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ORIGINAL RESEARCH

Impact of Fungal Co-Infection on Teicoplanin Plasma Trough Concentration in Critically Ill Adults: A Novel Consideration for Dose Adjustment

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Objective: The pathophysiology and disease status of critically ill patients have a significant impact on the pharmacokinetics/pharmacodynamics (PK/PD) of antimicrobial agents. However, the effect of fungal co-infection on the plasma trough concentration (C_{min}) of teicoplanin in critically ill patients remains unclear.

Materials and Methods: A retrospective cohort study was carried out. Clinical data of patients admitted to the intensive care unit and receiving teicoplanin therapeutic drug monitoring were collected. Multiple linear stepwise regression analysis and binary logistic regression analysis were used to identify the factors influencing teicoplanin C_{min} and the achievement of the target C_{min} (≥15.0 μg/mL).

Results: A total of 404 teicoplanin C_{min} values from 231 patients were included. The mean teicoplanin C_{min} was 20.63 ± 10.40 μg/mL, and the percentage of C_{min} > 30.0 μg/mL was 15.8%. In the multivariate analysis, fungal co-infection was identified as an independent factor affecting teicoplanin C_{min} (B=4.056, 95% CI 2.089–6.023; p<0.001) and the attainment of the target C_{min} (OR=3.233, 95% CI 1.538–6.795; p=0.002). Sex, weight, teicoplanin dose, levels of direct bilirubin, blood urea nitrogen, estimated glomerular filtration rate, and uric acid were also found to be influencing factors. Patients with fungal co-infection had a higher teicoplanin C_{min} (p<0.001) and a higher percentage of C_{min} > 30.0 μg/mL (20.3% vs 12.0%; p=0.022) compared to those without, despite similar teicoplanin doses (p=0.302). The percentage of patients receiving continuous renal replacement therapy was higher in the fungal co-infection cohort (p=0.016), along with an older age and a lower body weight.

Conclusion: For critically ill patients with fungal co-infections, the teicoplanin dose should be decreased, or at least not increased. This is essential for reducing the potential risk of toxicity and customizing dosing strategies to meet individual patient needs. A large-scale, multi-center, prospective study is necessary to confirm the findings related to this dosing approach.

Keywords: teicoplanin, critically ill patients, therapeutic drug monitoring, fungal infection, direct bilirubin

Introduction

Teicoplanin, a glycopeptide antibiotic, is mainly used to treat a variety of severe Gram-positive bacterial infections, such as those caused by *Staphylococcus, Streptococcus, Enterococcus*, and most anaerobic positive bacteria, especially in patients who cannot tolerate penicillins and cephalosporins.[1] Compared with vancomycin, teicoplanin shows similar antimicrobial activity but has fewer adverse effects, such as nephrotoxicity and infusion reactions.[2,3] The plasma concentration of teicoplanin is closely related to its clinical efficacy. In different diseases, the teicoplanin plasma trough concentration (C_{min}) needs to reach the corresponding target value to meet the treatment requirements.[4,5] For patients with severe infections, monitoring teicoplanin C_{min} can improve the cure rate.[6–8] In febrile neutropenic patients with hematological malignancies, achieving a teicoplanin C_{min} ≥20 μg/mL at 48 hours significantly improves treatment success rates.[9,10] However, sustained C_{min} elevation over 10 days during therapy increases the risk of adverse events.[8]

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For patients with renal dysfunction, prompt attainment of teicoplanin C_{min} within 15–30 μg/mL is critical to optimize clinical outcomes, with comparable nephrotoxicity and hepatotoxicity incidence rates to those with C_{min} <15 μg/mL.[7]

Extreme inter- and intra-individual pharmacokinetic (PK) variability exists in intensive care unit (ICU) patients.[11] The variability in teicoplanin exposure is also significant in critically ill patients.[12–15] Due to the complex pathophysiology and disease status of critically ill patients, the incidence of suboptimal teicoplanin C_{min} during conventional dosing is relatively high.[16,17] Thus, therapeutic drug monitoring (TDM) of teicoplanin C_{min} in critically ill patients is recommended. Previous studies on teicoplanin C_{min} in critically ill patients mainly focused on the influence of various physiological factors such as age and renal function on the achievement of C_{min} (≥ 15–30 μg/mL).[18–20] However, patients with severe infections admitted to the ICU are often associated with multiple bacterial or fungal infections and the combined use of various antimicrobial agents. In a worldwide multicenter study involving 1150 centers in 88 countries, Gram-negative bacteria were detected in 67% of ICU patients, Gram-positive bacteria in 37%, and fungal microorganisms in 16%.[21] Moreover, critically ill patients usually undergo extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), mechanical ventilation, etc.[6,22] The impact of these factors on the C_{min} and standard attainment rate of teicoplanin has been rarely reported. It is necessary to investigate the effect of these factors on teicoplanin C_{min} in critically ill patients.

