Development of a teicoplanin loading regimen that rapidly achieves target serum concentrations in critically ill patients with severe infections

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Abstract

We performed high-dose loading (12 mg/kg every 12 h for 48 h; 4 doses total) of teicoplanin (TEIC) in patients with severe methicillin-resistant *Staphylococcus aureus* (MRSA) infections, with the goal of achieving target serum concentration (TEICc) ≥15 mg/l within 48 h of starting administration. The safety and effectiveness of the fixed, early-stage administration method were evaluated across a range of kidney dysfunction severity levels.

TEIC high-dose loading was administered to 106 patients with MRSA infection from February 2010 to February 2013. After high-dose loading, maintenance doses based on therapeutic drug monitoring (TDM) of TEICc were administered via 30-min intravenous drips, every 24 h. Subjects were divided into 4 groups based on kidney function and renal replacement therapy (RRT) status for safety and effectiveness evaluation: group 1 (G1) did not undergo RRT and exhibited creatinine clearance (Ccr; ml/min/m^2) >50, group 2 (G2) exhibited Ccr ≤50, group 3 (G3) underwent continuous RRT (CRRT), and group 4 (G4) underwent intermittent RRT (IRRT). TEICc was measured after 24, 48, 72, and 144 h, immediately before TEIC administration.

Target TEICc was reached in all groups, and bacteriological effectiveness and utility were high in G1, G2, and G3. The maximum TEICc (≥28.0 mg/l) and serum albumin (≤1.84

g/dl) were associated with organ toxicity. Fixed high-dose loading of TEIC achieved the target therapeutic range (≥15 mg/l) within 48 h of the start of administration regardless of kidney dysfunction, and exhibited sufficient utility.

Keywords: teicoplanin, high-dose loading, hypoalbuminemia, MRSA

Introduction

Teicoplanin (TEIC) is a glycopeptide antibiotic that possesses a structure resembling that of vancomycin (VCM), and it is effective against methicillin-resistant *Staphylococcus aureus* (MRSA). Moreover, with its high protein binding rate of about 90% [1] and long serum elimination half-life of about 50 h, TEIC requires a loading dose, after which serum concentrations quickly reach a stationary state [2].

The TEIC serum concentration (TEICc) needs to be maintained at a level of at least 10–15 mg/l [2], and for severe cases or complex infections, TEICc ≥20 mg/l is recommended to obtain a positive effect [3]. Therefore, high-dose loading is required to maintain TEICc in its therapeutic range in the early stages of treatment. Regarding high-dose loading, administration regimens of 3 doses of 11–15 mg/kg every 12 h or 10.2 ± 1.3 (mean ± S.D.) mg/kg/d during the first 3 d rapidly induced effective drug concentrations [4][5]. Moreover, regardless of the severity of kidney dysfunction, the distribution volume of TEIC is considered fixed, so reduction of the loading dose is not required for TEIC administration to patients with kidney dysfunction [2,6]. However, previous studies used relatively low loading doses (3–6 mg/kg), and an effective high-dose TEIC loading regimen has not been established in critically ill patients with organ failure, such as acute kidney injury patients.

Herein, we performed fixed high-dose loading of TEIC in patients with MRSA infection, regardless of kidney dysfunction, with a target TEICc ≥15 mg/l. Furthermore, we investigated TEICc utility and safety in patients with a range of kidney functioning.

Patients and methods

This prospective study was performed on 106 patients with MRSA infection who were hospitalized at the Kurume University Hospital Advanced Emergency Medical Service Center from February 2010 to February 2013. Based on treatment results, the patients were divided into 4 groups with respect to their kidney function and renal replacement therapy (RRT) status for the evaluation of TEIC utility and safety. Group 1 (G1) and group 2 (G2) did not receive RRT. G1 exhibited creatinine clearance (Ccr) >50 ml/min/m^2, G2 exhibited Ccr ≤50 ml/min/m^2, group 3 (G3) underwent continuous RRT (CRRT), and group 4 (G4) underwent intermittent RRT (IRRT). The Ccr of G1 and G2 patients was measured as the actual Ccr by considering the urinary output for 24 h immediately before TEIC administration. A polymethylmethacrylate (PMMA) membrane hemofilter (Hemofeel® CH-1.0, Toray Medical, Co., Ltd., Tokyo, Japan) was used for all G3 patients. MRSA infection was detected from a sterile site or diagnosed on the basis of culture and positive inflammatory reaction.

The loading dose of 12 mg/kg TEIC was administered 4 times at 12-h intervals. After the

48-h loading period, maintenance doses based on therapeutic drug monitoring (TDM) of TEICc were administered. The fifth dose was administered 48 h after the start of TEIC administration (12 h after the last dose) and afterward every 24 h. TEIC was administered via 30-min intravenous drips. TEICc was measured immediately before TEIC administration on the first day of administration (day 1, D1), day 2 (D2; after 24 h, 12 h after the last dose), day 3 (D3; after 48 h, 12 h after the last dose), and day 4 (D4; after 72 h, 24 h after the last dose). TEICc was measured on day 7 (D7; after 144 h, 24 h after the last dose) immediately before administration and twice per week. The target TEICc was more than 15 mg/l for all dosage periods. In particular, TEICc should be 15 mg/l or more early in the dosage regimen, and maintenance TEICc should not exceed 30 mg/l. Maintenance doses maintain a TEICc of 20 mg/l based on TDM and dose regulation. In addition, the maintenance dose is set via TDM using the TEICc on D3. Maintenance doses were decided based on analysis of the fifth dose, administered just after D3 (12 h after the last dose). Maintenance doses were administered on D4, D7, and 2 times per week afterward based on a target TEICc of 20 mg/l, and the dose was adjusted if necessary. Blood samples were collected in blood-collection tubes without a blood coagulation accelerator and immediately centrifuged at 3,000 rpm for 10 min. TEICc was measured using a fluorescence polarization immunoassay with a TDXFLX analyzer (Abbott Japan

