



Evaluating the optimal dose of teicoplanin with therapeutic drug monitoring: not too high for adverse event, not too low for treatment efficacy

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Received: 4 June 2019 / Accepted: 17 July 2019 / Published online: 1 August 2019
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Abstract

Therapeutic drug monitoring (TDM) of teicoplanin is aimed at minimizing the clinical impact of pharmacokinetic variability; however, its benefits are still being defined. We performed a retrospective study of teicoplanin TDM focusing on the dose-serum concentration relationship and clinical outcomes in a clinical setting. From January 2017 to December 2018, patients receiving teicoplanin ≥ 72 h with TDM were enrolled. Patients were divided into three groups: non-loading (NL) group, low-dose loading (LD) group (loading dose < 9 mg/kg), and high-dose loading (HD) group (≥ 9 mg/kg). Serum teicoplanin trough concentration (C_{\min}) and adverse events (AEs) were evaluated in each regimen. A subgroup of patients with bacteremia was analyzed to evaluate clinical efficacy. Among 65 patients, 12, 18, and 35 were grouped in NL, LD, and HD, respectively. Achievement rates of $C_{\min} > 20$ mg/L within 10 days were significantly different among the groups (25.0%, 38.9%, and 68.6% in the NL, LD, and HD groups, respectively; $P = 0.014$). Fourteen patients (21.5%) had AEs, and higher C_{\min} over 10 days (adjusted odds ratio 2.08 per every 20 mg/L increases, 95% CI 1.13–3.84, $P = 0.019$) and age ≥ 65 years ($P = 0.009$) were identified as independent risk factors. In the subgroup analysis, HD regimen ($P = 0.050$) and high mean C_{\min} over 10 days ($P = 0.025$) were significantly associated with treatment success. Although HL regimen could achieve C_{\min} targets and improve clinical outcome during teicoplanin treatment, high C_{\min} was associated with AEs during treatment. Routine TDM can be helpful to optimize teicoplanin administration.

Keywords Teicoplanin · Therapeutic drug monitoring · Loading dose · Bacteremia · Adverse event

Introduction

Teicoplanin is a glycopeptide antimicrobial agent that has a long half-life, permitting once-daily dosing. Because of its long elimination half-life that ranges from 69 to 327 h, it takes

10 to 14 days to achieve steady state [1, 2]. Based on a pharmacokinetics study of healthy volunteers, multiple-dose teicoplanin administration from 3 to 12 mg/kg of body weight showed a linear dose-serum concentration relationship [3]. However, dose-serum concentration in critically ill patients can be highly variable [4–6].

Bacteriological response to glycopeptides has a close relationship with area under the drug concentration-time curve during 24 h (ACU_{24})/minimal inhibitory concentration (MIC). In a clinical setting, trough serum concentration (C_{\min}) is used as a surrogate marker for predicting appropriate AUC_{24}/MIC [7]. A greater than 10 mg/L teicoplanin C_{\min} is considered the therapeutic range [1], and $C_{\min} \geq 20$ mg/L is recommended for patients with gram-positive cocci bacteremia [8, 9]. Therefore, high-dose regimen of teicoplanin has been emphasized to obtain optimal serum concentration [10, 11]. Meanwhile, $C_{\min} \geq 60$ mg/L is usually regarded as a toxic level [12, 13]; however, data of AEs during teicoplanin were not sufficient.

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In this regard, we conducted a retrospective study of therapeutic drug monitoring (TDM) for teicoplanin focusing on the dose-serum concentration relationship and clinical outcomes including AEs during treatment.

Patients and methods

Study population

This retrospective study was conducted at Samsung Medical Center, a 1950-bed tertiary-care referral hospital in Seoul, South Korea. Patients ≥ 18 years of age who had been administered teicoplanin ≥ 72 h and who received TDM from January 2017 to December 2018 were enrolled. Only C_{\min} values measured at the appropriate time point (defined as below) were included in our data. Patients who received teicoplanin irregularly or without information of dose were excluded.