In patients with severe infections, teicoplanin is often empirically combined with anti-Gram-negative antibiotics. These patients may also be frequently infected with fungi. Critically ill patients with fungal infections are often immunocompromised,[23] and the influence on the PK of antimicrobial agents may be more pronounced. In fungal infections, pathogen-associated molecular patterns activate pattern recognition receptors, initiating inflammatory cytokine production.[24] Systemic inflammatory response syndrome-driven cytokine overexpression enhances vascular permeability, expanding the volume of distribution for hydrophilic antimicrobials. Concurrently, these cytokines downregulate metabolic enzymes, reducing drug clearance.[25] In addition, anti-fungal drugs amphotericin B exhibits pronounced nephrotoxic potential, whereas triazole antifungals pose minimal indirect nephrotoxic risks.[26] Caspofungin demonstrates high albumin binding (≈97%), while voriconazole (58% binding) displays nonlinear pharmacokinetics and hepatotoxicity.[27,28] These factors collectively influence teicoplanin metabolism.

Currently, the effect of fungal co-infection on teicoplanin C_{min} in critically ill patients remains unclear. In this study, we explored the influencing factors of teicoplanin C_{min} in critically ill adult patients using real-world data. Common physiological parameters, fungal co-infection status, combined use of potentially nephrotoxic antimicrobials, liver function indicators, and the receipt of CRRT, ECMO, and mechanical ventilation were included as influencing factors.

Patients and Methods

Patients and Study Design

This was a retrospective study. Patients who met the following criteria and were admitted to Southwest Hospital, Chongqing, China, from January 1, 2018, to December 31, 2023, were included: a) admitted to the ICU; b) aged ≥ 18 years; c) received teicoplanin TDM, and the C_{min} was at steady state (measured before the next dose after at least 6 doses); d) had the required clinical data; e) was not currently pregnant.

Teicoplanin C_{min} Measurement

Venous blood was drawn before the next dose after at least 6 doses of teicoplanin administration. Plasma total teicoplanin concentrations were determined using the high-performance liquid chromatography method. The linear range of teicoplanin was 3.125–100.0 μg/mL.

Data Collection

The following data were collected: a) Baseline characteristics: These included sex, age, height, weight, clinical diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, details regarding whether the patient underwent CRRT or ECMO, mechanical ventilation duration, as well as the types of infected bacteria and fungi. b) Combination drug information: This involved the dosage of teicoplanin and details about the concurrent use of other antimicrobials. c) Laboratory test indices measured within 3 days before detecting the teicoplanin concentration: Liver function parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transferase (γ-GT), alkaline phosphatase (ALP), albumin, total bile acid

(TBA), total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL). Renal function indicators like serum creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), and uric acid.

Statistical Analysis

Sample size was calculated using the Events Per Variable principle. With 12 variables included in regression analysis and a 40% probability of suboptimal teicoplanin C_{min}, the required sample size was determined as 12×10/0.4=300. Missing data were managed as follows: <20% missingness was imputed with the latest available values, followed by recalculating missing proportions. If ≥90% data remained after imputation, median substitution was applied; otherwise, cases were excluded. Variables with >20% missingness were removed entirely.

IBM SPSS 26.0 software was employed for statistical analysis. Counting data were expressed as the rate (%), and were compared using the chi-square test. For measurement data that conform to a normal distribution, they are presented as the mean ± standard deviation, and compared by means of the *t*-test. Data with a non-normal distribution are shown as the median (interquartile range), and compared through the Mann–Whitney *U*-test. Multiple linear stepwise regression analysis was carried out to determine the factors affecting teicoplanin C_{min}. Binary logistic regression analysis was used to identify the factors influencing the attainment of the teicoplanin C_{min} target. Multicollinearity was evaluated via tolerance values and variance inflation factors (VIF). Tolerance <0.1–0.2 and VIF >5–10 indicated significant collinearity issues. The covariates with a *p*-value of < 0.1 in the univariate analysis were included in the multivariate analysis. For critically ill patients, a teicoplanin C_{min} ≥ 15.0 μg/mL was set as the research target.[4,29] A *p*-value < 0.05 was considered to indicate a statistically significant difference.

