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A simplified chart for determining the initial loading dose of teicoplanin in critically ill patients

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Aim of the study: A simplified chart to determine the initial loading dose of teicoplanin (TEIC chart) for achieving the target trough concentration was developed. The aim of the present study was to evaluate the usefulness of this chart in critically ill patients. **Patients and methods:** The initial loading dose and maintenance dose to achieve a target trough concentration ≥ 10 $\mu\text{g/mL}$ on day 4 was determined using the teicoplanin TDM software and presented in a TEIC chart. The dosage of teicoplanin, including the loading dose for the first 2 days and the maintenance dose thereafter, was selected from the chart (chart method, $N = 41$) or calculated using TDM software (software method, $N = 39$). **Results:** The performance rate of initial loading of teicoplanin increased from 83.0% to 100% after the TEIC chart was introduced ($P = 0.016$). The TEIC chart significantly reduced the time required for determining the initial loading dose compared with the use of software (1.9 ± 0.6 min vs. 29.7 ± 13.8 min, $P < 0.001$). No significant differences were observed in the rates of achieving a target level ≥ 10 $\mu\text{g/mL}$ ($P = 0.766$). **Conclusion:** The TEIC chart enables a simple, rapid, and reliable determination of teicoplanin dosage.

1. Introduction

Teicoplanin is a glycopeptide antibiotic that is effective against a wide variety of gram-positive bacteria, including *staphylococci*, *streptococci*, *enterococci*, and many anaerobic gram-positive bacteria (Wilson et al. 1994). Teicoplanin yields clinical outcomes similar to vancomycin, but is less frequently associated with nephrotoxicity, ototoxicity, and red man syndrome (Svetitsky et al. 2009). Therefore, teicoplanin is relatively easier to use in MRSA-infected patients with renal dysfunction.

In clinical practice, therapeutic drug monitoring (TDM) for teicoplanin is recommended to maintain adequate serum trough concentrations (MacGowan et al. 1998). The optimal plasma trough concentration of teicoplanin is considered to be ≥ 10 $\mu\text{g/mL}$ for MRSA infections and ≥ 20 $\mu\text{g/mL}$ for deep-seated infections (Graninger et al. 1997; Greenberg et al. 1990; Lamont et al. 2009; Harding et al. 2000; Brink et al. 2008). Poor clinical outcome is associated with a trough concentration below 10 $\mu\text{g/mL}$ (Sato et al. 2006).

On the other hand, it takes a long time for the injected teicoplanin to reach an effective plasma concentration since it has a long elimination half-life (MacGowan et al. 1992). Therefore, an adequate initial loading dose is required for rapid achievement of an effective plasma concentration in the clinical setting. In our previous study, we reported that individualised adjustment of the initial loading dose of teicoplanin using software for therapeutic teicoplanin monitoring (TEICTDM v. 2.0; Astellas Pharma, Tokyo, Japan) is potentially useful for achieving the optimal concentration (10–20 $\mu\text{g/mL}$) within 72 hours of injection (Niwa et al. 2010). However, initial loading dose selection using the TEICTDM software (software method) is time-consuming and requires well-trained healthcare professionals. In addition, it is still unclear whether the initial loading dose selected is adequate for critically ill patients.

In the present study, a simplified chart for determining the initial loading dose as well as the maintenance dose for teicoplanin based on patient body weight and creatinine clearance was developed using TEICTDM software (TEIC chart, Fig. 1). Subsequently, the

usefulness of this chart in critically ill patients was evaluated by comparing the rate of attaining an effective plasma concentration using the chart method versus the software method.

2. Investigations and results

2.1. Patients demographics

Before the TEIC chart was introduced, 83.0% (39/47) of patients received an initial loading dose of teicoplanin. On the other hand, all 41 patients who were admitted with teicoplanin received an initial loading since the TEIC chart was introduced ($P = 0.016$).

As shown in Table 1, there were no significant differences in the characteristics of the study patients in the software and chart groups. In both groups, the most frequent type of infection was catheter-related bloodstream infection, followed by either skin or soft tissue infection in the chart group, and respiratory infection in the software group. Isolated organisms in the two groups were generally similar. Severe adverse events were not observed in the two groups.

The time required for determining the initial loading dose using the TEIC chart was significantly shorter than the time required for calculation with TEICTDM software (29.7 ± 13.8 min for the software method vs. 1.9 ± 0.6 min for the chart method, $P < 0.001$) (Fig. 2).