Definitions, outcomes, data collection, and measurement of teicoplanin serum concentration

To compare patients' teicoplanin dose-serum concentration relationship at similar conditions, the pre-specified teicoplanin regimen was defined as follows: non-loading (NL) group (without loading), low-dose loading (LD) group (loading dose < 9 mg/kg every 12 h for 3 doses and any dose every 24 to 72 h for maintenance according to renal dose adjustment), and high-dose loading (HD) group (loading dose ≥ 9 mg/kg every 12 h for 3 doses and any dose every 24 to 72 h for maintenance according to renal dose adjustment). In our study, patients with creatinine clearance (CrCl) ≥ 50 mL/min, 10–49, and < 10

received teicoplanin every 24, 48, and 72 h for maintenance, respectively. Appropriately measured C_{\min} was defined as a trough level measured within 2 h before the next teicoplanin administration. Additionally, TDM performed within less than 48 h after treatment initiation was considered inappropriate. In this study population, maintenance dose was allowed to change according to C_{\min} .

We collected the following data from electronic medical records: single loading dose (mean of three loading doses [mg]/actual body weight [kg]), single initial maintenance dose (first maintenance dose [mg]/actual body weight [kg]), administration duration, time interval between the first teicoplanin administration and the first TDM, teicoplanin use for definitive or empirical therapy, use of vancomycin immediately before teicoplanin administration, age, sex, body mass index, actual body weight, renal replacement therapy, baseline CrCl calculated by Cockcroft-Gault formula [14], serum albumin, intensive care unit stay, initial sequential organ failure assessment score [15], and Charlson comorbidity index [16].

The primary endpoint was achievement of $C_{\min} \geq 10$ mg/L and ≥ 20 mg/L within 10 days. The secondary endpoints were mean C_{\min} within 10 days (defined as the sum of all C_{\min} values of TDM within 10 days divided by the number of total TDM) and the following AEs during treatment: neutropenia, thrombocytopenia, skin eruption, drug fever, and acute kidney injury (AKI) (all AEs \geq grade 2), defined as Common Terminology Criteria for Adverse Events [17], which were relative frequently reported in a prior teicoplanin study [12]. Causal association was evaluated by World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria [18]. Only certain, probable, and possible cases defined by WHO-UMC causality criteria were recorded

