cl_{cr}$  ( $R=0.59, P<0.001$ ).

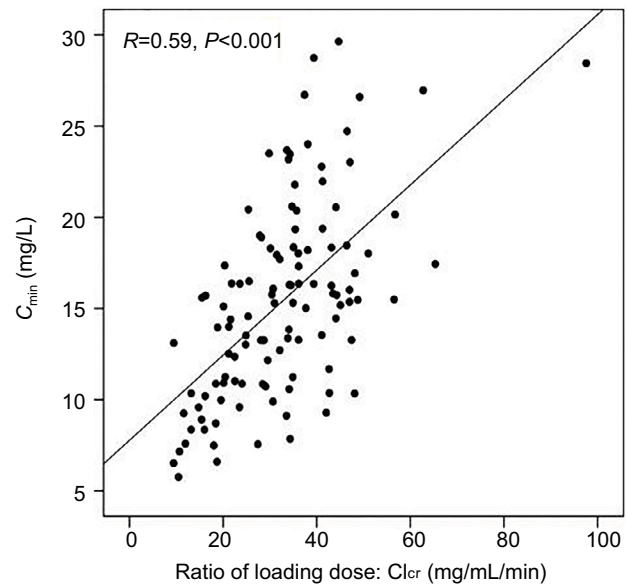
### Clinical efficacy of teicoplanin

Efficacy among the four groups differed significantly (Table 3). Compared with patients in group D, patients in groups A, B, and C had significantly higher clinical response rates ( $\chi^2=11.438, P=0.001$ ;  $\chi^2=5.455, P=0.020$ ;  $\chi^2=5.797, P=0.016$ ). No obvious differences were seen in clinical efficacy for

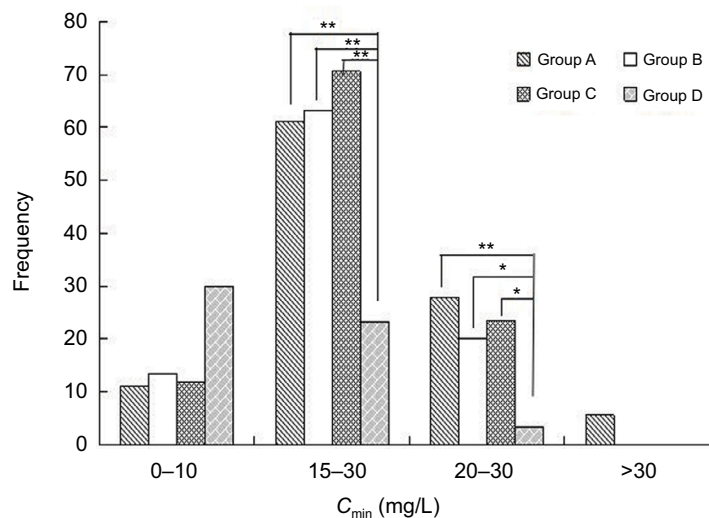
patients in group A (80.56%, 29 of 36), group B (70%, 21 of 30), or group C (76.47%, 13 of 17) ( $\chi^2=1.001, P=0.606$ ). Body temperature did not significantly differ among the four groups after treatment. White blood cell counts and CRP were lower for patients in groups A, B, and C than group D. However, no significant differences were observed among groups A, B, and C posttreatment. Differences in bacteriological efficacy rates were significant among the four groups ( $\chi^2=11.999, P=0.007$ ). As a result, the mean teicoplanin  $C_{min}$  for a successful response



**Figure 2** Mean teicoplanin  $C_{min}$ , measured on the fourth day in all patients.  
**Notes:** Teicoplanin  $C_{min}$  shown as mean  $\pm$  SD for each group: A, n=36; B, n=30; C, n=17; D, n=30. Blocks, mean teicoplanin  $C_{min}$ ; vertical lines, SD. Comparison between groups with one-way analysis of variance. \*\* $P<0.01$  (group A vs group D, group B vs group D, group C vs group D).  
**Abbreviation:**  $C_{min}$ , minimum concentration.



**Figure 4** Relationship between serum trough concentration and ratio of loading dose for 3 days to  $Cl_{cr}$  in 113 patients.  
**Notes:** There was a significant correlation between serum trough concentration and ratio of loading dose for 3 days to  $Cl_{cr}$  ( $R=0.59, P<0.001$ ).  
**Abbreviations:**  $C_{min}$ , minimum concentration;  $Cl_{cr}$ , creatinine clearance.