2.2. Comparison of predictive accuracy between the software and chart groups

The trough concentrations in the two groups were similar. The average trough concentration was higher than 15 $\mu\text{g/mL}$ in both groups (16.8 ± 5.7 $\mu\text{g/mL}$ for the software method vs. 15.8 ± 5.7 $\mu\text{g/mL}$ for the chart method, $P = 0.435$) (Fig. 3). The proportion of patients achieving a trough concentration ≥ 10 $\mu\text{g/mL}$ or ≥ 15 $\mu\text{g/mL}$ was similar between the two groups (89.7% vs. 90.2% for ≥ 10 $\mu\text{g/mL}$, $P = 0.766$, and 64.1% vs. 58.5% for ≥ 15 $\mu\text{g/mL}$, $P = 0.610$), although the proportion of patients who achieved a trough concentration ≥ 15 $\mu\text{g/mL}$ in both groups was low (Fig. 3). Average trough

Simplified chart for dosages of teicoplanin							
Target trough concentration : >10 µg/ml							
Creatinine Clearance (ml/min)		10 – 30 ml/min		31 – 70 ml/min		71 – 100 ml/min	
Body Weight (kg)		Dose	Interval	Dose	Interval	Dose	Interval
40 kg	Day 1	600 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 2	400 mg	q12h	400 mg	q12h	600 mg	q12h
	Day 3 & thereafter	200 mg	q48h	200 mg	q24h	400 mg	q24h
50 kg	Day 1	600 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 2	400 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 3 & thereafter	200 mg	q24h	200 mg	q24h	400 mg	q24h
60 kg	Day 1	600 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 2	400 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 3 & thereafter	200 mg	q24h	200 mg	q24h	400 mg	q24h
70 kg	Day 1	600 mg	q12h	600 mg	q12h	800 mg	q12h
	Day 2	400 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 3 & thereafter	200 mg	q24h	200 mg	q24h	400 mg	q24h
80 kg	Day 1	600 mg	q12h	600 mg	q12h	800 mg	q12h
	Day 2	400 mg	q12h	600 mg	q12h	600 mg	q12h
	Day 3 & thereafter	200 mg	q24h	200 mg	q24h	400 mg	q24h

Fig. 1: TEIC chart for determining the initial loading dose and maintenance dose of teicoplanin.

concentrations by body weight and CLcr in the chart group are shown in Table 2. All categories in both renal function and body weight were achieved the target trough concentration ≥ 10 µg/mL. The difference between the predicted value and the actual concentration on day 4 was similar in the two groups ($P = 0.733$) (Fig. 4).

2.3. Microbiological and clinical success

The rates of microbiological and clinical success were not significantly different between the software and chart groups (microbiological success rate, 90.9% (30/33) vs. 90.1% (29/32), $p = 0.649$; clinical success rate, 87.2% (34/39) vs. 90.2% (37/41), $P = 0.911$).

3. Discussion

Several lines of evidence suggest that an initial loading dose of teicoplanin that achieves the optimal trough concentration is necessary to obtain favourable clinical outcomes (Lamont et al. 2009; Harding et al. 2000; Brink et al. 2008; Sato et al. 2006). TDM is thus recommended to ensure an optimal teicoplanin trough concentration (Ueda et al. 2014; Seki et al. 2012; Roberts et al. 2009). We have previously reported that individualised dose adjustment based on renal function and body weight using TEICTDM software is useful for increasing the rate of reaching the optimal teicoplanin trough concentration. Pharmacists commonly manage the initial and subsequent dose adjustments for antibiotics, which may lead to clinical and economic benefits. However, in a number of medical institutions, pharmacists may not be available around the clock to adjust the dosing schedule for every patient receiving intravenous antibiotics in the intensive care unit. In addition, it is a time-consuming process to determine the initial loading dose of teicoplanin using TEICTDM software (Niwa et al. 2006). In fact, 83.0% (39/47) of patients received an initial loading dose of teicoplanin before the TEIC chart was introduced. Therefore, we developed the TEIC chart for rapid determination of the optimal teicoplanin dosing schedule for critically ill patients. As a result, all patients who were prescribed teicoplanin received an initial loading dose, regardless of whether pharmacists were present,