Fig. 1 Patient population. TDM, therapeutic drug monitoring

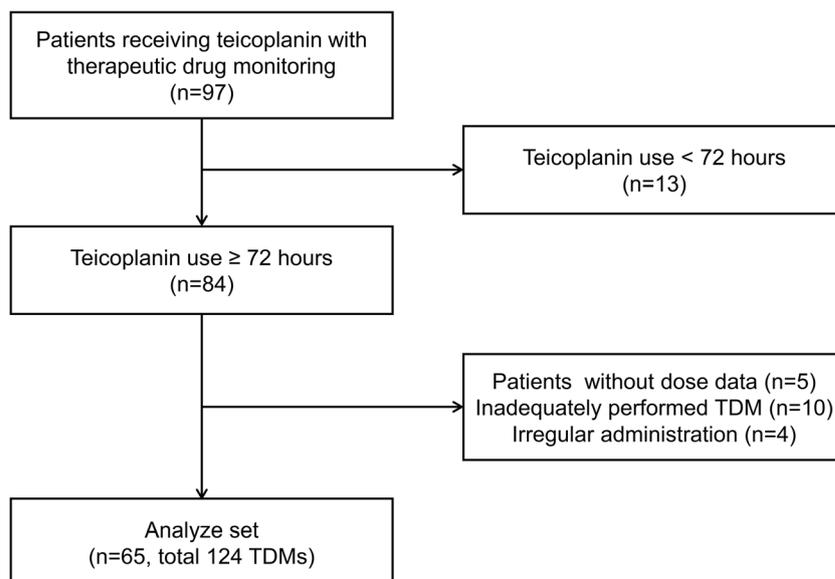


Table 1 Clinical characteristics and outcome of patients receiving teicoplanin

	All patients (65)	NL group (12)	LD group (18)	HD group (35)	<i>P</i> value
Treatment dosage, duration, and mode					
Loading dose (mg/kg) (mean ± SD)	N/A	N/A	6.69 ± 1.28	11.31 ± 1.93	< 0.001
Maintenance dose (mg/kg) (mean ± SD)	8.94 ± 2.58	6.58 ± 1.29	7.02 ± 2.01	10.68 ± 1.85	< 0.001 ^d
Treatment duration (hour) (mean ± SD)	313.2 ± 275.43	281.1 ± 192.8	223.9 ± 129.4	370.2 ± 338.3	0.341
Interval between initial administration and 1st TDM (days) (mean ± SD)	4.61 ± 2.44	4.26 ± 2.67	5.05 ± 2.40	4.51 ± 5.82	0.378
Teicoplanin use for definitive therapy	50 (76.9)	8 (66.7)	12 (66.7)	30 (85.7)	0.178
Receipt of vancomycin immediately before teicoplanin administration ^a	34 (52.3)	7 (58.3)	7 (38.9)	20 (57.1)	0.406
Duration of vancomycin administration (days) (median, IQR) ^b	9.5 (7–14.5)	9 (7–10.5)	12 (9.6–16.5)	9 (5.75–13.5)	0.286
Patient characteristics					
Age (mean ± SD)	57.98 ± 17.81	62.3 ± 15.0	49.4 ± 20.0	60.9 ± 16.4	0.073
Sex (female)	27 (41.5)	7 (58.3)	5 (27.8)	15 (42.9)	0.244
Body mass index (kg/m ²) (mean ± SD)	23.56 ± 4.45	23.54 ± 2.91	23.39 ± 3.75	23.66 ± 5.24	0.941
Body weight (kg) (mean ± SD)	62.71 ± 15.78	59.56 ± 9.18	65.23 ± 14.95	62.49 ± 17.97	0.663
Renal replacement therapy	9 (13.8)	3 (25.0)	2 (11.1)	4 (11.4)	0.496
Baseline CrCl (mL/min) (mean ± SD) ^c	63.45 ± 49.00	50.17 ± 38.13	98.16 ± 68.03	49.58 ± 26.99	0.076
Serum albumin (g/dL) (mean ± SD)	3.07 ± 0.47	3.08 ± 0.40	3.17 ± 0.39	3.01 ± 0.41	0.508
Underlying malignancy	19 (29.2)	1 (8.3)	5 (27.8)	13 (37.1)	0.163
Diabetes mellitus	10 (15.3)	2 (22.2)	2 (11.1)	6 (17.1)	0.902
ICU stay	15 (23.1)	1 (8.3)	4 (22.2)	10 (28.6)	0.418
Initial SOFA score (median, IQR)	4 (0–6)	4.5 (0–7.5)	4 (0–6)	3 (1–7)	0.951
CCI (median, IQR)	2 (1–4)	2 (1–3.75)	2 (0.75–3.5)	2 (0–5)	0.951
Outcome					
<i>C</i> _{min} > 10 mg/L within 10 days	55 (84.6)	5 (41.7)	15 (83.3)	35 (100.0)	< 0.001 ^e
<i>C</i> _{min} > 20 mg/L within 10 days	34 (52.3)	3 (25.0)	7 (38.9)	24 (68.6)	0.014 ^f
Mean <i>C</i> _{min} over 10 days (mean ± SD)	22.47 ± 14.42	10.80 ± 7.39	16.91 ± 5.39	29.33 ± 15.70	< 0.001 ^g
Adverse event	14 (21.5)	1 (8.3)	2 (11.1)	11 (31.4)	0.164

Data represent the number (%) of patients, unless otherwise specified; *NL*, non-loading; *LD*, low-dose loading; *HD*, high-dose loading; *SD*, standard deviation; *IQR*, interquartile range; *TDM*, therapeutic drug monitoring; *CrCl*, creatinine clearance; *ICU*, intensive care unit; *SOFA*, sequential organ failure assessment; *CCI*, Charlson comorbidity index; *C*_{min}, serum teicoplanin trough concentration

^a Data of 56 patients (patients who had not undergone RRT). ^b The most common reason for switching regimen from vancomycin to teicoplanin was acute kidney injury due to vancomycin (18/34, 52.9%). ^c Data of 34 patients (patients who received vancomycin immediately before teicoplanin administration). ^d NL vs. HD, *P* < 0.001; LD vs. HD, *P* < 0.001. ^e NL vs. HD, *P* < 0.001; ^f NL vs. HD, *P* = 0.025; ^g NL vs. LD, *P* = 0.023; LD vs. HD, *P* = 0.001; NL vs. HD, *P* < 0.001

as significant AEs. In addition, risk factors for significant AEs during treatment were evaluated.

