Vancomycin loading dose is associated with increased early clinical responses without attainment of initial target trough concentration at a steady state in patients with normal renal function

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Abstract

Background Vancomycin therapeutic guidelines suggest a loading dose of 25–30 mg/kg for seriously ill patients. However, high-quality data to guide the use of loading dose are lacking. Evaluate whether a loading dose 1) achieves a target trough concentration (C_{min}) at steady state and 2) improves early clinical responses. **Methods** Patients with an estimated glomerular filtration rate ≥ 90 mL/min/1.73 m² were included. A loading dose of 25 mg/kg vancomycin followed by 15 mg/kg twice daily was compared with traditional dosing. A C_{min} sample was obtained before the fifth dose. An early clinical response 48–72 h after the start of therapy and clinical success at end of therapy (EOT) was evaluated in patients with methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococci*, or *Enterococcus faecium*. **Results** There was no significant difference in C_{min} between the regimen with and without a loading dose (median: 10.4 μ g/mL and 10.2 μ g/mL, $P=0.538$). Proportions of patients achieving 10–20 μ g/mL and 15–20 μ g/mL were 56.9% and 5.6%, respectively, in patients with a loading dose. Although there was no significant difference in success rate at EOT between groups, loading dose was associated with increased early clinical responses for all infections [adjusted odds ratio (OR): 4.829, 95% confidence interval (CI): 1.441–16.188] and MRSA infections (OR: 10.851, 95% CI: 1.701–69.233). Increased adverse events were not observed with the loading dose. Study limitations included no C_{min} measurements within 24 hours, and the inclusion of less critically ill patients. **Conclusions** Although the loading dose did not achieve optimal C_{min} at steady state, a higher early clinical response was obtained compared with traditional dosing.

Background

Although the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has gradually decreased over the past decade [1, 2], MRSA remains one of the most prevalent resistant organisms in health care associated infections [3]. Vancomycin is a commonly used antibiotic for the treatment of MRSA infections. The optimization of vancomycin dosing is important and a target trough concentration (C_{min}) of 10–20 μ g/mL has been proposed [4, 5]. The C_{min} should be maintained above 10 μ g/mL to avoid the development of resistance [6]. A C_{min} of 15–20 μ g/mL improved outcomes in patients with complicated MRSA bacteremia [7].

Vancomycin is commonly initiated at a standard dose of 15 mg/kg every 12 h with dosage adjustment based on creatinine clearance (CL_{cr}) [4, 5]. However, with the same dosage regimen, the median C_{min} remained 9.4 μ g/mL (62% of patients were < 10 μ g/mL) on day 3 of a study for the treatment of complicated skin and soft tissue infections caused by MRSA [8]. In a randomized trial for the treatment of nosocomial pneumonia caused by MRSA, the median C_{min} on day 3 was 12.3 μ g/mL, and 25% of patients had a $C_{min} < 7.9$ μ g/mL [9]. The standard dosing regimen was inadequate at achieving the target C_{min} [10]. In patients with sepsis, fluid extravasation causes an increase in interstitial volume. For hydrophilic antibiotics such as vancomycin, these pathophysiological changes might increase the volume of distribution and cause low antibiotic serum concentration [11]. Therefore, initial loading is important to avoid the risk of underexposure.

Vancomycin therapeutic guidelines [4, 5] suggest a loading dose of 25–30 mg/kg for seriously ill patients. However, high-quality data to guide the use of loading dose are lacking. In a systematic review, Reardon et al. [12] suggested that a loading dose may attain target C_{min} of 15–20 μ g/mL. However, they included studies that evaluated efficacy of dosing nomogram or which assessed early concentrations before steady state. The aim of this study was to evaluate the efficacy of a loading dose to achieve the target C_{min} at a steady state in patients with normal renal function. A second aim was to evaluate early clinical responses [13] obtained by the loading dose, because it is intended to achieve a rapid attainment of optimal concentrations, and clinical responses can be affected by a change in vancomycin dose later in therapy.

Methods

Patients and protocol

This study was conducted between April 2011 and May 2018. Adult patients with an estimated glomerular filtration rate (eGFR) of ≥ 90 mL/min/1.73 m² who were treated with vancomycin, and in whom therapeutic drug monitoring (TDM) was performed, were included in the study. Exclusion criteria were patients with known hypersensitivity to vancomycin, pregnancy, below the age of 18 years, and body weight of ≥ 100 kg. Retrospective evaluation of the regimen without a loading dose was conducted between April 2011 and December 2015, and the evaluation of the regimen with a loading dose of 25 mg/kg was conducted between January 2016 and May 2018. A maintenance dose of 15 mg/kg every 12 h was administered to both regimens. An initial C_{min} sample was obtained before the fifth dose. Vancomycin concentration was measured using a commercial reagent kit (Vanc Flex; Siemens Healthcare Diagnostics, Tokyo, Japan).