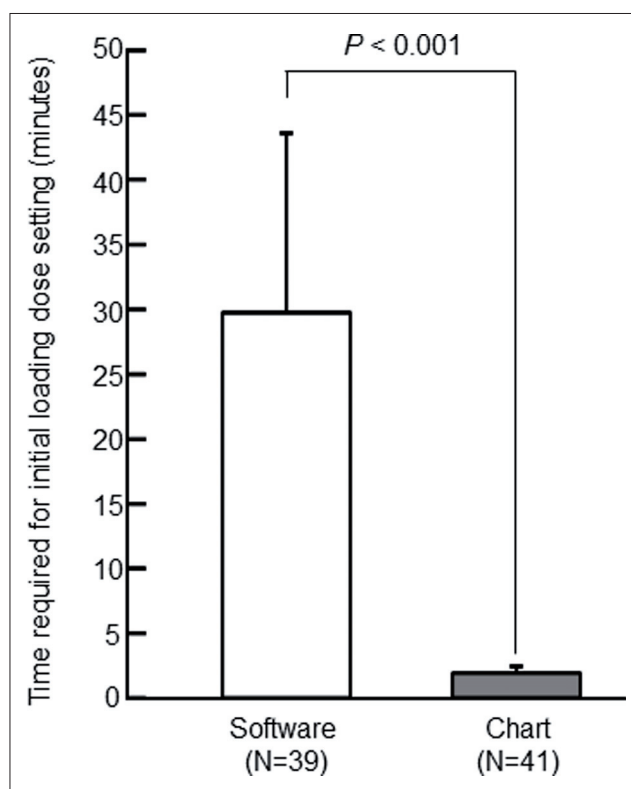


Fig. 2: Time required for determining the initial loading dose of teicoplanin. Data were analysed using the *t*-test.

since the TEIC chart was introduced. The TEIC chart is more user-friendly and helped to overcome the evidence-to-practice gap (Lang et al. 2007). Moreover, the TEIC chart significantly reduced the time required to determine the initial loading dose compared with the use of software (29.7±13.8 min for the software method vs. 1.9±0.6 min for the chart method, $P < 0.001$). The Surviving Sepsis Campaign guidelines recommended that the goal of therapy is to initiate effective intravenous antimicrobial therapy within one hour of recognition of septic shock and severe sepsis without septic shock (Dellinger et al. 2013). Thus, we expect that the shorter time required for determining the initial loading dose with the TEIC chart will lead to positive clinical outcomes. However, no significant differences in the rate of clinical or microbiological success were observed in the present study between the software and chart groups. Yamada et al. (2012) described simplified dosing regimens of teicoplanin based on renal function and weight using Monte Carlo simulation. However, it takes 3 days to achieve the target trough concentration using their method, whereas with the TEIC chart, the target trough concentration was attained within 2 days. The effectiveness of the regimens reported by Yamada et al. was not evaluated in critically ill patients. The mean trough concentration in patients who received teicoplanin according to the present TEIC chart was 15.8±5.7 µg/mL, which was very similar to that obtained in patients receiving teicoplanin according to the schedule determined with TEICTDM software (16.8±5.7 µg/mL). There was only one patient who had a trough concentration greater than 30 µg/mL in the chart group. Moreover, the rate of achieving the target trough concentration and the differences between predicted and measured trough concentrations were comparable between the chart and software groups. Thus, the present TEIC chart enabled us to rapidly and effectively establish a teicoplanin dosing schedule in critically ill patients. The general condition of critically ill patients fluctuates considerably within a short period, which makes it difficult to determine antibiotic dosages. Brink et al. (2008) recommended administering 6 mg/kg of teicoplanin every 12 h for the first 2 days, followed by the same dose once daily in patients with sepsis, which was associated with a mean plasma trough concentration of 19.1 µg/mL at 72 h after admin-