To assess the clinical efficacy of teicoplanin according to serum concentration, subgroup analysis for patients with bacteremia was conducted. Cases positive for the same isolates from more than two separate blood cultures and cases positive for a single blood culture in patients with concomitant clinical symptoms were considered as true bacteremia [19]. In this subgroup analysis, treatment failure was defined as patient death related to infection, sustained symptoms requiring change of teicoplanin therapy, or recurrence within 30 days.

Methods of teicoplanin TDM were described in our prior study [20]. Five major components (A2-1, A2-2, A2-3, A2-4,

and A2-5) of teicoplanin were measured by LC-MS/MS method.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 for Windows (IBM Corp., 2018). Student's *t* test or Mann-Whitney test was used to compare continuous variables of two groups, and one-way ANOVA or Kruskal-Wallis test was used to compare continuous variables of multiple groups. The chi-square test or Fisher's exact test was used to compare categorical variables. For post hoc analysis for multiple comparison, the Bonferroni method was used. In multivariable analysis,

variables of $P < 0.10$ in the univariate analysis were included in the logistic regression model. All P values were two-tailed, and P values < 0.05 were considered statistically significant.

Results

Study population

A total of 65 patients with 124 serum teicoplanin concentrations were included in this study (Fig. 1). Of these, 39 patients received teicoplanin TDM only once, and the first TDMs of each patient were performed within at least 10 days after initiation of teicoplanin administration. Patients numbered 12, 18, and 35 in NL, LD, and HD, respectively. More than half of patients received teicoplanin immediately after vancomycin administration (Table 1).

Achievement of therapeutic serum concentration of teicoplanin

Loading dose and maintenance dose of each group were significantly different, as shown in Table 1. Mean loading dose was 6.69 mg/kg and 11.31 mg/kg in the LD and HD groups, respectively ($P < 0.001$). Mean maintenance dose was 6.58 mg/kg, 7.02 mg/kg, and 10.68 mg/kg in NL, LD, and HD, respectively ($P < 0.001$). Although no patient characteristic was significantly different, baseline CrCl was high in the LD group.

Figure 2 showed C_{\min} in the NL, LD, and HD groups on days 2 to 3, days 4 to 6, and days 7 to 10 of therapy, respectively. The median value of C_{\min} on days 2 to 3 was only 4.9 mg/L in the NL group. However, C_{\min} on days 2 to 3 in HD was 22.15 mg/L. Achievements of $C_{\min} \geq 10$ mg/L and ≥ 20 mg/L within 10 days were significantly different between the HD and NL groups. For this, 100% and 68.6% of patients in the HD group achieved $C_{\min} \geq 10$ mg/L and ≥ 20 mg/L within 10 days, respectively; however, only 41.6% and 25.0% of patients in the NL group showed these levels. The mean C_{\min} over 10 days was significantly different among groups (NL versus LD, $P = 0.023$; LD versus HD, $P = 0.001$; NL versus HD, $P < 0.001$).

Risk factors for AEs during teicoplanin treatment

Among 65 patients, 14 (21.5%) had AEs, of which the most common was neutropenia (5/14, 35.7%) (Supplementary Table 1).

In the analysis for evaluating risk factors of AEs, higher mean C_{\min} over 10 days was shown in the AE group compared with the non-AE group (31.47 mg/L \pm 21.00 and 20.02 \pm 11.08 in the AE group and non-AE group, respectively, $P = 0.041$). Additionally, receipt of vancomycin immediately

before teicoplanin administration ($P = 0.026$) and age ≥ 65 years ($P = 0.023$) were risk factors for AEs in univariate analysis (Table 2). In multivariable analysis, higher C_{\min} over 10 days (adjusted odds ratio [aOR] 2.08 per 20 mg/L increases, 95% CI 1.13–3.84, $P = 0.019$) and age ≥ 65 years (aOR 7.50, 95% CI 1.65–34.04, $P = 0.009$) were shown to be independent risk factors.