Co., Tokyo, Japan) that used a TEIC TDM kit-IBL (OXIS International Inc., Beverly Hills, CA, USA). The pharmacokinetics of TEIC were analyzed with TEICTDM version 2.0 (Astellas Pharma Inc., Tokyo, Japan). Utility was determined based on clinical and bacteriological effects. Serological examinations were performed on D1, D4, D7, and at the end of administration. Bacteriological assessments were conducted using cultures taken from before the start of TEIC administration until 7 d after administration ended. The bacteriological results were evaluated as "effective" when MRSA disappearance, reduction in MRSA abundance, or microbial substitution was observed. Hepatotoxicity was determined as an increase in transaminase (AST) or alanine transaminase (ALT) to more than 3 times the upper limit of the institution's normal reference ranges (AST, 13–33; ALT, 6–30). However, patients that exhibited values above the normal range before starting treatment were determined to have hepatotoxicity if their later values were more than 3 times the pre-treatment value [7]. Nephrotoxicity was determined as an increase in serum creatinine to more than 150% of its pre-treatment value, or when it exceeded 0.5 mg/dl [8]. Furthermore, logistic regression analysis on adverse events was performed. JMP® 11 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The Mann-Whitney U test, Fisher's exact test, or chi-squared test was used to compare results between 2 groups. The test parameters were recorded as median values (25^{th}–75^{th}

percentiles) and percentiles. For adverse events, items that showed P-values <0.2 in univariate analysis were used in multivariate analysis with stepwise backward selection, in which $P < 0.05$ was considered to be a significant result. Cut-off values were the maximum area under the curve (AUC) as determined with a receiver operating characteristic curve. The maximum AUC values were taken as the maximum values of the Youden index [sensitivity-(1-specificity)] [9]. This study was approved by the Kurume University School of Medicine. The study subjects, including the patients or their family members, received a written explanation of the study's objectives and methods, and consented to participation.

Results

The characteristics of all 4 groups, which showed a range of kidney function, were evaluated (Table 1). No patient required a temporary pause in administration, a reduction in dose, or cessation of drug administration during the loading period. Changes in TEICc over the evaluation period were observed (Figure 1). The median (25^{th}–75^{th} percentile) maintenance doses for G1, G2, G3, and G4 were 9.5 (6.8–11.1), 5.6 (3.1–6.8), 7.8 (6.7–9.6), and 4.5 (2.6–6.8) mg/kg/d, respectively. Maintenance doses were calculated as follows:

Maintenance dose = total dose from administration on D3 to D6 / body weight (kg) / 4

(d). Table 2 shows the MRSA infection sites of patients in each group. Respiratory organ infection was the most common observation in all 4 groups, followed by bacteremia. Assessment of acute kidney injury (AKI) (Table 3) showed that 94.8% and 100% of group G3 and G4 patients with 1-d urinary output of 400–1,000 ml or <400 ml. RIFLE classification showed that the AKI stage was most advanced in group G4. Table 4 shows the clinical effect, bacteriological effect, and utility for each group. Clinical effects over time are shown in Figure 2. Significant improvements were observed over time in all measured clinical effects for groups G1, G2, and G3 ($P < 0.05$).

Adverse events that would have necessitated the cessation of administration were not observed. Table 5 shows the incidence rates of hepatotoxicity and nephrotoxicity. Furthermore, we compared the TEICc of the group that showed hepatotoxicity with that of the group that did not show hepatotoxicity, and performed a similar comparison for nephrotoxicity (Figure 3). In all dosage periods, the TEICc of the group showing hepatotoxicity was not different from that of the group that did not show hepatotoxicity. However, the TEICc of the group that did not show nephrotoxicity was significantly higher than that of the group that showed nephrotoxicity on D2 ($P < 0.01$) and D3 ($P < 0.05$). Maximum serum concentration was found to be an independent risk factor for hepatotoxicity ($P = 0.014$; odds ratio [OR] = 1.07; 95% confidence interval [CI] = 1.00–

1.14; Table 6). The optimal cut-off point for the effect of maximum serum concentration on hepatotoxicity incidence was 28.0 mg/l (Figure 4). Serum albumin level was found to be an independent risk factor for nephrotoxicity (P = 0.02; OR = 0.25; 95% CI = 0.07–0.86; Table 7). The optimal cut-off point for the effect of serum albumin on the incidence of nephrotoxicity was 1.84 g/dl (Figure 5).