Table 1: Characteristics of the study patients in the software and chart groups

	Software (N=39)	Chart (N=41)	P-value
Age, y (range)	64.7 (29-88)	68.5 (18-85)	0.645 ^{a)}
Sex, male/female	23 / 16	30 / 11	0.180 ^{b)}
Weight, kg	63.3 (14.4)	62.0 (11.3)	0.148 ^{c)}
Serum albumin, g/dl	2.56 (0.55)	2.51 (0.54)	0.529 ^{c)}
Aspartate transaminase, U/dl	46.4 (32.3)	35.2 (25.0)	0.160 ^{c)}
Serum creatinine, mg/dl	0.90 (0.87)	1.05 (1.50)	0.188 ^{c)}
Hemodiafiltration (with/without)	8 / 31	7 / 34	0.914 ^{b)}
SOFA score, median (range)	6 (3-14)	7 (0-14)	0.133 ^{a)}
28-d mortality, n (%)	4 (10.0)	3 (7.3)	0.945 ^{b)}
90-d mortality, n (%)	10 (26.0)	6 (14.6)	0.342 ^{b)}
Type of infection, n (%)			0.989 ^{a)}
Blood stream	24 (61)	20 (49)	
Respiratory	5 (13)	3 (7)	
Skin and soft tissue	4(10)	8(20)	
Intra-abdominal	3 (8)	2 (5)	
Urinary tract	1 (3)	2 (5)	
Endocarditis	0	1 (2)	
Mediastinitis	0	1 (2)	
Unknown	2 (5)	4 (10)	
Organism, n (%)			0.717 ^{d)}
<i>Staphylococcus aureus</i>			
MRSA	9 (23)	11 (27)	
MSSA	2 (5)	5 (12)	
Coagulase-negative <i>Staphylococcus</i>			
MRCNS	11 (28)	9 (22)	
MSCNS	1 (3)	1 (2)	
<i>Enterococcus</i> specise	7 (18)	3 (7)	
Others	3 (8)	3 (7)	
Culture negative	6 (15)	9 (22)	

Data are mean (SD) unless otherwise specified.

^{a)} Mann-Whitney-U test, ^{b)} Fisher exact probability test, ^{c)} Unpaired-t test,

^{d)} Chi square test.