**Figure 3** Distribution of teicoplanin  $C_{min}$  values on the fourth day.  
**Notes:** Frequency = (number of subjects achieving target range [15–30 mg/L] or [20–30 mg/L])/number in group. \* $P<0.05$ , \*\* $P<0.01$  (group A vs group D, group B vs group D, group C vs group D;  $\chi^2$  test).  
**Abbreviation:**  $C_{min}$ , minimum concentration.

(18.92±5.12 mg/L) was significantly higher than for a failure (10.01±2.37 mg/L) ( $t=12.451$ ,  $P<0.001$ ). The correlation between the estimated probability of a successful response and teicoplanin  $C_{\min}$  was assessed using binary logistic regression (OR 2.038, 95% CI 1.553–2.676;  $P<0.001$ ), which demonstrated that the  $C_{\min}$  was significantly associated with an improved clinical response to teicoplanin.

## Assessment of hepatotoxicity and nephrotoxicity

For all 113 included patients, 10.62% and 4.42% had hepatotoxicity and nephrotoxicity, respectively. Incidence rates for hepatotoxicity and nephrotoxicity are shown in Table 4, and they did not significantly differ among the four groups ( $P=0.859$ ,  $P=0.949$ ). Compared with baseline levels, AST, ALT, and  $S_{\text{cr}}$  did not significantly differ after teicoplanin therapy (AST, group A,  $P=0.12$ ; group B,  $P=0.471$ ; group C,  $P=0.256$ ; group D,  $P=0.323$ ; ALT, group A,  $P=0.251$ ; group B,  $P=0.367$ ; group C,  $P=0.189$ ; group D,  $P=0.403$ ;  $S_{\text{cr}}$ , group A,  $P=0.546$ ; group B,  $P=0.352$ ; group C,  $P=0.238$ ; group D,  $P=0.437$ ). The correlation between hepatotoxicity or nephrotoxicity and covariates was assessed using binary logistic regression. As shown in Table 5, no covariates significantly affected hepatotoxicity or nephrotoxicity.

## Discussion

Microorganisms resistant to antibiotics increase the mortality, morbidity, and cost of infections. MRSA is the most frequently identified antimicrobial drug-resistant pathogen in US and Chinese hospitals.<sup>1,3,10,24</sup> Appropriate antibiotic use can help preserve the efficacy of current antibiotics, extend their life span, and protect the public from antibiotic-resistant infections.<sup>2,3,6,7,10,28</sup>

For severe infections, loading dose should be increased to maintain the  $C_{\min} >20$  mg/L according to the recommended guide.<sup>20</sup> Quickly achieving the target  $C_{\min}$  helps to reduce drug resistance; however, methods for adopting the optimal individualized loading regimen should be explored for pneumonia patients with Gram-positive infections to achieve the target  $C_{\min}$ . In this study, we also explored the relationships among teicoplanin-loading regimens, serum  $C_{\min}$ , efficacy, and patient safety.

In our study, mean  $C_{\min}$  on the fourth day differed significantly among the four groups ( $F=7.849$ ,  $P<0.001$ ; Table 2); however, it did not differ between group A and group B ( $P=0.095$ ), group B and group C ( $P=0.477$ ), or group A and group C ( $P=0.499$ ). The proportion of patients who achieved the target range (15–30 mg/L) on day 4 was higher in groups A, B, and C than in group D (Table 2).

**Table 3** Comparisons of teicoplanin clinical efficacy, n (%)

	Group A, n=36	Group B, n=30	Group C, n=17	Group D, n=30
Cure	29 (80.56%)	21 (70%)	13 (76.47%)	12 (40%)
Failure	7 (19.44%)	9 (30%)	4 (23.53%)	18 (60%)
Bacteriological effectiveness rate	28 (77.78%)	18 (60%)	10 (58.82%)	13 (36.67%)

**Table 4** Adverse-effect rates, n (%)

	Group A, n=36	Group B, n=30	Group C, n=17	Group D, n=30	P
Hepatotoxicity	4 (11.11%)	2 (6.67%)	2 (11.76%)	4 (13.33%)	0.859
Nephrotoxicity	2 (5.56%)	1 (3.33%)	1 (5.88%)	2 (3.33%)	0.949

Note: Comparisons with  $\chi^2$  test.