Results

Patient Characteristics

A total of 404 teicoplanin C_{min} values from 231 patients were included in the analysis (Table 1). Most patients were male, accounting for 72.3%. The age of patients ranged from 19 to 101 years. The APACHE II score of patients was 27±10, 51.9% of patients received CRRT, and 12.1% received ECMO. The median duration of mechanical ventilation was 12

Table 1 Clinical Characteristics of Patients

Variable	n=231
Sex	
Male (n [%])	167 (72.3)
Female (n [%])	64 (27.7)
Age (y)	58±18
Weight (kg)	62.1±13.3
APACHE II score	27±10
CRRT (no. [%])	120 (51.9)
ECMO (no. [%])	28 (12.1)
Duration of mechanical ventilation (days)	12 (6, 26)
Combined antibiotics	
Meropenem (no. [%])	90 (39.0)
Imipenem/cilastatin (no. [%])	82 (35.5)
Piperacillin/tazobactam (no. [%])	28 (12.1)
Polymyxin B (no. [%])	26 (11.3)
Cefperazone/sulbactam (no. [%])	17 (7.4)
Tigecycline (no. [%])	6 (2.6)
Amikacin (no. [%])	3 (1.3)
Ceftazidime/avibactam (no. [%])	3 (1.3)
Levofloxacin (no. [%])	3 (1.3)
Cefepime (no. [%])	3 (1.3)

(*Continued*)

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Table 1 (Continued).

Variable	n=231
Combined antifungal drugs (no. [%])	
Caspofungin (no. [%])	51 (22.1)
Voriconazole (no. [%])	48 (20.8)
Amphotericin B (no. [%])	11 (4.8)
Micafungin (no. [%])	5 (2.2)
Fluconazole (no. [%])	4 (1.7)
Isavuconazole (no. [%])	2 (0.9)
Teicoplanin dosage (mg/d)	676±248
Teicoplanin trough concentration (μg/mL)	20.63±10.40

Note: Data are presented as the mean ± standard deviation or no. [%].
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

days. Each patient received at least one combination of antimicrobial agents. The main antibiotics used in combination were meropenem, imipenem/cilastatin, piperacillin/tazobactam, and polymyxin B. The main antifungal agents used in combination were caspofungin and voriconazole.

The dosage of teicoplanin was 676±248 mg/d, and the C_{min} was 20.63±10.40 μg/mL. Teicoplanin dosages (mg/d) from 2018–2023 were: 583±254, 733±247, 720±216, 696±289, 693±239, and 672±242. Dosages from 2019–2023 were significantly higher than in 2018 ($p<0.05$), with no significant interannual variations between 2019–2023. The percentages of teicoplanin C_{min} reaching the target from 2018 to 2023 were 24.0% (12/50), 61.1% (11/18), 65.0% (26/40), 69.4% (34/49), 75.0% (66/88), and 77.4% (123/159), respectively. The percentage of teicoplanin C_{min} > 30.0 μg/mL was 15.8% (64/404). Two patients had teicoplanin C_{min} > 60.0 μg/mL.

The main detected Gram-positive bacteria were *Enterococcus faecium, Staphylococcus aureus, Staphylococcus haemolyticus, Staphylococcus epidermidis, Enterococcus faecalis*, and *Streptococcus mitis*; the main detected Gram-negative bacteria were *Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Escherichia coli, Enterobacter cloacae*, and *Proteus mirabilis*; and the main detected fungi were *Candida, Aspergillus*, and *Saccharomyces* (Figure 1). Many patients received teicoplanin for empirical and combined use.

The laboratory data of patients are shown in Table 2. The median values of AST, γ-GT, TBIL, DBIL, IBIL, and BUN were higher than the upper limit of normal. The mean value of albumin was lower than the lower limit of normal.