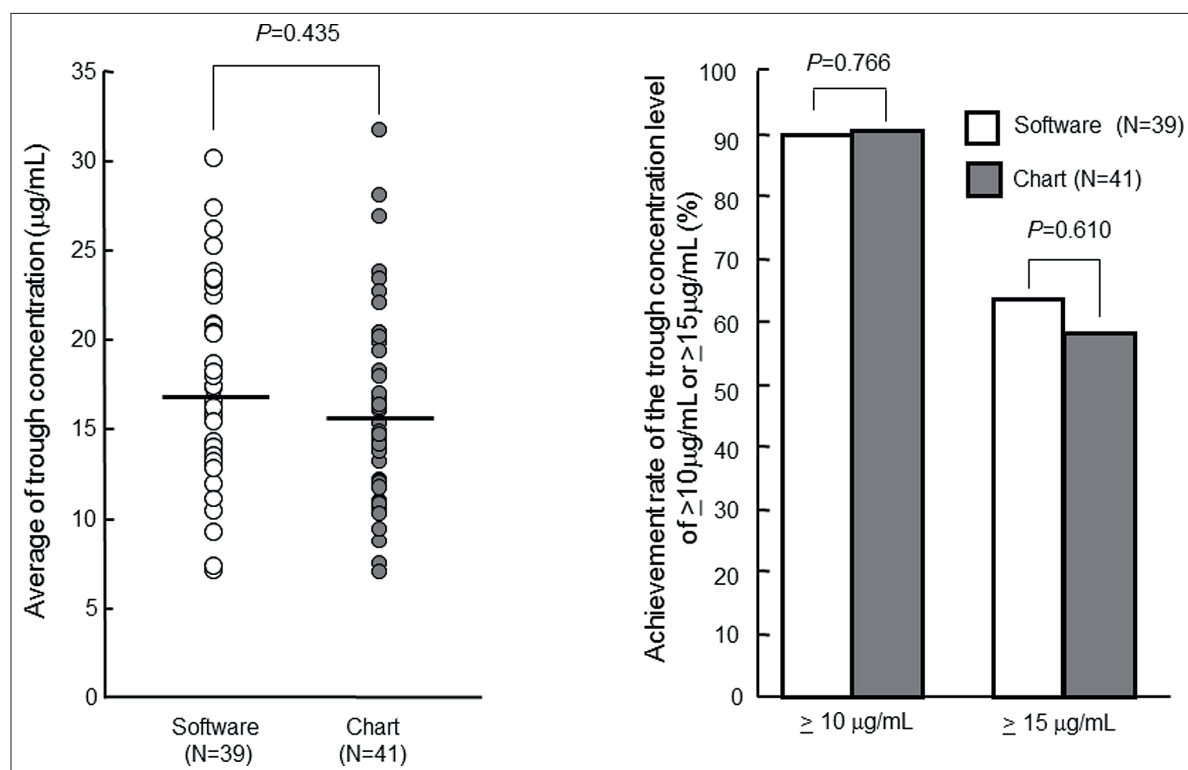


Fig. 3: Average trough concentration (A) and rate of achieving a trough concentration $\geq 10 \mu\text{g/mL}$ or $\geq 15 \mu\text{g/mL}$ (B) using the software and chart methods. Data were analysed using the *t*-test (A) or chi-square test with Yates correction (B).

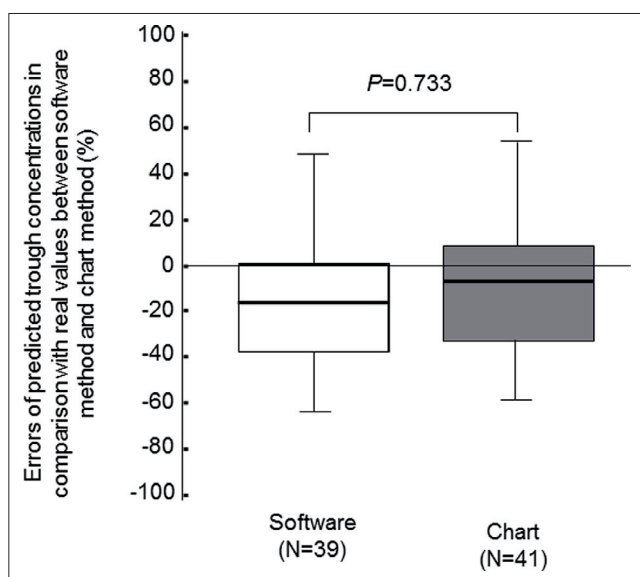


Fig. 4: Errors in predicted trough concentrations when compared to actual measured values using the software and chart methods. Data were analysed using the *t*-test.

Table 2: Average trough concentration by body weight and creatinine clearance in the chart group

Groups		N	Trough concentration (µg/mL)
Body weight (kg)	40	3	18.9 ± 5.0
	50	11	15.5 ± 6.4
	60	13	16.6 ± 7.3
	70	9	14.7 ± 4.1
	80	5	14.0 ± 2.4
Creatinine clearance (mL/min)	10-30	12	16.2 ± 6.9
	31-70	14	15.3 ± 4.9
	71-100	15	15.9 ± 6.0

istration (Brink et al. 2008). However, in their study, plasma trough concentration in patients with impaired renal function exceeded 40 µg/mL (Brink et al. 2008). The present TEIC chart enabled us to determine the teicoplanin dose for three categories of renal function (CLcr: 10–30 mL/min, 31–70 mL/min, and 71–100 mL/min) and five categories of body weight (40 kg, 50 kg, 60 kg, 70 kg, and 80 kg). The maintenance dose could also be determined based on body weight and renal function using this TEIC chart. However, the TEICTDM had several drawbacks: a trough concentration below 10 µg/mL was observed in 9.8% (4 of 41) and 10.3% (4 of 39) patients in the chart and software groups, respectively. In addition, the predicted trough concentration was more than 30% higher than the actual concentration in 36.6% (15 of 41) and 28.2% (11 of 39) of patients treated according to the TEIC chart and TEICTDM software results, respectively. It has been shown that the permeability of capillary vessels is higher in some critically ill patients, including those with multiple organ dysfunction, cutaneous injuries such as burns, pancreatitis, and multiple trauma, which leads to an increased volume of distribution (V_d) for hydrophilic drugs and decreased plasma drug concentrations (Roberts et al. 2009). In such patients, the target trough concentration of teicoplanin should be raised to at least ≥ 20 µg/mL.

This study has several limitations. First, this was a non-randomised single centre study. Second, the sample size was small and the patient population was limited. Finally, the initial loading dose in critically ill patients was determined based on body weight and renal function without taking V_d into account.