The analysis of safety population included all eligible patients. For the C_{min} evaluation, patients whose renal function deteriorated from the initiation of vancomycin to the initial TDM were excluded. The analysis of clinical efficacy population included patients who had infections with MRSA, methicillin-resistant coagulase-negative *Staphylococci* (MR-CNS) or *Enterococcus faecium*, who received at least 3 days of vancomycin treatment, who did not receive any concomitant antibiotics with anti-MRSA activity, and who did not receive the above mentioned antibiotics for > 24 h within the previous 3 days. The diagnosis of each type of infection, other than respiratory tract infection, was based on the definitions of the guidelines issued by the National Healthcare Safety Network. (CDC/NHSN surveillance definitions for surgical site infections. Centers for Disease Control and Prevention website: http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosindef_current.pdf. Published 2018. Accessed November 10, 2018.).

Infections with at least one of the following signs were analyzed: core temperature $>37.8^{\circ}\text{C}$, total peripheral white blood cell (WBC) count $>10,000/\text{mm}^3$, or C-reactive protein (CRP) $>3.0\text{ mg/dL}$. Diagnosis of pneumonia was defined as chest X-rays or CT scans consistent with pneumonia and at least two of the following signs or symptoms: (new onset or worsening cough; purulent sputum or increased suctioning requirements; auscultatory findings of pneumonia; dyspnea, tachypnea, or respiratory rate $\geq 30\text{ min}$; hypoxemia; worsening gas exchange, and at least one of the inflammatory signs described above [9]. The MIC of vancomycin was measured by microdilution methods in accordance with the Clinical and Laboratory Standards Institute testing guidelines (M02 and M07, 2018) [14].

Clinical efficacy

The primary endpoint was set as an early clinical response at 48–72 h after the start of therapy. We defined patients as responders if they had a 30% or greater decrease in total peripheral WBC count or CRP, decline of fever (defined as a daily maximum temperature decrease of $>0.3^{\circ}\text{C}$ for at least two consecutive days in febrile patients), without worsening of clinical features, and did not die within 96 h. Secondary efficacy end points were clinical success at the end of vancomycin therapy (EOT), which was defined as survival with resolution or improvement in all core symptoms and signs of infection in each infection to the extent that further antibacterial therapy with anti-MRSA activity was unnecessary. Microbiological assessments were conducted using cultures taken before the start of vancomycin administration and at the completion of treatment, and microbiological success was defined as “eradication” (admission pathogen absent in culture) or “presumed eradication” (no material available for culture because of the infection site being cured or attenuated).

Adverse effects

Adverse effects of nephrotoxicity and hepatotoxicity were evaluated on the third day of therapy and at the end of vancomycin therapy. Nephrotoxicity was defined as a serum creatinine (Cre) increase $>0.5\text{ mg/L}$ or 50% increase from the baseline. Hepatotoxicity was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels at or above three times the upper limit of normal. If the AST or ALT baseline was abnormal, hepatotoxicity was defined as AST or ALT at or above three times the baseline.

Statistical analysis

Parametric variables were analyzed using the Student’s *t*-test, while nonparametric variables were analyzed using the Mann–Whitney *U*-test or Fisher’s exact test. Multivariate analyses were performed to determine the odds ratio (OR) for early clinical responses. The crude OR in univariate analysis was estimated for each variable with the chi-squared test, and potential confounders were examined by cross tabulation. Variables selected by univariate analysis ($P<0.1$) were subsequently entered into a stepwise logistic regression model to estimate the magnitude of association [adjusted OR and 95% confidence interval (CI)]. The level of significance was set at $P<0.05$. SPSS ver. 24 (SPSS Inc., Chicago, IL, USA) was used to perform these analyses.