Associated factors of treatment success

A total of 20 patients with bacteremia were included in this subgroup analysis. The most common origin sites of bacteremia were bone and joint (6 cases) and catheter-associated infection (4 cases).

No patient characteristic was significantly different between the treatment failure and success groups. High-dose administration was significantly associated with treatment success ($P = 0.050$). Mean C_{\min} over 10 days was significantly higher in patients with treatment success compared with treatment failure (21.90 mg/L \pm 7.37 and 13.75 \pm 7.38, respectively, $P = 0.025$) (Table 3).

Discussion

This study showed that the HD regimen could produce an appropriate therapeutic teicoplanin level; however, AEs were noted at a serum concentration previously reported not toxic.

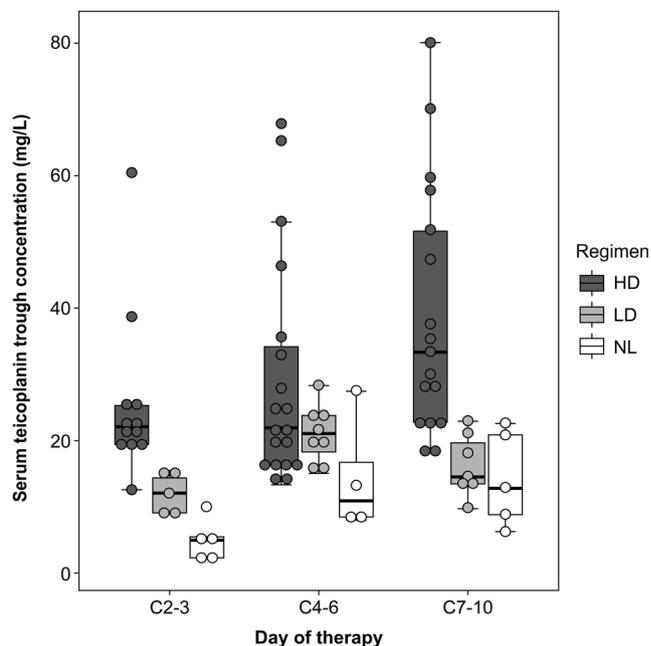


Fig. 2 Serum teicoplanin trough concentration of 65 patients measured on days 2–10 of therapy. NL non-loading, LD low-dose loading, HD high-dose loading

Table 2 Risk factors for adverse events during teicoplanin treatment

	With adverse event (14)	Without adverse event (51)	<i>P</i> value
Treatment dosage, duration, and mode			
Dosing regimen			0.164
NL group	1 (8.3)	11 (21.6)	
LD group	2 (14.3)	16 (31.4)	
HD group	11 (78.6)	24 (47.1)	
Mean C_{min} over 10 days (mean \pm SD)	31.47 \pm 21.00	20.02 \pm 11.08	0.041
The highest C_{min} during treatment (mean \pm SD)	35.67 \pm 23.18	22.99 \pm 14.28	0.053
C_{min} > 10 mg/L within 10 days	14 (100)	41 (80.4)	0.102
C_{min} > 20 mg/L within 10 days	9 (64.3)	25 (49.0)	0.375
The highest C_{min} > 60 mg/L during treatment	4 (28.6)	1 (2.0)	0.006
Receipt of vancomycin immediately before teicoplanin administration	11 (78.6)	23 (45.1)	0.026
Duration of vancomycin administration (days) (median, IQR) ^a	12 (8–16)	9 (6.5–12.5)	0.403
Teicoplanin use for definitive therapy	13 (92.9)	37 (72.5)	0.159
Treatment duration (hours) (mean \pm SD)	391.09 \pm 434.2	291.8 \pm 214.3	0.493
Concomitant other antibiotics use ^b	9 (64.3)	35 (68.6)	> 0.999
Patient characteristics			
Age \geq 65 years	10 (71.4)	19 (37.3)	0.023
Sex (female)	6 (42.9)	21 (41.2)	0.910
Body mass index (kg/m ²) (mean \pm SD)	22.63 \pm 3.92	23.77 \pm 4.73	0.848
Body weight (mean \pm SD)	62.41 \pm 16.03	59.28 \pm 13.91	0.696
Renal replacement therapy	1 (7.1)	8 (15.7)	0.670
Baseline CrCl (mL/min) (mean \pm SD) ^c	58.97 \pm 32.92	64.94 \pm 52.63	0.764
Serum albumin (g/dL) (mean \pm SD)	3.08 \pm 0.48	3.03 \pm 0.47	0.701
Underlying malignancy	3 (21.4)	19 (37.3)	0.349
Diabetes mellitus	2 (14.3)	8 (15.7)	> 0.999
ICU stay	3 (21.4)	12 (23.5)	> 0.999
SOFA score (mean, IQR)	2 (0–6)	4 (1–7)	0.315
CCI (mean, IQR)	1 (0–3.25)	2 (1–4)	0.809