In conclusion, the TEIC chart was developed for the rapid determination of the initial loading dose and the maintenance dose of teicoplanin. The dosing schedule based on this chart resulted in a markedly high rate (90.2%) of achieving the target trough concentration (≥ 10 µg/mL), which was quite similar to the rate obtained when the dosage schedule was determined using the teicoplanin TDM software program (89.7%). Notably, all patients who admitted with teicoplanin received an initial loading dose since the TEIC chart was introduced. Therefore, our TEIC chart was found to be highly reliable for determining the dosing schedule for teicoplanin. This chart may be very clinically useful.

4. Experimental

4.1. Development of the TEIC chart

The TEIC chart for selecting the initial loading and maintenance doses of teicoplanin based on patient body weight and renal function was developed using TEICTDM software, which was established using a two-compartment model in Japanese adult patients (Nakayama et al. 2006) (Fig. 1). A proportional error model was used to describe the interindividual variability and residual variability in the TEIC software program. Renal function was estimated based on creatinine clearance (CLcr) using the Cockcroft-Gault equation.

In the TEIC chart, the initial loading dose and maintenance dose were designed to achieve a target trough concentration of ≥ 10 µg/mL on day 4. Renal function was divided into three categories (CLcr: 10–30 mL/min, 31–70 mL/min, and 71–100 mL/min) and body weight was divided into five categories (40 kg, 50 kg, 60 kg, 70 kg, and 80 kg). In the TEIC software program, the upper limit of weight was 75 kg and there was little variation in the initial loading dose among patients with CLcr greater than 100 mL/min. Therefore, the cut-off values for body weight and CLcr were set at 80 kg and 100 mL/min, respectively. CLcr in patients undergoing hemodiafiltration was in the 31 to 70 mL/min range.

4.2. Study setting and patients

We conducted a single-center, retrospective before-and-after comparison study at the 614-bed tertiary-care Gifu University Hospital. Patients younger than 18 years of age were excluded from the study. Study participants included patients with suspected or documented MRSA infection who received intravenous teicoplanin in intensive care units between June 2007 and December 2014. Among them, 39 patients were treated with teicoplanin at the initial loading dose calculated using TEICTDM software from June 2007 and December 2010 (before introduction of the TEIC chart), in which the target trough concentration on day 4 was set at ≥ 10 µg/mL (software group). The initial loading dose for the other 41 patients was determined using the TEIC chart based on body weight and CLcr from January 2011 and December 2014 (after introduction of the TEIC chart) (chart group).

4.3. Teicoplanin treatment, blood sampling, and analysis

Patients received the initial loading dose of teicoplanin twice a day on the first and second days, followed by the maintenance dose once a day starting on day 3. Blood samples were collected immediately before teicoplanin administration in a plastic vial containing ethylene glycol-bis(2-aminoethylether)- N,N,N',N' -tetraacetic acid. Teicoplanin concentration was determined using a fluorescence polarisation immunoassay according to the method of Rybak et al. (1991) using the teicoplanin reagent set (Oxis International, Portland, OR, USA) and an automated fluorescence polarisation analyser (TDx FLx; Abbott Japan, Tokyo, Japan). The assay was performed in duplicate. Initial loading dose, plasma trough concentration, and the proportion of patients who achieved the optimal trough concentration on day 4 in the software and chart groups were compared. In both groups, the predicted trough concentration on day 4 calculated using TEICTDM software was compared to the actual measured concentration.

4.4. Evaluation of the usefulness of the TEIC chart

The time required for determining the initial loading dose of teicoplanin in the software and chart groups were compared. The trough concentration, proportion of patients with a target trough concentration ≥ 10 µg/mL or ≥ 15 µg/mL, and the difference between actual and predicted values of the teicoplanin trough concentration on day 4 of the software and chart groups were compared.

4.5. Rates of microbiological success and clinical success

Microbiological success was defined as the disappearance of bacteria from the site of infection during teicoplanin treatment. No relapse of infection within one week after completion of teicoplanin therapy was regarded as clinical success.

4.6. Data analysis

Data were analysed using SPSS version 11 (SPSS, Chicago, IL, USA). Parametric variables were analysed using the *t*-test, while non-parametric variables were analysed using the Mann–Whitney *U*-test. *p* values < 0.05 were considered statistically significant.

4.7. Ethical approval

This study was carried out in accordance with the guidelines for human studies adopted by the ethics committee of the Gifu University Graduate School of Medicine,

and notified by the Japanese government (Institutional review board approval No. 21-153). In view of the retrospective nature of the study, subjects' informed consent was not required.

Conflicts of interest: None declared.

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