Results

Baseline demographics

Overall, 157 patients were included in the safety analyses. In the TDM evaluation, four patients with worsening renal function at the initial TDM after the start of vancomycin were excluded, and 153 patients were assessed. Among 95 patients who had MRSA, MR-CNS, or *E. faecium* infections, seven patients who did not receive at least 3 days of vancomycin treatment, and six patients who received any concomitant antibiotics with anti-MRSA activity were excluded from the clinically efficacy evaluation. No patient had an infection with vancomycin resistant enterococci. Overall, 82 patients were analyzed for early clinical responses, and 55 patients with MRSA infections were also analyzed. The initial loading dose was $25.7 \pm 0.9\text{ mg/kg}$. There was no significant difference in the maintenance dose between regimens with and without a loading dose ($15.3 \pm 0.5\text{ mg/kg}$ vs $15.2 \pm 0.6\text{ mg/kg}$, $P=0.410$). Patient characteristics are shown in Table 1. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were approximately 8.0–9.0.

Measurements of $C_{\min}$

The median $C_{\min}$ was $10.4\text{ }\mu\text{g/mL}$ in the regimen with a loading dose, and $10.2\text{ }\mu\text{g/mL}$ in the regimen without a loading dose ($P=0.538$). The proportion of patients achieving the target range ($10\text{--}20\text{ }\mu\text{g/mL}$) was 41/72 (56.9%) in the regimen with a loading dose and 39/81 (48.1%) in the regimen without a loading dose ($P=0.277$). The higher target range of $15\text{--}20\text{ }\mu\text{g/mL}$ was achieved in only 4/72 patients with a loading dose and 8/81 patients without a loading dose ($P=0.321$) (Table 2). Body mass index (BMI) was 25–30 in 19 patients and ≥ 30 in 3 patients. Achievement of

the target C_{min} was obtained in 70% and 66% of obese/overweight patients and 54% and 44% of patients whose BMI was < 25 in the regimens with and without a loading dose, respectively. After the initial TDM, dosage was increased in 28 patients and decreased in 11 patients, and vancomycin was discontinued in 33 patients. The proportion of patients achieving a C_{min} of 10–20 µg/mL was significantly increased from 54.3% to 78.7% ($P<0.001$) in 94 patients who had follow-up TDM (4.3 ± 1.9 days after initial TDM) and was increased from 7.4% to 74.1% of patients in whom the dosage was increased after initial TDM.

Clinical efficacy and mortality

Early clinical responses were obtained in 53/82 patients (64.6%), and clinical success at EOT was obtained in 58/82 patients (70.7%). The 28-day mortality rate was 6/82 patients (7.3%). In patients with a loading dose, the early clinical response rate tended to be higher compared with patients without a loading dose [27/36 (75.0%) vs. 26/36 (56.5%), $P=0.082$]. In MRSA infections, the early clinical response rate in patients with a loading dose was significantly higher than that in patients without a loading dose [18/23 (78.3%) vs 16/32 (50.0%), $P=0.033$]. However, there was no significant difference in the clinical success rate at EOT between the two regimens (all: 72.2% vs 69.6%, $P=0.793$; MRSA: 69.6% vs 56.3%, $P=0.316$) (Table 3). The 28-day mortality rate was 8.3% in the regimen with a loading dose and 6.5% in the regimen without a loading dose ($P=1.000$), and 4.3% and 9.4% in patients with MRSA infections ($P=0.632$), respectively.

By univariate analysis, collagen disease, ICU stay, hypoalbuminemia, ventilator use, APACHE II score > 10, and respiratory tract infections were factors associated with a poor early clinical response in all clinical efficacy populations (Table 4). In patients with MRSA infections, collagen disease, total parenteral nutrition, ventilator use, APACHE II score > 10, and steroid use were the factors associated with a poor early clinical response, and skin and skin-structure infections and loading dose were associated with a favorable early clinical response (Table 5). By multivariate analysis, a loading dose regimen was associated with an early clinical response in the whole clinical efficacy population (adjusted OR: 4.829, 95% CI: 1.441–16.188) and MRSA infection group (adjusted OR: 10.851, 95% CI: 1.701–69.233). The factors for a poor early clinical response were APACHE II score > 10 in the whole clinical efficacy population, and APACHE II score >10 and osteomyelitis/arthritis in MRSA infection group, respectively.

Adverse effects

In the assessment of safety population, there was no significant difference in the occurrence of nephrotoxicity between regimens with and without a loading dose [3.6% and 1.4% on the third day ($P = 0.624$); 8.2% and 6.0% at EOT ($P= 0.579$), respectively]. There was also no significant difference in the occurrence of hepatotoxicity [1.2% and 1.4% on the third day ($P = 1.000$); 3.6% and 4.1% at EOT ($P= 1.000$), respectively].