Discussion

In this study, high-dose loading of TEIC achieved TEICc >15 mg/l in 71% of patients within 48 h of the start of administration, indicating that the therapeutic range of TEIC can be reached quickly with this method. Mimoz et al. administered a high-dose TEIC regimen (12 mg/kg every 12 h for 2 consecutive days, followed by 12 mg/kg once daily) to patients with ventilator-assisted pneumonia (Ccr >60 ml/min), and reported a mean trough value of 15.9 mg/l on D4 of TEIC administration [13]. With the high-dose (12 mg/kg), 4-administration loading method reported herein, the target TEIC therapeutic range can be reached in about 24 h—a period shorter than that reported for other methods [2,13]. Thus, it is important to measure TEICc on D3 of treatment. Ueda et al. administered a high-dose TEIC regimen (10.2 ± 1.3 (mean ± S.D.) mg/kg/d during the first 3 d) to patients with normal renal function (Ccr > 60 ml/min), and reported a mean trough value of 20.0 mg/l on D4 of TEIC administration [5], which was slightly higher

than the TEICc of G1 on D4 in this study. These results suggest that differences in TEICc can be affected by the background of the patient (e.g., severity and serum albumin levels). The protein binding rate (PBR) of TEIC is relatively high (90%), and it has been suggested that TEICc is influenced by serum albumin level at the time of administration, which may cause the TEIC binding rate to vary [1]. The unbound concentration (C_{free}) rises as serum albumin concentration declines [14]. In particular, reduced PBR (as low as 58%) thought to be caused by hypoalbuminemia has been reported during the treatment of severe infections [13]. In this study, the median serum albumin level of the 106 patients at the start of TEIC administration was 2.4 g/dl (interquartile range 2.0–2.6), which was lower than levels reported in other studies [2,15,16], so the potential influence of elevated C_{free} on the therapeutic effect of TEIC and on the appearance of adverse events should be considered.

With regard to changes in TEICc during RRT, in a report on CRRT, the adsorption rate when PMMA was used as the membrane material was significantly higher than that achieved with a polysulfone membrane, and it was surmised that the TEIC that did not bind with albumin was adsorbed by the hemofiltration membrane [17]. Similarly, in this study, the TEICc of group G1 on D3 was not significantly different from that of group G3, although group G3 exhibited kidney dysfunction more severe than that of group G1.

That is, when TEIC is administered during CRRT using a PMMA membrane, free TEIC that does not bind to albumin may be adsorbed and affect TEICc. TEICc is also affected by hypoalbuminemia, because this condition increases C_{free}. High incidence rates of hepatotoxicity have been reported at TEICc ≥20 mg/l [18], which does not contradict the finding of our multivariate analysis that TEICc ≥ 28.0 mg/l is a risk factor for hepatotoxicity. High incidence rates of nephrotoxicity have been reported at TEICc >60 mg/l [19]. The multivariate analysis showed that serum albumin of ≤1.84 g/dl was a risk factor for nephrotoxicity. With VCM, the risk of nephrotoxicity is reported to increase in hypoalbuminemia patients due to elevated free serum concentrations and prolonged serum half-life [20]. Similarly, TEIC reduces PBR and increases free serum concentrations in low albumin environments, which are expected to increase the risk of nephrotoxicity. In both hepatotoxicity and nephrotoxicity, the temporary appearance of abnormal examination values was not linked to severe visceral symptoms.

One limitation of this study is that free serum TEIC concentration was not measured, so there is no estimated range for increases in free serum TEIC concentration in hypoalbuminemia patients. Furthermore, the temporary appearance of hepatotoxicity and nephrotoxicity of group G2 subjects was problematic. It may be necessary to consider reducing the single dose of TEIC for patients with Ccr ≤ 50 ml/min/m^2.In this study, fixed

high-dose loading of TEIC achieved TEICc within the target therapeutic range (≥15 mg/l). The target TEICc was achieved within 48 h of the start of administration, and the treatment exhibited sufficient utility. With this high-dose loading method, the target therapeutic range can be reached in about 24 h, which is a shorter period than can be achieved with methods reported elsewhere. Furthermore, in the presence of hypoalbuminemia, the high-dose loading method might be affected by variation in TEICc and nephrotoxicity, confirming the need for clinicians to pay careful attention to such changes when TEIC is administered to patients with a serum albumin level of ≤1.84 g/dl. In addition, TEICc >28.0 mg/l was a risk factor for hepatotoxicity in this study, so the upper limit of the optimal TEICc in critical MRSA infections similar to those evaluated in this study was around 20 mg/l, from the perspective of utility and adverse events.

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Conflict of Interest

None

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Figure legends

Fig. 1 Teicoplanin serum concentrations in different study groups. G1: group 1 (control), G2: Group 2, G3: Group 3, G4: Group 4. 2: Day 2; 3: Day 3; 4: Day 4; 7: Day 7; L: end of administration. Day 2: Control vs. G2, $P < 0.01$, Control vs. G4, $P = 0.02$. Day 3: Control vs. G2, $P = 0.03$, Control vs. G4, $P = 0.01$. Day 4: Control vs. G2, $P < 0.01$, Control vs. G4, $P = 0.04$. Significant differences were not observed in teicoplanin serum concentration between Day 7 and the end of administration. Results are presented as median (interquartile range)

Fig. 2 Clinical effect details. Results are presented as median (interquartile range). WBC (/mm3): white blood cell count; CRP (mg/dl): C-reactive protein; SOFA score: sequential organ failure assessment score [10]; JAAM DIC score: Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) score [12]. G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4. D1: Day 1; D4: Day 4; D7: Day 7. *: $P < 0.05$; **: $P < 0.01$