**Table 5** Binary logistic regression of hepatotoxicity and nephrotoxicity

	Hepatotoxicity					Nephrotoxicity				
	B	$\chi^2$	OR	95% CI	P	B	$\chi^2$	OR	95% CI	P
Sex	-0.045	0.699	0.956	0.243–3.762	0.948	0.034	0.975	1.035	0.153–6.988	0.972
Age	-0.192	0.3	0.826	0.458–1.487	0.523	-0.242	0.409	0.785	0.352–1.749	0.553
Albumin (g/L) <sup>a</sup>	-0.061	0.429	0.941	0.406–2.182	0.887	-0.726	0.541	0.484	0.168–1.397	0.180
Loading dose for 3 days (mg)	-0.032	0.381	0.969	0.459–2.042	0.933	-0.327	0.555	0.721	0.243–2.141	0.556
$C_{\min}$ (mg/L) <sup>b</sup>	0.478	0.507	1.613	0.597–4.361	0.346	0.946	0.724	2.575	0.623–10.633	0.191
$Cl_{\text{cr}}$ (mL/min) <sup>c</sup>	0.278	0.401	1.321	0.602–2.899	0.488	0.014	0.554	1.014	0.342–3.004	0.98

Notes: Data analyzed between safety assessment and  $C_{\min}$  using binary logistic regression. <sup>a</sup>Day 1 of teicoplanin therapy; <sup>b</sup>30 minutes before teicoplanin administration on day 4; <sup>c</sup> $Cl_{\text{cr}} = ([140 - \text{age (years)}] \times \text{body weight [kg]}) / ([0.818 \times S_{\text{cr}} [\mu\text{mol/L}]] (\text{male}), Cl_{\text{cr}} = ([140 - \text{age (years)}] \times \text{body weight [kg]}) / ([0.818 \times S_{\text{cr}} [\mu\text{mol/L}]] \times 0.85 (\text{female}))$ .

Abbreviations:  $C_{\min}$ , minimum concentration;  $Cl_{\text{cr}}$ , creatinine clearance;  $S_{\text{cr}}$ , serum creatinine.

Therefore, a high-loading-dose regimen is necessary to achieve the target  $C_{\min}$  range. This is consistent with previous research.<sup>9,14,15,17,20,21,23,27,29</sup> All patients were divided into groups based on  $Cl_{cr}$  and loading regimens. As a result, ratios of the 3-day loading dose to  $Cl_{cr}$  and  $C_{\min}$  were significantly correlated ( $R=0.59$ ,  $P<0.001$ ; Figure 4). This illustrated that a high loading regimen helped to achieve a high  $C_{\min}$  with normal renal function.

Previous findings implied that a high  $C_{\min}$  might be associated with better outcomes.<sup>15,16,18,21,30</sup> In this study, the mean teicoplanin  $C_{\min}$  of the 75 patients who had a successful response (clinical cure;  $18.92\pm 5.12$  mg/L) was significantly higher than that of the 38 patients who got a failed response ( $10.01\pm 2.37$  mg/L;  $P<0.001$ ).  $C_{\min}$  was significantly associated with an improved clinical response to teicoplanin using binary logistic regression ( $P<0.001$ ).

In general, patients with teicoplanin  $C_{\min} >60$  mg/L had high incidence of hepatotoxicity and nephrotoxicity.<sup>12,14,17,21,23,31</sup> In this study, hepatotoxicity and nephrotoxicity incidence rates did not differ significantly among the four groups (group A, 11.11%, 5.56%; group B, 6.67%, 3.33%; group C, 11.76%, 5.88%; group D, 13.33%, 3.33%;  $P=0.859$ ,  $P=0.949$ ) (Table 4). Correlations between hepatotoxicity/nephrotoxicity and covariates were assessed using binary logistic regression. None of the covariates significantly affected hepatotoxicity or nephrotoxicity (Table 5). In other words, the  $C_{\min}$  was not correlated with hepatotoxicity or nephrotoxicity. In our study, no patients had  $C_{\min} >40$  mg/L. Therefore, it could be inferred that the  $C_{\min}$  range in the loading regimen was not associated with hepatotoxicity or nephrotoxicity based on the  $Cl_{cr}$ . Therefore, teicoplanin is suggested as safe for patients infected with Gram-positive bacteria if  $C_{\min} <30$  mg/L.

## Conclusion

This study evaluated the relationships among teicoplanin-loading regimen,  $C_{\min}$ , clinical efficacy, and patient safety. The  $C_{\min}$  on day 4 was significantly associated with an improved clinical response to teicoplanin. A loading dose of 400 mg at 12-hour intervals three to six times is needed to achieve the early target range (15–20 mg/L) and improve clinical efficacy. Therefore, therapeutic drug monitoring is recommended to ensure teicoplanin  $C_{\min}$  is maintained within the target therapeutic range. Based on the day 4  $C_{\min}$ , the maintenance dose was adjusted to achieve the optimal  $C_{\min}$  and clinical efficacy and to avoid hepatotoxicity or nephrotoxicity. It is urgently necessary to revise the drug label on the recommended regimen to achieve satisfactory clinical efficacy.

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## Disclosure

The authors report no conflicts of interest in this work.

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