Discussion

Recent guidelines [4, 5] suggest a loading dose of 25–30 mg/kg to achieve the targeted range for treatment with vancomycin. In our study, however, the proportions of patients achieving 10–20 µg/mL and 15–20 µg/mL at 48 h after the first dose were 56.9% and 5.6%, respectively, in patients with an $eGFR \geq 90$ mL/min/1.73 m² who received a regimen with a loading dose of 25 mg/kg. There was no significant difference in the C_{min} between the regimen with and without a loading dose. Rosini et al. [15] reported that the 12-h C_{min} allowed a significantly greater proportion of patients to achieve 15 µg/mL among patients with a loading dose of 30 mg/kg followed by 15 mg/kg twice daily compared with those without a loading dose. However, the effect of the loading dose was attenuated at the steady state, and only 20% of patients with a loading dose attained the target C_{min} at steady state. Most of their study patients also had a high CL_{cr} (mean 93 mL/min). However, in a study including patients with deteriorated renal function, a loading dose resulted in a higher concentration at steady state [16, 17]. In patients with deteriorated renal function, not only a loading dose but also a maintenance dose had a significant impact on the C_{min} .

Why the C_{min} was low in our study might be explained by only three obese patients being included. Pharmacokinetic (PK) data indicated a larger volume of distribution and accelerated renal clearance of vancomycin in obese patients [18], which might justify a weight-based dosing regimen. However, a study using weight-based regimens by Reynolds et al. [19] reported a $C_{min} > 20$ µg/mL in approximately 50% of obese patients. Richardson et al. [20] reported that increasing BMI categories were associated with a $C_{min} > 20$ µg/mL. Leong et al. [21] demonstrated that an adjusted body weight was more accurate at predicting vancomycin clearance in obese individuals.

A loading dose alone may not be sufficient to increase the C_{min} measured 48 h after the initial dose in patients without decreased vancomycin clearance. However, the main purpose of a loading dose is not to obtain the target C_{min} at steady state, but the rapid achievement of a therapeutic concentration within 12–24 h [15]. To maintain a high concentration thereafter, an increase in the maintenance dose from 15 mg/kg to 20 mg/kg might be required [22]. Many studies reported a higher achievement of a $C_{min} > 15$ µg/mL after the first dose in patients with a loading dose compared with patients without a loading dose [10, 15, 23, 24]. Casapao et al. [25] evaluated the association between the day 1 vancomycin exposure profile and outcomes among patients with MRSA infective endocarditis, and an AUC/MIC of < 600 was independently associated with failure.

Few studies have focused on the use of a loading dose to increase clinical efficacy for the treatment of MRSA infections. Jeon et al. [26] reported an initial daily dose per weight < 40 mg/kg was a strong risk factor for vancomycin non-responsiveness in patients with MRSA pneumonia. Wesolek et al. [27] reported that an initial dose > 20 mg/kg led to a faster resolution of systematic inflammatory response syndrome (> 20 mg/kg: 67 h vs ≤ 20 mg/kg: 109 h). In our study, a loading dose increased the rate of early clinical response at 48–96 h after the start of therapy. However, there was no significant difference in clinical success at EOT between the regimen with and without a loading dose. Clinical response beyond 72 h of treatment can be affected by changes in the vancomycin dose later in therapy, based on the initial TDM conducted. Indeed, the achievement rate of target C_{min} of 10–20 µg/mL was increased from 7.4% to 74.1% of patients in whom the dosage was increased after initial TDM in our study.

PK analysis indicated that a loading dose of 25–30 mg/kg could be applied irrespective of renal function [28]. Clinicians, however, tend to be reluctant to use a loading dose, especially in patients with decreased renal function, for fear of causing renal injury. Alvarez et al. [10] demonstrated that all patients with a loading dose who presented with decreased vancomycin clearance before the administration of vancomycin had an elevated serum concentration (>28 µg/mL) in the first 24 h of treatment. These patients, however, did not have nephrotoxicity. Although prolonged exposure to elevated C_{min} causes nephrotoxicity, a temporary increase in the C_{min} with an initial loading dose might not cause nephrotoxicity. Marvin et al. [29] reported that a loading dose > 20 mg/kg was not associated with increased nephrotoxicity in patients with a CL_{cr} < 30 mL/min compared with a standard dosing regimen.