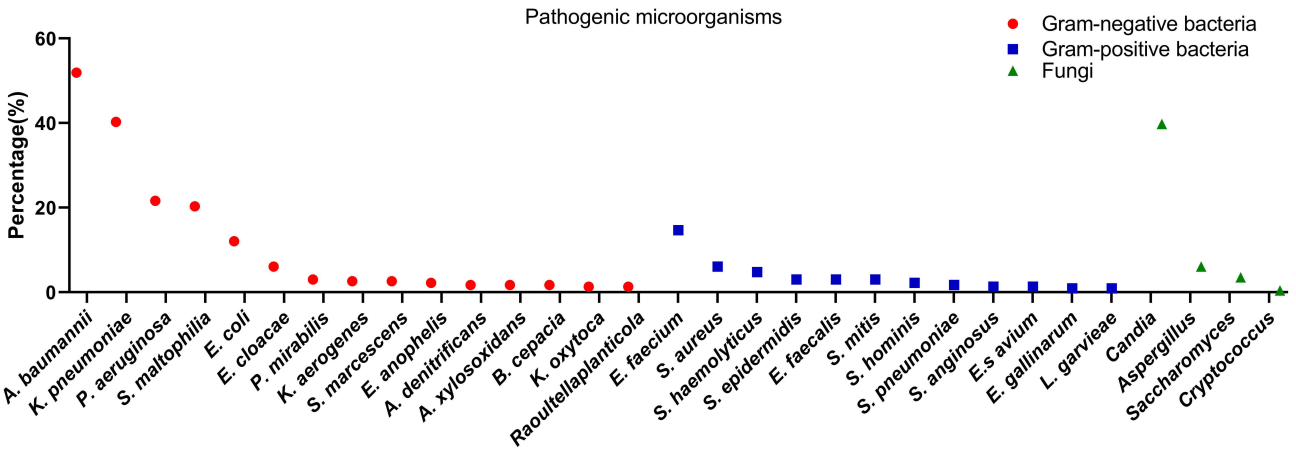

Figure 1 Pathogenic microorganisms cultured.

Table 2 Laboratory Data of Patients

Variable	n=404
Liver function	
ALT (0–42 U/L)	33.8 (17.3, 74.4)
AST (0–42 U/L)	53.9 (32.5, 108.3)
γ-GT (4–50 U/L)	84.4 (41.6, 146.0)
ALP (50–135 U/L)	114 (77, 171)
Albumin (38–51 g/L)	34.1±5.1
TBIL (6–21 μmol/L)	30.4 (16.6, 81.8)
DBIL (0–6 μmol/L)	12.1 (5.1, 44.6)
IBIL (3–16 μmol/L)	16.6 (10.0, 31.5)
TBA (0–10 μmol/L)	7.9 (4.0, 16.8)
Renal function	
BUN (1.7–8.3 mmol/L)	12.5 (7.9, 19.6)
Creatinine (59–104 μmol/L)	88.2 (56.7, 148.9)
eGFR (80–120 mL/min)	77.3 (38.6, 112.8)
Uric acid (155–428 mmol/L)	180 (112, 302)

Note: Data are presented as the mean ± standard deviation or median (interquartile range).

Abbreviations: ALT, glutamic-pyruvic transaminase; AST, glutamic-oxalacetic transaminase; γ-GT, γ-glutamyl transferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TBA, total bile acid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Factors Influencing Teicoplanin C_{min}

In the multivariate analysis, factors influencing teicoplanin C_{min} were sex, teicoplanin dose, levels of DBIL and BUN, and fungal co-infection (Table 3). In the univariate analysis, factors influencing the attainment of teicoplanin target C_{min} were sex, weight, APACHE II score, teicoplanin dose, combined use of polymyxin B, amikacin, and amphotericin B, levels of TBIL, DBIL, serum creatinine, uric acid, BUN, and eGFR, and fungal co-infection (Figure 2). We also compared the teicoplanin C_{min} values between patients who used caspofungin and those who did not, as well as between patients who used voriconazole and those who did not. The results showed no significant differences. For the caspofungin comparison, the values were 20.12 (14.67, 26.68) μg/mL and 19.67 (12.38, 25.45) μg/mL with a *p*-value of 0.172. For the voriconazole comparison, the values were 18.48 (10.84, 24.24) μg/mL and 19.74 (13.22, 26.18) μg/mL with a *p*-value of 0.172. The independent risk factors for the attainment of teicoplanin target C_{min} were female, low weight, high teicoplanin dose, low eGFR, high uric acid, and fungal co-infection (Table 4). Our findings demonstrate that fungal co-infection independently influences both teicoplanin C_{min} and achievement of target C_{min}, representing a novel observation not previously documented in the literature.

