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Sakurai N., Kawaguchi H., Kuwabara G., Imoto W., Shibata W., Yamada K., Nakamura Y., Kakeya H.

Research Article

Body mass index of elderly patients with normal renal function as a determining factor for initial vancomycin regimen designing

Norihiro Sakurai [a, b], Hiroshi Kawaguchi [a, c], Gaku Kuwabara [a], Waki Imoto [a, b], Wataru Shibata [a, b], Koichi Yamada [a, b], Yasutaka Nakamura [d], Hiroshi Kakeya [a, b]

[a] Department of Infection Control Science, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka, Japan

[b] Department of Infection Control, Osaka City University Hospital, 1-5-7 Asahi-machi, Abeno-ku, Osaka, Japan

[c] Department of Quality and Safety Management, Osaka City University Hospital, 1-5-7 Asahi-machi, Abeno-ku, Osaka, Japan

[d] Department of Pharmacy, Osaka City University Hospital, 1-5-7 Asahi-machi, Abeno-ku, Osaka, Japan

Short Title: Impact of BMI in VCM initial regimen design

Corresponding Author:

Hiroshi Kakeya, MD, PhD

Department of Infection Control Science, Osaka City University

1-4-3 Asahi-machi, Abeno-ku, Osaka, 545-8585 (Japan)

E-mail: kakeya@med.osaka-cu.ac.jp

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Abstract

Introduction: Currently, the use of actual body weight is recommended for dosing in vancomycin regimen designs and it is important to perform therapeutic drug monitoring for efficacy and safety. However, the method to determine the appropriate vancomycin regimen for underweight or obese patients remains controversial. The aim of this study was to evaluate the impact of body mass index (BMI) on the relationship among vancomycin doses, trough concentration, and area under the curve (AUC). In addition, we identified the group of patients who were potentially more affected by BMI and evaluated the optimal dosing regimen to achieve the target AUC.

Methods: We retrospectively collected data from 462 patients who received vancomycin at the Osaka City University Hospital between January 2013 and September 2019. Patients were classified by their BMI group (underweight < 18.5, normal weight 18.5–25.0, and obese ≥ 25.0 kg/m^2). We assessed the association between vancomycin dose versus trough concentration or AUC as well as dose-adjusted trough concentration and AUC in each BMI subgroup to determine the doses for achieving the target AUC.

Results: The dose-adjusted trough concentration and AUC in elderly patients with normal renal function appeared to increase significantly with an increase in BMI ($P < 0.05$). Vancomycin doses that enabled the achievement of AUC_{400} in elderly patients with normal renal function decreased with increasing BMI: 17.7, 15.8, and 12.9 mg/kg per time in the underweight, normal weight, and obesity groups, respectively ($P < 0.05$).

Conclusion: Elderly patients with normal renal function were the most affected by BMI on vancomycin trough concentration and AUC. The vancomycin regimen design in these patients should be adjusted carefully, not only based on the patient's renal function but also based on BMI.

Introduction

Vancomycin, a glycopeptide antibiotic, exerts its action by inhibiting the synthesis of the bacterial cell wall. Vancomycin is widely used as a first-line antibiotic in the treatment of severe infections such as pneumonia, sepsis, infectious endocarditis, skin and soft tissue infection, and meningitis, caused by antimicrobial-resistant gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Streptococcus pneumoniae (PRSP), and methicillin-resistant coagulase-negative staphylococci (MRCNS) [1– 4].

Due to its narrow therapeutic range, it is important to conduct therapeutic drug monitoring (TDM) for vancomycin, a renally excreted agent, to ensure both efficacy and safety [5]. The current American TDM guidelines recommend the administration of vancomycin at 15 to 20 mg/kg (based on actual body weight) every 8 to 12 h as an intermittent infusion for most patients with normal renal function [6]. In addition, the current guidelines in Japan have configured the dose per body weight for each estimated glomerular filtration rate (eGFR) as an index of renal function and recommend twice-daily administration for patients with normal renal function [7]. However, since the recommended doses in these guidelines are related to the actual body weight, the effects of body mass index (BMI) are not considered. Therefore, in patients whose weight is outside the normal range (underweight and obese patients), it is difficult to predict the vancomycin serum concentration even if the recommended dose of vancomycin is administered due to variations in the volume of distribution and in the clearance of the drug [8]. In fact, in clinical practice, we often experience cases where the vancomycin trough concentrations are outside the target range that cause concern regarding reduced efficacy and increased adverse effects such as acute kidney injury. Therefore, it might be necessary to consider the impact of BMI in establishing an optimal vancomycin dosing regimen.