Limitations

This study had some limitations. First, we did not measure the C_{min} 24 h after the first dose, and the early attainment of the target C_{min} with a loading dose was not confirmed. Second, early clinical responses were evaluated at 48–72 h after the first dose. Although an early clinical response was defined as improvement at 48–72 h after the start of therapy in patients with acute bacterial skin and skin-structure infections [13], a significantly lower response rate in respiratory tract infection in our study might be caused by this early clinical response evaluation. Third, APACHE II scores were approximately 8.0, indicating mild-to-moderate severity. Although the Infectious Diseases Society of America guidelines³ recommend a loading dose for seriously ill patients, the efficacy of a loading dose was not confirmed in severely ill patients in our study. Fourth, patients with an $eGFR \geq 90$ mL/min/1.73m² were included in our study, which might explain the low C_{min} value observed, and thus exaggerate the weakness of the regimen without a loading dose.

Conclusions

In conclusion, a loading dose of 25 mg/kg followed by 15 mg/kg twice daily did not achieve the optimal C_{min} at steady state in patients with normal renal function. However, higher early clinical responses were obtained by a loading dose compared with traditional dosing, possibly because of a prompt but temporary achievement of the optimal concentration.

Abbreviations

C_{min} : trough concentration; EOT: end of therapy; MRSA: methicillin-resistant *Staphylococcus aureus*; CL_{cr} : creatinine clearance; $eGFR$: estimated glomerular filtration rate; TDM: therapeutic drug monitoring; MR-CNS: methicillin-resistant coagulase-negative *Staphylococci*; WBC: white blood cell; CRP: C-reactive protein; Cre: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: Body mass index; OR: odds ratio; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; PK: Pharmacokinetic

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Hyogo College of Medicine (No. 2239). The institutional review board waived the requirement for informed consent from patients included in this study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

1. Takesue has received grant support from Shionogi & Co., Ltd., and payment for lectures from Astellas Pharma Inc., and MSD Japan. Other authors have no conflict of interest to declare.

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Authors' contributions

TU was involved in the conception of the study, collection, analysis and interpretation of data, the creation of new software used in the work, draft the work and substantively revised of the manuscript. YT was involved in the design of the study and draft the work. KN, KI, Kaori Ishikawa, YT, KY, YW, TT, NO, Yoshiko Takahashi, MI, SS, HI, MT and TK contributed to the data collection and interpretation. All authors had substantial input to the drafting and review of the manuscript and approved the final version prior to publication.

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Tables

Table 1. Baseline demographics of patients included in the pharmacokinetics, safety, and clinical efficacy analyses.

Baseline demographics	All patients (n=157)			All infections (n=82)			MRSA infections (n=55)		
	Regimen without a loading dose (n=84)	Regimen with a loading dose (n=73)	P-value	Regimen without a loading dose (n=46)	Regimen with a loading dose (n=36)	P-value	Regimen without a loading dose (n=32)	Regimen with a loading dose (n=23)	P-value
Sex male (%)	53 (63.1%)	40 (54.8%)	0.291	31 (67.4%)	19 (52.8%)	0.178	23 (71.9%)	12 (52.2%)	0.134
Age (range) (years)	65.1±12.0	61.5±13.5	0.077	65.7±11.6	64.2±13.0	0.469	64.0±10.4	63.2±13.7	0.801
Body weight (range) (kg)	56.7±12.6	54.3±10.8	0.201	56.4±13.2	53.4±9.2	0.097	58.3±14.4	52.6±9.6	0.077
Body mass index ≥25	12 (14.3%)	11 (15.1%)	0.890	5 (10.9%)	4 (11.1%)	1.000	4 (12.5%)	3 (13.0%)	1.000
APACHE II score	8.0±4.5	8.7±5.5	0.528	8.7±5.1	9.8±5.8	0.451	8.3±4.5	8.5±5.1	0.966
Estimated glomerular filtration rate (range) (mL/min/1.73m ²)	117.6±40.7	120.7±27.1	0.586	122.9±29.4	120.8±23.2	0.159	123.3±56.6	120.4±24.1	0.820
Type of infection									
Blood stream	22 (26.2%)	30 (41.1%)	0.048	13 (28.3%)	17 (47.2%)	0.077	6 (18.8%)	6 (26.1%)	0.516
Respiratory	15 (17.9%)	6 (8.2%)	0.077	14 (30.4%)	6 (16.7%)	0.150	14 (43.8%)	6 (26.1%)	0.179
Intraabdominal	12 (14.3%)	3 (4.1%)	0.054	10 (21.7%)	1 (2.8%)	0.019	4 (12.5%)	0 (0.0%)	0.131
Skin & soft tissue	9 (10.7%)	8 (11.0%)	0.961	7 (15.2%)	8 (22.2%)	0.416	6 (18.8%)	8 (34.8%)	0.178
Osteomyelitis and arthritis	14 (16.7%)	10 (13.7%)	0.606	5 (10.9%)	3 (8.3%)	1.000	4 (12.5%)	3 (13.0%)	0.630
Mediastinitis	3 (3.6%)	5 (6.8%)	0.474	1 (2.2%)	2 (5.6%)	0.579	1 (3.1%)	1 (4.3%)	0.666
Unknown (empiric therapy)	13 (16.7%)	15 (20.5%)	0.408	–	–	–	–	–	–
Isolated Gram-positive cocci									
MRSA	39 (59.1%)	28 (48.3%)	0.267	32 (69.6%)	23 (63.9%)	0.587	32	23	
MSSA	6 (5.1%)	8 (13.8%)	0.392	–	–	–	–	–	
MR-CNS	7 (10.6%)	12 (20.7%)	0.120	7 (15.2%)	12 (33.3%)	0.054	–	–	
MS-CNS	2 (5.0%)	4 (6.9%)	1.000	–	–	–	–	–	
<i>Enterococcus faecalis</i>	2 (5.0%)	1 (1.7%)	1.000	–	–	–	–	–	
<i>Enterococcus faecium</i>	8 (52.1%)	1 (1.7%)	0.090	7 (15.2%)	1 (2.8%)	0.073	–	–	
<i>Streptococcus</i> sp	1 (5.5%)	2 (3.4%)	0.541	–	–	–	–	–	
<i>Bacillus</i> sp	2 (3.0%)	3 (5.2%)	0.589	–	–	–	–	–	