Fig. 3 Teicoplanin serum concentration, hepatotoxicity, and nephrotoxicity. Results are presented as median (range). D2: Day 2; D3: Day 3; D4: Day 4; D7: Day 7; DL: end of administration; Max: maximum serum concentration; nH: no hepatotoxicity; H: hepatotoxicity; nN: no nephrotoxicity; N: nephrotoxicity. * D2: nN vs. N, $P < 0.01$; * D3:

nN vs. N, $P < 0.05$. Significant differences were not observed for the other comparisons

Fig. 4 Receiver operating characteristic (ROC) curve between maximum serum concentration and hepatotoxicity. Maximum area under the curve (AUC): 0.567; optimal cut off point: 28.0 mg/l (sensitivity: 0.55; specificity: 0.75)

Fig. 5 Receiver operating characteristic (ROC) curve between serum albumin at the start of administration and nephrotoxicity. Maximum area under the curve (AUC): 0.680; optimal cut off point: 1.84 g/dl (sensitivity: 0.50; specificity: 0.83)

Fig. 1

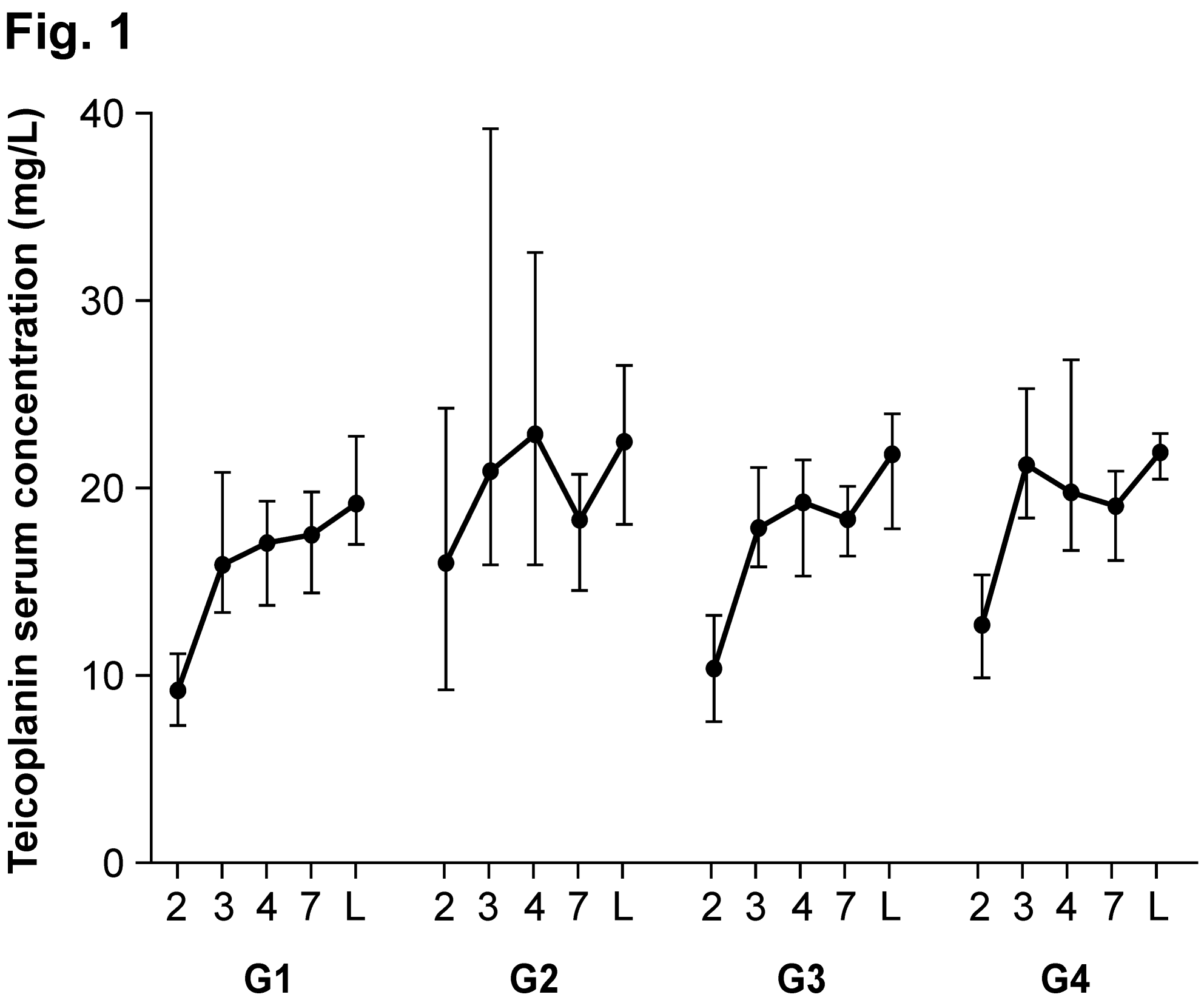
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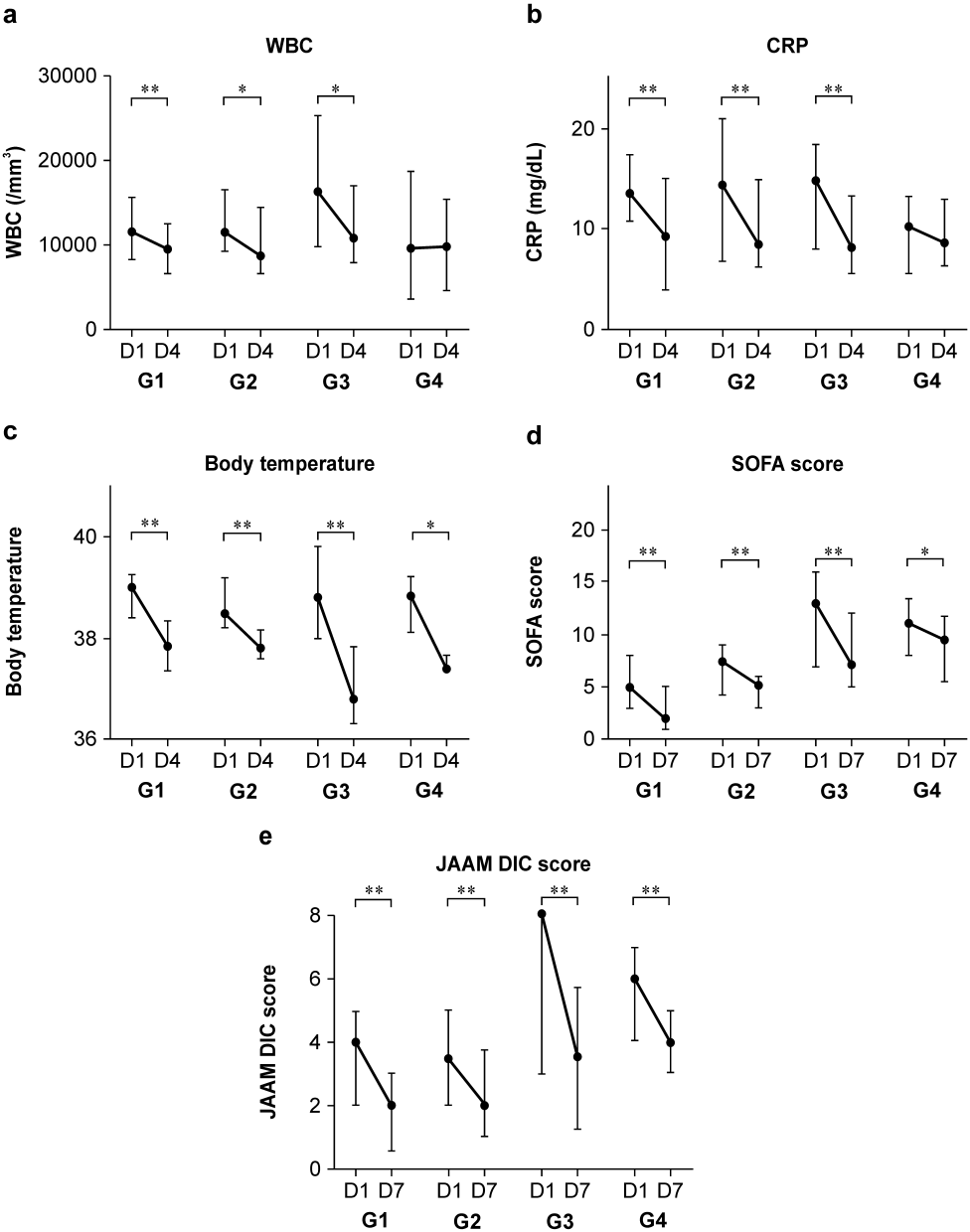
Fig. 2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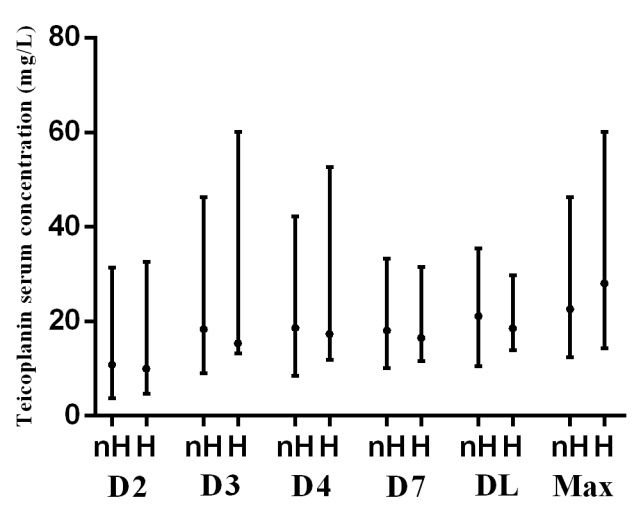
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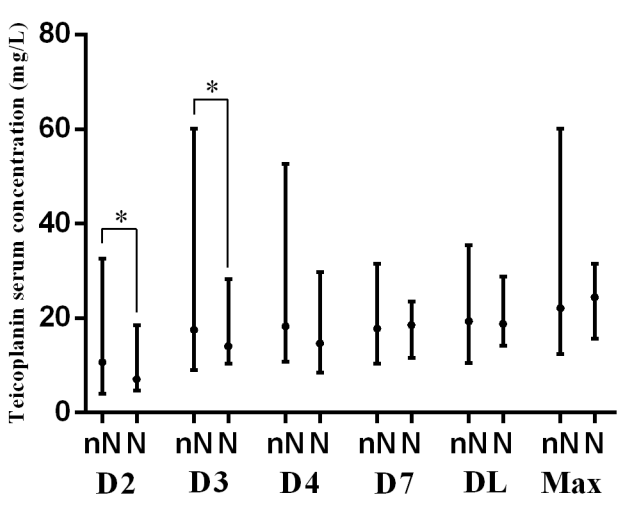
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Fig 4