Data represent the number (%) of patients, unless otherwise specified; *NL*, non-loading; *LD*, low-dose loading; *HD*, high-dose loading; C_{min} , serum teicoplanin trough concentration; *SD*, standard deviation; *IQR*, interquartile range; *CrCl*, creatinine clearance; *ICU*, intensive care unit; *SOFA*, sequential organ failure assessment; *CCI*, Charlson comorbidity index

^aData of 34 patients (patients who received vancomycin immediately before teicoplanin administration). ^bNo specific antibiotic agent showed significant difference between two groups. ^cData of 56 patients (patients who had not undergone RRT)

Since teicoplanin was first used in the 1980s, its recommended single-loading doses and maintenance doses did not usually exceed 400 mg/day or 6 mg/kg/day through the 1990s [21]. However, suboptimal trough teicoplanin concentration was frequently reported with conventional low-dose regimen [5, 22, 23]. Thereafter, a high-dose fixed regimen (fixed dose for 600 mg to 800 mg/day) and a high-dose regimen based on body weight (12 mg/kg/day) were suggested, and these regimens showed improved clinical outcomes [11, 24, 25]. However, even in one study using the high-dose fixed regimen, only 37.9% of the study population achieved C_{min} > 20 at 72 h [6]. Our study showed that improved clinical outcome was associated with appropriate C_{min} , which could be achieved by a high-dose regimen based on body weight.

To date, teicoplanin has been known to have a wide therapeutic range; however, its cut-off value for toxicity—60 mg/L—is anecdotal rather than confirmatory. Reviews from the 1980s and early 1990s on the safety profile of teicoplanin showed that 10% of patients had one or more AEs, which were not associated with age or with teicoplanin dose range from 3 to 10 mg/kg [26]. However, probability of a relationship between a high-dose regimen (\geq 12 mg/kg/day) and AEs was also reported. Greenberg reported that 5 of 18 patients (28%) with bone and joint infection who had been administered teicoplanin \geq 12 mg/kg/day developed drug fever with rash, leading to discontinued use [13]. One Japanese study reported that a C_{min} of teicoplanin \geq 28 mg/L was a risk factor for hepatotoxicity (defined as an increase in transaminase to more