Age, body weight and estimated glomerular filtration rate are expressed as the mean ± S.D. and range.

MRSA; Methicillin-resistant *Staphylococcus aureus*, MSSA; Methicillin-sensitive *Staphylococcus aureus*, MR-CNS; Methicillin-resistant coagulase-negative *Staphylococci*, MS-CNS; Methicillin-sensitive coagulase-negative *Staphylococci*.

Table 2. Vancomycin initial trough concentration (C_{min}) in each regimen group

	Regimen without a loading dose (n=81)	Regimen with a loading dose (n=72)	P-value
Median (IQR, Range) of C _{min} (µg/mL)	10.2 (7.9–12.5, 3.2–19.8)	10.4 (8.8–12.3, 5.1–17.2)	0.538
No. of patient according to the initial C _{min} categories (%)			
< 10 µg/mL	42 (51.9%)	31 (43.1%)	0.277
10–15 µg/mL	31 (38.3%)	37 (51.4%)	0.103
15–20 µg/mL	8 (9.9%)	4 (5.6%)	0.321
≥ 20 µg/mL	0 (0.0%)	0 (0.0%)	-

Table 3. Efficacy and mortality in patients with MRSA, *Enterococcus faecium*, or methicillin-resistant coagulase-negative *staphylococci* (MR-CNS) infections treated by vancomycin with or without a loading dose.

Clinical results	MRSA			<i>Enterococcus faecium</i>			MR-CNS			Total		
	Regimen without a loading dose	Regimen with a loading dose	P-value	Regimen without a loading dose	Regimen with a loading dose	P-value	Regimen without a loading dose	Regimen with a loading dose	P-value	Regimen without a loading dose	Regimen with a loading dose	P-value
Early clinical response	16/32 (50.0%)	18/23 (78.3%)	0.033	5/7 (71.4%)	0/1 (0.0%)	0.375	5/7 (71.4%)	9/12 (75.0%)	1.000	26/46 (56.5%)	27/36 (75.0%)	0.082
Clinical success at the end of therapy	18/32 (56.3%)	16/23 (69.6%)	0.316	7/7 (100.0%)	0/1 (0.0%)	0.125	7/7 (100.0%)	10/12 (83.3%)	0.509	32/46 (69.6%)	26/36 (72.2%)	0.793
Microbiological success	18/32 (56.3%)	16/22* (72.7%)	0.218	5/7 (71.4%)	0/1 (0.0%)	0.375	5/7 (71.4%)	10/12 (83.3%)	1.000	30/46 (65.2%)	27/35 (77.1%)	0.244
28 days mortality	3/32 (9.4%)	1/23 (4.3%)	0.632	0/7 (0.0%)	1/1 (100%)	0.125	0/7 (0.0%)	1/12 (8.3%)	1.000	3/46 (6.5%)	3/36 (8.3%)	1.000

*: One patient in whom culture results after start of therapy were not obtained was excluded

Table 4. Variable factors associated with an early clinical response in patients with MRSA, *Enterococcus faecium*, or methicillin-resistant coagulase-negative *staphylococci* (MR-CNS): univariate and multivariate analyses.