Table 3 Influencing Factors for Teicoplanin C_{min}

Variable	B (95% CI)	Beta	*p*-value
Constant	6.501 (1.121, 11.881)	–	0.018
Teicoplanin dose	0.014 (0.010, 0.017)	0.348	<0.001
Urea nitrogen	0.269 (0.177, 0.360)	0.273	<0.001
Female	6.084 (3.873, 8.294)	0.255	<0.001
Without fungal co-infection	−4.056 (−6.023, −2.089)	−0.189	<0.001
DBIL	−0.028 (−0.049, −0.007)	−0.121	0.010

Abbreviation: DBIL, direct bilirubin.

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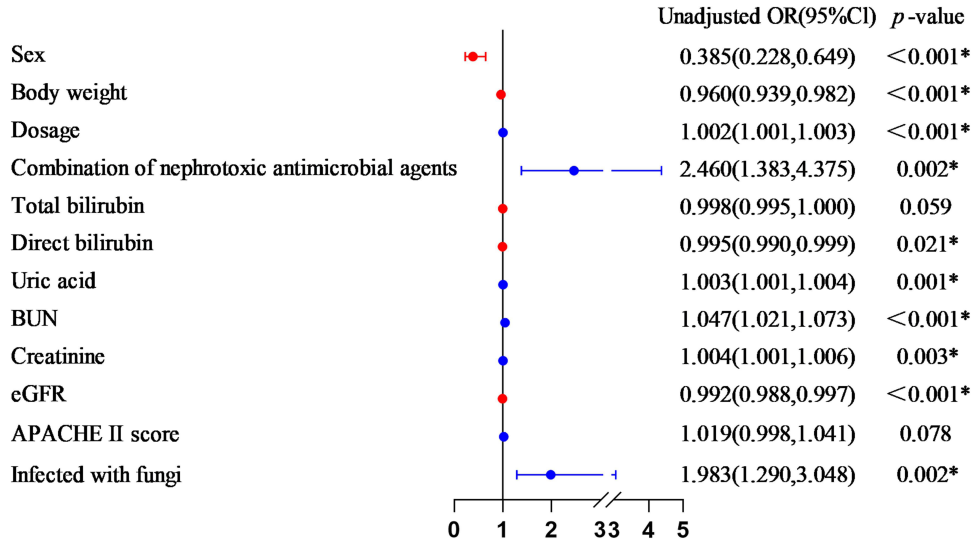

Figure 2 Factors influencing the attainment of teicoplanin target C_{min} in the univariate analysis. *p<0.05.

Clinical Characteristics of Patients with Fungal Co-Infection

A total of 100 (43.3%) patients had fungal co-infection. The comparison of clinical characteristics between patients with and without fungal co-infection was shown in Table 5. Patients with fungal co-infection had a higher teicoplanin C_{min} compared to those without (p<0.001), although the teicoplanin doses were similar (Figure 3). Compared with patients without fungal infection, the percentage of teicoplanin C_{min} >30.0 μg/mL was also higher in patients with fungal co-infection (20.3% vs 12.0%; p=0.022). Additionally, the percentage of patients receiving CRRT was higher in the fungal co-infection cohort (p=0.016), along with an older age and a lower body weight. Liver and renal functions were similar in the two cohorts (p>0.05).

Discussion

In this study, the percentages of teicoplanin C_{min} reaching the target increased year by year from 2018 to 2023, ranging from 24.0% in 2018 to 77.4% in 2023. According to the latest consensus review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring, a target C_{min} value ranging from 15 to 30 μg/mL leads to better clinical efficacy and comparable adverse effects in patients with non-complicated methicillin-resistant *Staphylococcus aureus* (MRSA) infections compared to a C_{min} value of less than 15 μg/mL.[30] This study investigated the influencing factors of teicoplanin C_{min} in critically ill patients based on 6-year data and found that sex, DBIL, and fungal co-infection were new factors influencing teicoplanin C_{min}, in addition to previously known factors such as dose, body weight, and renal function.[17,31–33]

Table 4 Factors Influencing the Achievement of Teicoplanin Target C_{min}

Variable	B	OR (95% CI)	*p*-value
Male	−1.551	0.212 (0.073, 0.617)	0.004
Body weight	−0.047	0.954 (0.923, 0.980)	0.006
Teicoplanin dose	0.004	1.004 (1.002, 1.005)	<0.001
eGFR	−0.010	0.990 (0.981, 0.999)	0.029
Uric acid	0.004	1.004 (1.001, 1.007)	0.015
Fungal co-infection	1.174	3.233 (1.538, 6.795)	0.002

Abbreviation: eGFR, estimated glomerular filtration rate.