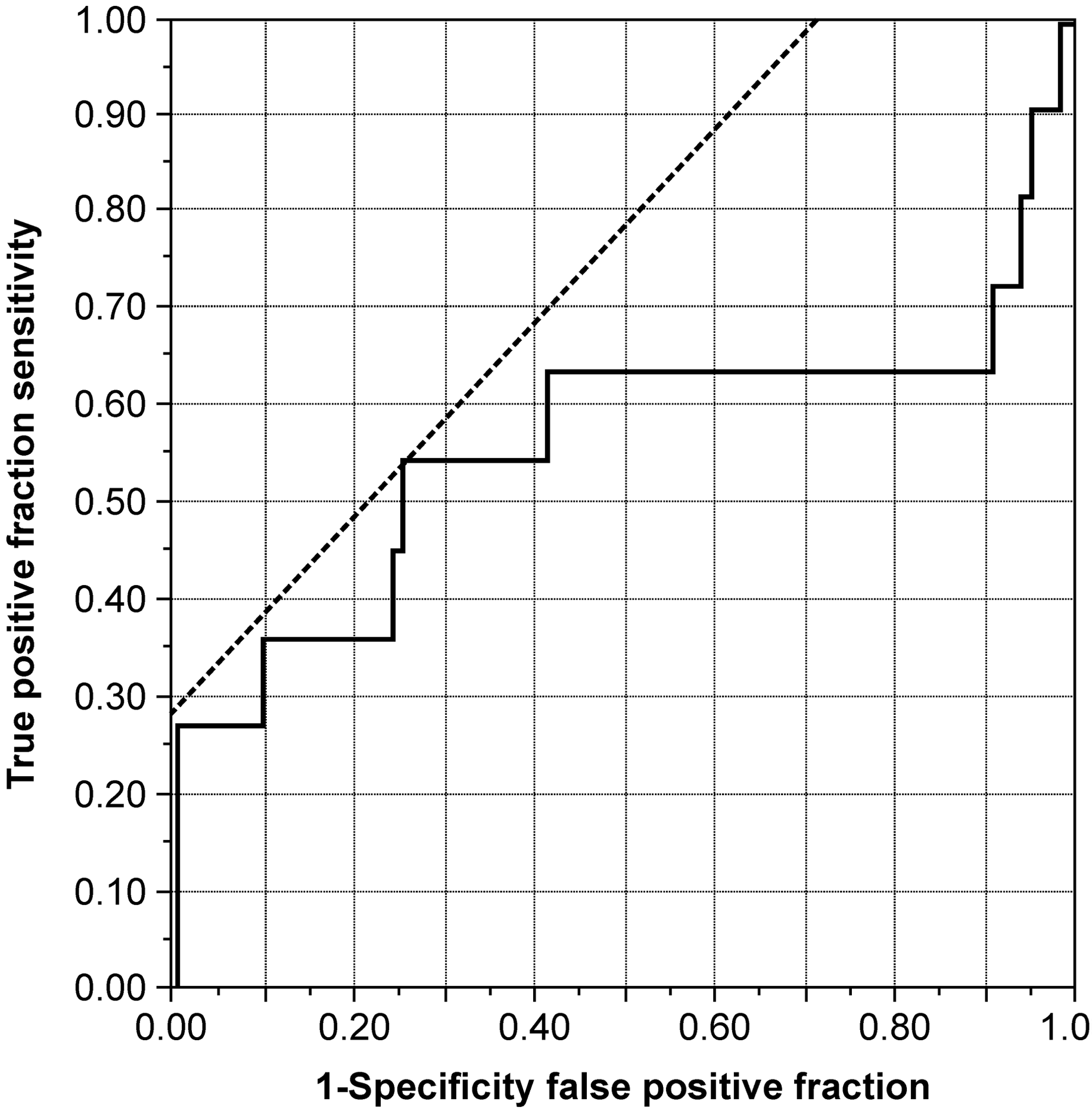
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Fig 5