Factors	No of patients with early clinical response (%)		P-value	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	Patients with factor	Patients without factor			
Sex (male)	31/49 (63.3%)	22/33 (66.7%)	0.752	0.477 (0.165-1.378)	
Age (>65 years)	29/45 (64.4%)	24/37 (64.9%)	0.968	0.770 (0.282-2.099)	
Body Mass Index <18.5	18/23 (78.3%)	35/59 (59.3%)	0.107	1.493 (0.418-5.334)	
Body Mass Index ≥25	5/9 (55.6%)	48/73 (65.8%)	0.714	1.885 (0.359-9.898)	
Heart disease	9/14 (64.3%)	44/68 (64.7%)	0.601	3.300 (0.373-29.194)	
Diabetes mellitus	10/13 (76.9%)	43/69 (62.3%)	0.364	2.917 (0.583-14.603)	
Collagen disease	4/11 (36.4%)	49/71 (69.0%)	0.046	0.159 (0.037-0.693)	
Chronic respiratory disease	4/7 (57.1%)	49/75 (65.3%)	0.694	0.303 (0.047-1.958)	
Liver cirrhosis/chronic hepatic dysfunction	3/6 (50.0%)	50/76 (65.8%)	0.660	1.000 (0.169-5.909)	
Malignant tumor	31/44 (70.5%)	22/38 (57.9%)	0.236	1.299 (0.476-3.541)	
Total parenteral nutrition	10/21 (47.6%)	43/61 (70.5%)	0.059	0.148 (0.039-0.557)	
Hypoalbuminemia (serum albumin <2.5 g/dL)	12/26 (46.2%)	41/56 (73.2%)	0.017	0.265 (0.089-0.794)	
Surgery within 28 days	24/33 (72.7%)	29/49 (59.2%)	0.208	1.092 (0.398-2.993)	
Ventilator use	3/12 (25.0%)	50/70 (71.4%)	0.003	0.104 (0.020-0.553)	
ICU stay	3/10 (30.0%)	50/72 (69.4%)	0.029	0.106 (0.011-1.008)	
APACHE II score > 10	11/27 (40.7%)	42/55 (76.4%)	0.002	0.162 (0.053-0.498)	0.188 (0.057-0.616)
Steroid use	6/14 (42.9%)	47/68 (69.1%)	0.073	0.281 (0.084-0.946)	
Immunosuppressive therapy	0/2 (0.0%)	53/80 (66.3%)	0.122	0.233 (0.020-2.720)	
Anticancer therapy	6/8 (75.0%)	47/74 (63.5%)	0.706	1.000 (0.226-4.420)	
Blood stream infection	20/30 (66.7%)	33/52 (63.5%)	0.770	1.116 (0.360-3.457)	
Respiratory tract infection	9/20 (45.0%)	44/62 (71.0%)	0.035	0.265 (0.089-0.794)	
Intra-abdominal infection	7/11 (63.6%)	46/71 (64.8%)	0.594	1.535 (0.151-15.631)	
Skin & soft tissue infection	12/15 (80.0%)	41/67 (61.2%)	0.168	4.594 (0.946-22.315)	
Osteomyelitis and arthritis	3/8 (37.5%)	50/74 (67.6%)	0.124	0.646 (0.180-2.315)	
Mediastinitis	2/3 (66.7%)	51/79 (64.6%)	0.716	0.477 (0.063-3.626)	
MRSA	34/55 (61.8%)	19/27 (70.4%)	0.447	0.270 (0.055-1.327)	
Loading dose regimen	27/36 (75.0%)	26/46 (56.5%)	0.082	3.373 (1.126-10.100)	4.829 (1.441-16.188)
Vancomycin, MIC <1 µg/mL	8/13 (61.5%)	45/69 (65.2%)	0.516	1.197 (0.279-5.132)	
Vancomycin, MIC 2 µg/mL	5/7 (71.4%)	48/75 (64.0%)	0.522	1.406 (0.255-7.746)	
VCM initial C _{min} ≥10µg/mL	32/49 (65.3%)	21/33 (63.6%)	0.877	1.418 (0.519-3.873)	
VCM initial C _{min} ≥15µg/mL	7/9 (77.8%)	46/73 (63.0%)	0.481	2.095 (0.221-19.904)	

95% CI: 95% confidence interval; APACHE II : Acute physiology and chronic health evaluation II score

Table 5 Variable factors associated with an early clinical response in patients with MRSA infections: univariate and multivariate analyses.