Table 5 Clinical Characteristics of Patients with and without Fungal Co-Infection

Variable	Fungal Co-Infection (n=100)	Without Fungal Co-Infection (n=131)	*p*-value
Sex			0.613
Male (n [%])	74 (74.0)	93 (71.0%)	
Female (n [%])	26 (26.0)	38 (29.0)	
Age (y)	61±19	56±17	0.065
Weight (kg)	59.8±12.7	63.8±13.5	0.075
APACHE II score	28±10	27±9	0.139
CRRT (no. [%])	61 (61.0)	59 (45.0)	0.016
ECMO (no. [%])	11 (11.0)	72 (55.0)	0.648
Duration of mechanical ventilation (days)	16 (6, 28)	11 (6, 26)	0.216
Teicoplanin dosage (mg/d)	680±262	709±297	0.302
Teicoplanin plasma concentration (μg/mL)	21.83 (15.41, 28.14)	17.52 (11.30, 22.98)	<0.001
Liver function			
ALT (0–42 U/L)	31.3 (15.8, 58.5)	37.1 (18.7, 85.4)	0.087
AST (0–42 U/L)	47.4 (30.0, 99.0)	58.6 (34.0, 122.1)	0.067
γ-GT (4–50 U/L)	76.6 (41.6, 135.6)	89.4 (41.4, 153.4)	0.650
ALP (50–135 U/L)	121.7 (80.0, 168.5)	109.0 (72.8, 179.3)	0.380
Albumin (38–51 g/L)	33.8±4.5	34.4±5.5	0.251
TBIL (6–21 μmol/L)	30.3 (15.5, 76.2)	30.5 (17.4, 85.7)	0.413
DBIL (0–6 μmol/L)	12.1 (4.4, 45.2)	12.2 (5.1, 44.6)	0.581
IBIL (3–16 μmol/L)	16.1 (9.2, 29.2)	16.8 (10.9, 35.4)	0.128
TBA (0–10 μmol/L)	8.2 (4.2, 16.4)	7.2 (3.8, 17.8)	0.373
Renal function			
Urea nitrogen (1.7–8.3 mmol/L)	12.8 (7.8, 21.8)	12.5 (8.0, 17.4)	0.317
Creatinine (59–104 μmol/L)	69.8 (33.5, 116.5)	81.5 (44.0, 110.2)	0.281
eGFR (80–120 mL/min)	91.9 (53.8, 167.0)	82.0 (59.1, 138.6)	0.166
Uric acid (155–428 mmol/L)	192.6 (113.6, 327.2)	171.5 (108.8, 278.0)	0.117

Note: Data are presented as the mean ± standard deviation, median (interquartile range) or no. [%].
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ALT, glutamic-pyruvic transaminase; AST, glutamic-oxalacetic transaminase; γ-GT, γ-glutamyl transferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TBA, total bile acid; eGFR, estimated glomerular filtration rate.

Teicoplanin has a high plasma protein binding rate, a binding rate of 90% to 95% with albumin, and a long elimination half-life.[14,34] Except for 2–3% metabolized by the liver, most is excreted by the kidney. Some studies have suggested that body weight, albumin level, and renal function play significant roles in influencing free teicoplanin C_{min} and PK parameters.[13,35,36] In critically ill patients, a high Sequential Organ Failure Assessment (SOFA) score and low serum albumin have been reported as risk factors for decreased teicoplanin C_{min} during initial dosing.[37] However, hypoalbuminemia did not seem to affect total teicoplanin concentrations.[13] In this study, we measured total plasma teicoplanin concentrations and did not find an effect of serum albumin on the concentration, but DBIL significantly affected teicoplanin C_{min}. The possible mechanism is that bilirubin is mainly (up to 90%) bound to proteins, which in turn causes the displacement of drugs from albumin.[38]

In a prospective study investigating the population PK model of teicoplanin concentrations in patients hospitalized in the ICU, eGFR was associated with systemic clearance.[16,39] We also found that eGFR was an independent factor influencing the achievement of the teicoplanin C_{min} target, along with other renal function indicators BUN and uric acid.