Table 3 Treatment outcomes of patients with bacteremia treated with teicoplanin

	Success (11)	Failure (9)	<i>P</i> value
Treatment dosage, duration, and mode			
Dosing regimen			0.050
NL	1 (9.1)	5 (55.6)	
LD	1 (9.1)	0 (0.0)	
HD	9 (81.8)	4 (44.4)	
Mean C_{\min} over 10 days (mean \pm SD)	21.90 \pm 7.37	13.75 \pm 7.38	0.025
C_{\min} > 10 mg/L within 10 days	10 (90.9)	5 (55.6)	0.127
C_{\min} > 20 mg/L within 10 days	8 (72.7)	3 (33.3)	0.175
Receipt of vancomycin immediately before teicoplanin administration	8 (72.7)	5 (55.6)	0.642
Duration of vancomycin administration (days) (median, IQR) ^a	6 (4–9)	7.5 (6.5–10.5)	0.524
Time delay for appropriate antibiotics (days)	0 (0–2)	0 (0–1.5)	> 0.999
Adverse event during treatment	3 (27.3)	1 (11.1)	0.591
Pathogen			0.470
Methicillin-resistant <i>S. aureus</i>	7 (63.6)	4 (44.4)	
Vancomycin-resistant <i>Enterococcus</i>	2 (18.2)	4 (44.4)	
Others ^b	2 (18.2)	1 (11.1)	
Patient characteristics			
Age (mean \pm SD)	60.27 \pm 20.96	65.00 \pm 13.35	0.909
Sex (female)	3 (30)	4 (57.1)	0.350
Body mass index (kg/m ²) (mean \pm SD)	24.48 \pm 4.99	21.79 \pm 3.31	0.210
Body weight	68.66 \pm 19.19	54.54 \pm 11.11	0.102
Renal replacement therapy	1 (9.1)	3 (33.3)	0.285
Baseline CrCl (mL/min) (mean \pm SD) ^c	52.75 \pm 43.31	45.40 \pm 21.73	0.914
Serum albumin (g/dL) (mean \pm SD)	2.85 \pm 0.53	2.73 \pm 0.27	0.879
Underlying malignancy	5 (45.5)	4 (44.4)	> 0.999
Diabetes mellitus	6 (54.5)	2 (22.2)	0.197
ICU stay	4 (36.4)	2 (22.2)	0.642
SOFA score	6 (0–9)	6 (2–9.5)	0.603
CCI	4 (0–7)	2 (1–4)	0.766

Data represent the number (%) of patients, unless otherwise specified; *NL*, non-loading; *LD*, low-dose loading; *HD*, high-dose loading; C_{\min} , serum teicoplanin trough concentration; *SD*, standard deviation; *IQR*, interquartile range; *CrCl*, creatinine clearance; *ICU*, intensive care unit; *SOFA*, sequential organ failure assessment; *CCI*, Charlson comorbidity index

^a Data of 13 patients (patients who received vancomycin immediately before teicoplanin administration). ^b Two methicillin-resistant coagulase-negative staphylococci and one methicillin-susceptible coagulase-negative staphylococci. ^c Data of 16 patients (patients who had not undergone RRT)

than 3 times the upper limit of normal reference ranges or the pre-treatment value) [10]. In our study, the mean C_{\min} of patients having significant AEs was 31.47 mg/L. Therefore, we cautiously suggest that cut-off values of toxic teicoplanin should be lowered, and there is no specific reason for increasing teicoplanin to C_{\min} of 30 mg/L or more. Therefore, TDM should be implemented during teicoplanin treatment. However, a survey conducted in the UK and Ireland revealed that only 12% of hospitals conducted teicoplanin TDM routinely in 2014 [27].

There are some limitations in our study. First, we tried to exclude inappropriately measured TDM. However, due to limitations of the retrospective study, TDM was not performed

in the same manner and duration. Second, use of teicoplanin in this study reflected the practice in our medical center. Considering that more than half of patients in this study received vancomycin before teicoplanin use, the data cannot be generalized directly to other medical centers where clinicians prescribe teicoplanin as a primary agent.

In conclusion, the high-dose teicoplanin therapy based on body weight is clinically important for not only effectiveness of the treatment but also potential association with AE. The therapeutic window of teicoplanin might be narrower than previously believed. Therefore, TDM should be considered to obtain appropriate teicoplanin concentration: not too high for adverse event, not too low for treatment efficacy.

Acknowledgments The authors thank Junsang Yoo who helped with the graphs and Hyo Jung Park, MS, who provided advice for TDM analysis.

Funding This material is based upon work supported by the Ministry of Trade, Industry, & Energy (MOTIE, Korea) under the Industrial Technology Innovation Program (No. 10080648: Antibiotics monitoring point-for-care test).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The study was approved by the local ethical research committee (IRB number 2018-07-162-003).

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