Factors	No of patients with early clinical response (%)		P-value	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	Patients with factor	Patients without factor			
Sex (male)	20/35 (57.1%)	14/20 (70.0%)	0.345	0.571 (0.178-1.836)	
Age (>65 years)	16/27 (59.3%)	18/16 (64.3%)	0.701	0.808 (0.272-2.402)	
Body Mass Index <18.5	11/15 (73.3%)	23/40 (57.5%)	0.282	2.033 (0.551-7.495)	
Body Mass Index ≥25	5/7 (71.4%)	29/48 (60.4%)	0.696	1.638 (0.288-9.322)	
Heart disease	4/5 (80.0%)	30/50 (60.0%)	0.639	2.667 (0.277-25.637)	
Diabetes mellitus	8/10 (80.0%)	26/45 (57.8%)	0.287	2.923 (0.557-15.352)	
Collagen disease	2/9 (22.2%)	32/46 (69.6%)	0.020	0.125 (0.023-0.679)	
Chronic respiratory disease	2/5 (40.0%)	32/50 (64.0%)	0.359	0.375 (0.057-2.458)	
Liver cirrhosis/chronic hepatic dysfunction	2/3 (66.7%)	32/52 (61.5%)	1.000	1.250 (0.106-14.699)	
Malignant tumor	22/31 (71.0%)	12/24 (50.0%)	0.112	2.444 (0.802-7.450)	
Total parenteral nutrition	3/11 (27.3%)	31/44 (70.5%)	0.014	0.157 (0.036-0.688)	
hypoalbuminemia (Alb<2.5 g/dL)	7/17 (41.2%)	27/7 (71.1%)	0.070	0.285 (0.086-0.941)	
Surgery within 28 days	17/26 (65.4%)	17/29 (58.6%)	0.606	1.333 (0.446-3.985)	
Ventilator use	2/9 (22.2%)	32/46 (69.6%)	0.020	0.125 (0.023-0.679)	
ICU stay	1/4 (20.0%)	33/50 (66.0%)	0.064	0.129 (0.013-1.244)	
APACHE II score > 10	6/17 (35.3%)	28/38 (73.7%)	0.007	0.195 (0.057-0.666)	0.025 (0.003-0.221)
Steroid use	4/12 (33.3%)	30/43 (69.8%)	0.041	0.217 (0.055-0.849)	0.079 (0.011-0.578)
Immunosuppressive therapy	0/2 (0.0%)	34/53 (64.2%)	0.141	-	
Anticancer therapy	5/7 (71.4%)	29/48 (60.4%)	0.696	1.638 (0.288-9.322)	
Blood stream infection	7/12 (58.3%)	27/43 (62.8%)	1.000	0.830 (0.225-3.055)	
Respiratory tract infection	9/20 (45.0%)	25/35 (71.4%)	0.052	0.327 (0.104-1.030)	
Intra-abdominal infection	3/4 (75.0%)	31/51 (60.8%)	1.000	1.935 (0.188-19.932)	
Skin & soft tissue infection	12/14 (85.7%)	22/41 (53.7%)	0.033	5.182 (1.028-26.130)	
Osteomyelitis and arthritis	2/7 (28.6%)	32/48 (66.7%)	0.092	0.200 (0.035-1.147)	0.021 (0.002-0.259)
Mediastinitis	1/2 (50.0%)	33/53 (62.3%)	1.000	0.606 (0.036-10.239)	
Loading dose regimen	18/23 (78.3%)	16/32 (50.0%)	0.033	3.600 (1.074-12.062)	10.851 (1.701-69.233)
Vancomycin, MIC <1 µg/mL	7/10 (70.0%)	27/45 (60.0%)	0.725	0.643 (0.147-2.819)	
Vancomycin, MIC 2 µg/mL	0/0 (0.0%)	34/55 (61.8%)	-	-	
VCM initial C _{min} ≥10µg/mL	19/30 (63.3%)	15/25 (60.0%)	0.800	1.152 (0.387-3.431)	
VCM initial C _{min} ≥15µg/mL	3/4 (75.0%)	31/51 (60.8%)	0.504	1.935 (0.188-19.932)	

95% CI: 95% confidence interval; APACHE II : Acute physiology and chronic health evaluation II score