Previous studies on therapeutic monitoring of teicoplanin were mostly focused on critically ill patients infected with Gram-positive bacteria. In a prospective study evaluating the effect of CRRT on the clearance of teicoplanin, the early stage albumin level could significantly affect the initial C_{min} and the eradication of Gram-positive bacteria, and also had an effect on the clearance of teicoplanin by CRRT.[6] In a study focused on optimizing the antimicrobial dosing regimen for critically ill patients with MRSA infections, the dose of CRRT has an effect on the probability of reaching the target,

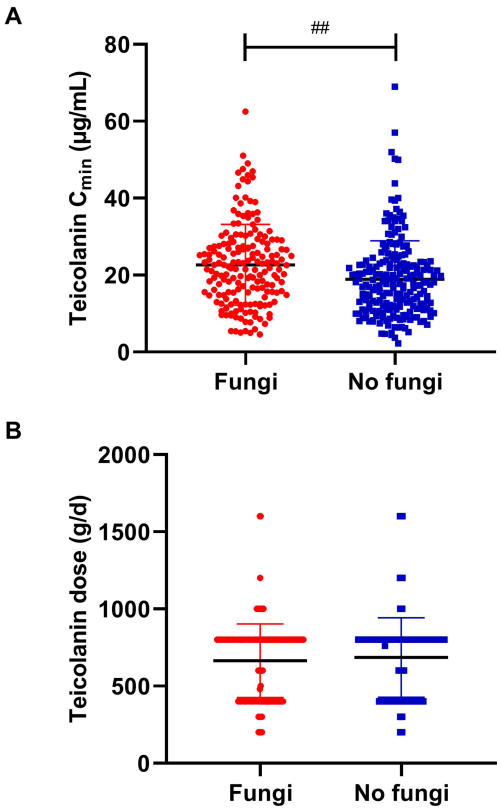

Figure 3 Comparison of teicoplanin C_{min} and dosage between patients with and without fungal co-infection. (**A**) Patients with fungal co-infection had a significantly higher teicoplanin C_{min} than those without. (**B**) The teicoplanin dosages were comparable between patients with and without fungal co-infection. $^{##}p<0.01$.

and the CRRT modality influences the clearance of teicoplanin.[40] We did not find the effect of CRRT on teicoplanin C_{min} in the present study. However, the percentage of patients receiving CRRT was higher in patients with fungal co-infection, and these patients had a higher teicoplanin C_{min}.

Disease severity, concurrent antimicrobial therapies, and inflammatory responses can all have an impact on teicoplanin metabolism. They do so by influencing liver and kidney function and triggering drug-drug interactions. In the present study, the APACHE II score demonstrated a trend of influencing the teicoplanin C_{min}, which was set as the research target. The combined use of polymyxin B, amikacin, and amphotericin B had a notable effect on teicoplanin C_{min}. However, in the multiple regression analysis, neither the use of other antimicrobial agents nor disease severity emerged as an independent influencing factor. Additionally, there were no significant differences in teicoplanin C_{min} between patients who used caspofungin and those who did not, and between patients who used voriconazole and those who did not. This suggests that a combination of multiple factors in fungal-infected critically ill patients likely affects teicoplanin concentrations. Further exploration of the underlying mechanisms connecting fungal co-infection to the altered pharmacokinetics of teicoplanin could offer valuable insights for optimizing antimicrobial regimens in complex clinical settings.

The recommended blood concentration of teicoplanin shows substantial variability depending on the severity and location of infections, rather than on the severity of the underlying illness.[18] However, limited data were available for critically ill patients with fungal co-infection. Infected critically ill patients may have unfavorable outcomes due to inadequate antibiotic exposure resulting from altered PK and pharmacodynamic parameters of antibiotics. Conversely, in patients with fungal co-infection, these critically ill patients may also experience adverse outcomes owing to a compromised immune system and excessive exposure to teicoplanin.[41] In our study, the proportion of patients with fungal co-infection was high, and teicoplanin C_{min} were significantly higher in patients with fungal infection, as well as the percentage of teicoplanin C_{min} >30.0 μg/mL at a similar teicoplanin dose. For critically ill patients with fungal co-infections, maintaining a teicoplanin C_{min} above 30.0 μg/mL for an extended period may pose a high risk of toxicity. It is

worth noting that patients with fungal infection were older and had a lower body weight, who may be more likely to develop adverse reactions.