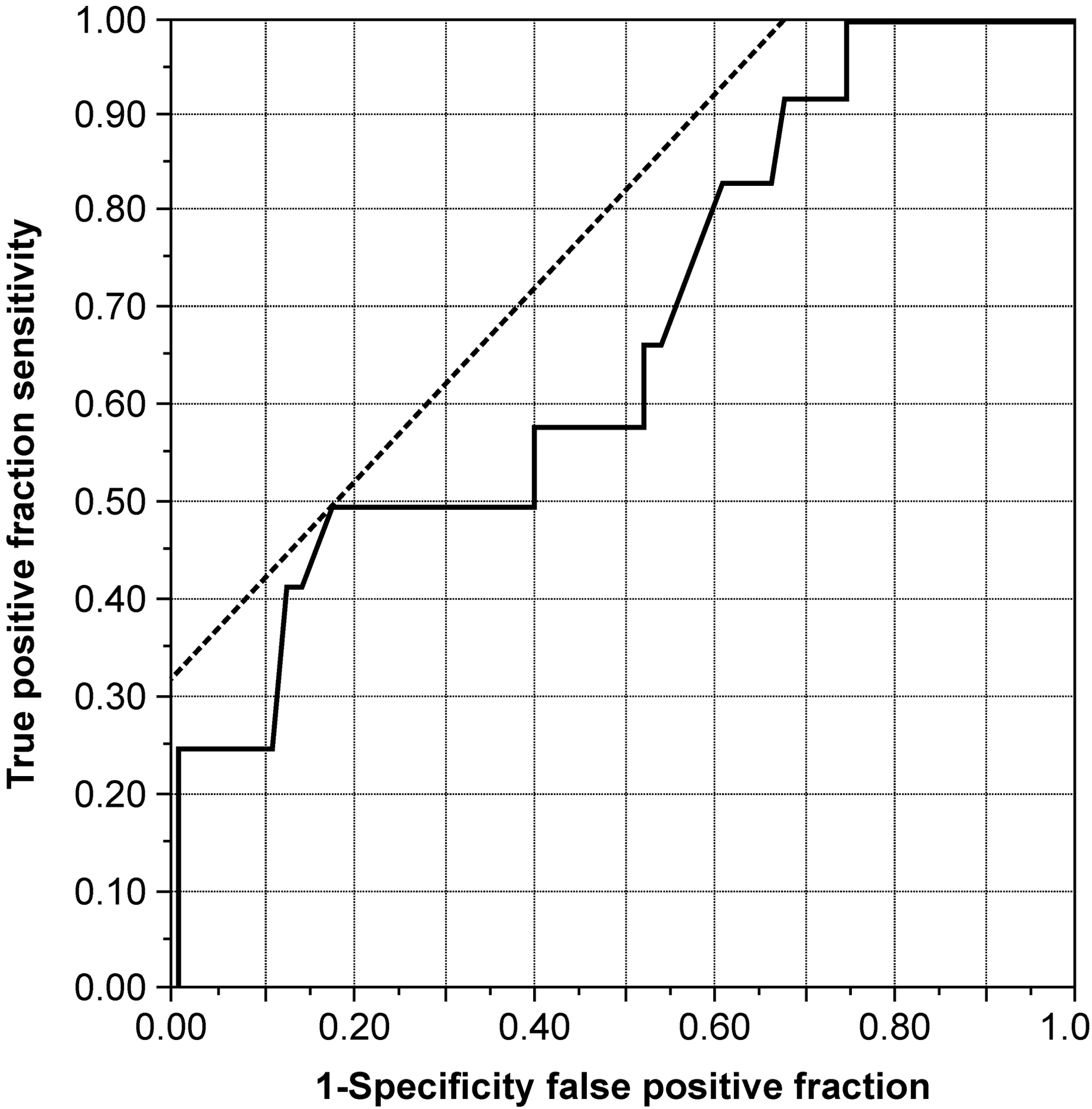
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Table 1. Baseline patient characteristics and treatments.

	Group 1 (control) Ccr‖ >50 (n = 50)	Group 2 Ccr ≤50 (n = 20)	Group 3 CRRT (n = 19)	Group 4 IRRT (n = 17)
Age, years	72 (56–79)	73 (64–77)	75 (62–80)	63 (57–74)
Gender, male	28 (56%)	10 (50%)	13 (68%)	12 (71%)
Body weight (kg) at the start of administration	59.8 (52.0–72.0)	54.7 (48.7–60.1)	67.0 (58.0–73.6)	63.0 (57.9–73.8)
SOFA score at the start of administration†	5 (3–8)	7.5 (4.3–9)	13 (7–16)*	11 (8–13.5)*
Serum albumin levels at the start of administration	2.5 (2.1–2.7)	2.1 (1.8–2.6)	2.4 (2.1–2.5)	2.3 (2.0–2.4)
Loading dose‡ (mg/kg)	50.4 (44.3–57.3)	55.8 (44.4–60.1)	45.4 (40.0–51.2)	46.9 (40.0–52.1)
Day 3 TEICc§ ≥15 (mg/l)	31 (62%)	16 (80%)	15 (78.9%)	13 (76.5%)
Day 3 TEICc ≥30 (mg/l)	1 (2%)	5 (25%)**	2 (10.5%)	1 (5.9%)
Duration of TEIC therapy (d)	12 (10–18)	12 (10–16)	14 (9–19)	13 (10–17)
In-hospital deaths	13 (26%)	3 (15%)	9 (47%)***	10 (59%)****

Results are presented as median (interquartile range) or actual values (percentage); † SOFA: sequential organ failure assessment [10]

‡ Loading dosage regimen is 12 mg/kg every 12 h, for a total of 4 times; § TEICc: teicoplanin serum concentration

* versus control, P < 0.001; ** versus control, P = 0.006; *** versus control, P = 0.047; **** versus control, P = 0.019

|| Ccr: actual creatinine clearance; Ccr was calculated using the following formula:

Ccr (ml/min/m^2) = [urinary creatinine concentration (mg/dl) / serum creatinine concentration (mg/dl)] × urinary output (ml/min) × (1.73 / body surface area [m^2])

Body surface area was calculated as follows: body surface area = body weight (kg) $^{0.425}$ × height (cm) $^{0.725}$ × 0.007184.

Table2. Site of infection due to MRSA.