Fungal products, such as beta-glucans and candidalysin, can activate the host's immune system, thereby exacerbating liver and biliary diseases.[42] Additionally, immune complexes are formed and can be deposited in the kidney tissue, resulting in inflammation and damage. Fungi are capable of directly invading the kidney tissue, causing cellular damage and triggering inflammatory reactions. Moreover, certain fungi produce toxins that exert toxic effects on kidney cells, contributing to the development of nephritis. In the context of acute kidney injury, the clearance of antimicrobials that are primarily excreted by the kidneys, like teicoplanin, is affected.

In critically ill patients, simulations have shown that the standard dosage regimen is only adequate for patients with severe renal dysfunction (eGFR ≤30 mL/min/1.73 m²) to reach the target C_{min}, with a probability of target attainment (PTA) of 52.8%. When the eGFR is greater than 30 mL/min/1.73 m², adjusting the dose by increasing it and modifying the administration frequency of the loading doses are preferable strategies to achieve the target C_{min}, depending on the patient's renal function and the type of infection.[16] In critically ill patients with sepsis, simulations based on a population PK model have indicated that for patients with varying renal functions, administering 3 or 5 loading doses of 12/15 mg/kg every 12 hours, followed by a maintenance dose of 12/15 mg/kg every 24 to 72 hours, is necessary to achieve a target C_{min} of 15 μg/mL.[39] In elderly critically ill patients with pneumonia, model-based simulations have demonstrated that a PTA of at least 85% can only be achieved with higher-dose regimens (12 mg/kg) when the minimum inhibitory concentration (MIC) is up to 0.5 mg/L.[20] Optimal teicoplanin dosing under CRRT doses ≤25 mL/kg/h was determined in previous study; When CRRT doses increased to 30–35 mL/kg/h, teicoplanin dosing required a 30–40% escalation.[40] However, all of these existing studies have not taken into account the influence of fungal co-infection. Hence, it is essential to establish further population PK models that specifically focus on critically ill patients with fungal co-infection, so as to optimize the teicoplanin dosage for these patients.

There were several limitations in this study. First of all, this analysis relies on data collected from a single center of critically ill patients, and there might be certain biases. Secondly, as a single-center retrospective study, our research was unable to conduct external validation or perform other types of analyses. Nevertheless, two regression analysis models were employed in this study. The outcomes of the multiple linear stepwise regression analysis and the binary logistic regression analysis demonstrated that fungal co-infection acts as both an independent influencing factor for the teicoplanin C_{min} and the attainment of the target C_{min}. Thirdly, disease severity may independently impact teicoplanin C_{min}. In our analysis, we only incorporated the APACHE II score. Although some patients with sepsis had SOFA scores, the proportion of such patients was relatively low, and thus, they were not included in the analysis. Additionally, we did not analyze the association between teicoplanin C_{min} and clinical outcome. However, many patients in our study received teicoplanin for empirical use, and it is difficult to evaluate the association between teicoplanin C_{min} and clinical outcome. Future studies exploring the correlation between drug exposure and therapeutic efficacy or toxicity in critically ill patients with fungal co-infection are needed. Finally, although the sample size is adequate, a larger sample size could assist in including more covariates.

Conclusion

In summary, we reported for the first time that fungal co-infection was an independent risk factor influencing teicoplanin C_{min} in critically ill adult patients. Patients with fungal co-infection had a higher teicoplanin C_{min} and a higher percentage of the concentration >30.0 μg/mL. In critically ill patients with fungal co-infection, the teicoplanin dosage should either be lowered or, at the very least, not be increased. This is to minimize the risks of toxicity and to fine-tune individualized dosing strategies. In addition, sex and DBIL were also factors influencing teicoplanin C_{min}, in addition to body weight, teicoplanin dose, and renal function indicators, which should be considered in the clinical use of teicoplanin in critically ill adult patients. Considering that the data were collected from a single center, a larger-scale, multi-center, prospective study is essential to validate the findings of this research. Developing a population PK model is crucial for optimizing the dosage of teicoplanin in critically ill patients with fungal co-infections. Additionally, further investigations focusing on elucidating the mechanism by which fungal co-infections affect the teicoplanin C_{min} are highly warranted.

Data Sharing Statement

Data are available under reasonable requirements.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of the Army Medical University (approval number: KY2024122). The Ethics Committee of the First Affiliated Hospital of the Army Medical University approved this study to be exempt from individual patient consent for publication as existing data were collected and de-identified.

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Disclosure

Lin Cheng and Lina Wang contributed equally to this work as co-first authors. The authors declare no conflicts of interest in this work.

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