	Group 1 (control) Ccr >50 (n = 50)	Group 2 Ccr ≤50 (n = 20)	Group 3 CRRT (n = 19)	Group 4 IRRT (n = 17)
Respiratory	23 (46.0%)	9 (45.0%)	7 (36.8%)	7 (41.2%)
Blood stream	17 (34.0%)	8 (40.0%)	6 (31.6%)	6 (35.3%)
Skin and soft tissue	3 (6.0%)	2 (10.0%)	3 (15.8%)	0
Intra-abdominal	2 (4.0%)	1 (5.0%)	3 (15.8%)	3 (17.6%)
Mediastinitis	3 (6.0%)	0	0	0
Empyema	1 (2.0%)	0	0	1 (5.9%)
Osteomyelitis and arthritis	1 (2.0%)	0	0	0
Total	50 (100%)	20 (100%)	19 (100%)	17 (100%)

Results are presented as number (percentage)

Significant differences regarding the MRSA infection site ratios were not observed between group 1 (control) and groups 2, 3, or 4

Table 3. Kidney function.

		Group 1 (control) Ccr >50 (n = 50)	Group 2 Ccr ≤50 (n = 20)	Group 3 CRRT (n = 19)	Group 4 IRRT (n = 17)
Ccr (ml/min/m^2)†		96.8 (73.8–100)	30 (20.8–40)	-	-
Urinary output classification‡	>1000	47 (94.0%)	19 (95.0)	1 (5.2%)	0
	400–1000	3 (6.0%)	1 (5.0)	8 (42.1%)	2 (11.8%)
(ml/d)	<400	0	0	10 (52.7%)	15 (88.2%)
RIFLE classification§	non	43 (86.0%)	2 (10.0%)	0	0
	Risk	5 (10.0%)	2 (10.0%)	1 (5.2%)	0
	Injury	2 (4.0%)	11 (55.0%)	4 (21.1%)	0
	Failure	0	5 (25.0%)	9 (47.4%)	4 (23.5%)
	Loss	0	0	5 (26.3%)	9 (53.0%)
	ESKD	0	0	0	4 (23.5%)

Results are presented as median (interquartile range) or number (percentage)

† Ccr: actual creatinine clearance;‡ Urinary output classification (ml/d): urinary output for 3 d from 24 h before starting administration;§ RIFLE: risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-

stage kidney disease. The four groups (G1-G4) were divided with respect to 24-hour urinary output and RIFLE categorization [11] of acute kidney injury (AKI).

Table 4. Teicoplanin utility

	Group 1 (control) Ccr >50 (n = 50)	Group 2 Ccr ≤50 (n = 20)	Group 3 CRRT (n = 19)	Group 4 IRRT (n = 17)
Clinical effectiveness rate	44 (68%)	14 (70%)	13 (68.4%)	7 (41.2%)
Bacteriological effectiveness rate	42 (84%)	19 (95%)	16 (84.2%)	13 (76.5%)
Utility rate	35 (70%)	15 (75%)	12 (63.2%)	7 (41.2%)

Results are presented as number (percentage); Significant differences with group 1 (control) were not observed for clinical effectiveness, bacteriological effectiveness, or utility

Table 5. Rates of adverse events in each group.

	Group 1 (control) Ccr† >50 (n = 50)	Group 2 Ccr ≤50 (n = 20)	Group 3 CRRT (n = 19)	Group 4 IRRT (n = 17)
Hepatotoxicity	5 (10%)	5 (25%)	1 (5.2%)	0
Nephrotoxicity	8 (16%)	4 (20%)	-	-

Results are presented as number (percentage)

† Ccr: actual creatinine clearance

Table 6. Results of multivariate logistic regression analysis for hepatotoxicity.

	Multiple logistic regression analysis			Stepwise backward selection		
	Odds ratio	95% CI	P-values	Odds ratio	95% CI	P-values
Age, years	0.99	0.96–1.05	0.94	-	-	-
Gender, male	1.88	0.53–6.95	0.32	-	-	-
Serum albumin† (g/dl)	1.96	0.55–7.19	0.29	-	-	-
Maximum serum concentration (mg/l)	1.08	1.01–1.15	0.01*	1.07	1.00–1.14	0.014**
Loading dose (mg/kg)	1.35	0.96–1.95	0.08*	1.23	0.85–1.83	0.28
Administration period (d)	1.02	0.95–1.09	0.45	-	-	-
Reduced kidney function group (Group 2, Group 3, Group 4), yes	1.08	0.31–3.97	0.90	-	-	-

† Start of administration; * $P < 0.2$; ** $P < 0.05$

Table 7. Results of multivariate logistic regression analysis for nephrotoxicity.

	Multiple logistic regression analysis			Stepwise backward selection		
	Odds ratio	95% CI	P-values	Odds ratio	95% CI	P-values
Age, years	1.02	0.98–1.08	0.37	-	-	-
Gender, male	0.33	0.07–1.25	0.11*	0.44	0.09–1.80	0.26
Serum albumin† (g/dl)	0.23	0.06–0.74	0.01*	0.25	0.07–0.86	0.02**
Maximum serum concentration (mg/l)	0.99	0.90–1.05	0.7	-	-	-
Loading dose (mg/kg)	1.35	0.67–1.24	0.54	-	-	-
Administration period (d)	0.99	0.90–1.08	0.93	-	-	-
Actual Ccr	0.99	0.98–1.02	0.83	-	-	-

† Start of administration; * $P < 0.2$; ** $P < 0.05$