Furthermore, in vancomycin TDM, trough concentration has been recommended as a surrogate marker for the area under the curve over 24 h to minimum inhibitory concentration (AUC/MIC) [9]. The target trough concentration of 10–20 μg/mL is advocated to improve efficacy, prevent the development of vancomycin-resistant bacteria, and reduce the risk of nephrotoxicity in Japan [10]. However, recent reports have demonstrated that AUC-guided TDM, which targets an AUC/MIC ratio of 400 to 600 mg·h/L (assuming an MIC of 1 mg/L), is superior to trough concentration-guided TDM in achieving clinical efficacy and ensuring patient safety [11, 12]. Although several studies have been conducted on the optimal vancomycin administration regimen for obese patients [13, 14] or patients with different physical types using the trough concentration-guided TDM [15], little information is available on using the AUC-guided TDM [16].

The purpose of this study was to retrospectively examine the impact of BMI on the relationship among vancomycin doses, trough concentration, and AUC. In addition, we investigated the group of patients who were potentially more affected by BMI on a vancomycin regimen and examined the optimal dosing regimen for achieving the target AUC.

Materials and Methods

Study design

We conducted a single-center, retrospective, observational study of patients who were intravenously administered vancomycin twice a day at the Osaka City University Hospital between January 2013 and September 2019. This study was carried out in compliance with the ethical guidelines on clinical research and was approved by the ethics review committee of the Osaka City University Hospital (Ethics Committee approval number: 2019-042). We included data from patients who received vancomycin and achieved an initial trough concentration at steady-state (≥ 3 days after initial administration). The exclusion criteria were as follows: 1) patients with eGFR < 60 mL/min/1.73 m^2 or patients receiving renal replacement therapy, 2) unstable renal function (serum creatinine of ≥ 0.3 mg/dL or a 1.5-fold increase from baseline following vancomycin administration), 3) age < 18 years, 4) patients receiving vancomycin doses once or three times a day (to exclude the effect of different dosing frequency), and 5) dose change prior to measurement of the initial trough concentration.

Data collection and definitions

All data, such as patient characteristics, laboratory data, and vancomycin administration information, were retrospectively obtained from electronic medical records. Patient characteristics included gender, age (year), height (m), weight (kg). Laboratory data included vancomycin serum concentration and serum creatinine (Cr). Vancomycin administration information included the single doses of vancomycin (adjusted by the patient's weight) and the day of TDM. AUC was estimated by Bayesian analysis, using the steady-state trough concentration. Calculations were performed using the vancomycin-TDM software (Shionogi and Co., Osaka, Japan). BMI and eGFR were calculated using the following formulae:

BMI (kg/m^2) = weight / $(height)^2$

eGFR (mL/min/1.73 m^2) = 194 × Cr $(mg/dL)^{-1.094}$ × $age^{-0.287}$ (if female: × 0.739)

Association between vancomycin dose versus trough concentration or AUC and determination of optimal dosing to achieve target AUC in BMI subgroups

According to the Japan Society for the Study of Obesity, patients were classified according to three BMI groups: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), and obese (BMI ≥ 25.0 kg/m^2). We assessed the initial vancomycin trough concentrations (μg/mL), AUC (μg·h/mL), dose (mg/kg per time), dose-adjusted trough concentration, and dose-adjusted AUC in each BMI subgroup. The dose-adjusted trough concentration and AUC were surveyed to evaluate the rate of increase per 1 mg/kg dose and were calculated by dividing the trough concentration and AUC by the dose per body weight [15]. The primary outcome of this study was to compare the median vancomycin dose within each of the vancomycin trough concentrations and AUC values to clarify the effects of BMI on vancomycin regimen design. For the secondary outcome, we investigated the group of patients who were potentially more affected by BMI on a vancomycin regimen. Additionally, we evaluated the optimal dosing regimen to achieve the target AUC of 400 μg·h/mL. To determine this, we corrected the actual doses using the following formulae:

Target vancomycin dose (mg/kg per time) = actual vancomycin dose (mg/kg per time) × 400 / Bayesian estimated individual AUC (μg·h/mL)

Statistical analysis

To compare the patient characteristics and vancomycin administration information in the three BMI groups, statistical analysis was performed using Statcel, a useful add-in for Excel 4.0 (OMS, Tokyo).

The Kruskal-Wallis test was used for data with unequal variances or non-parametric data. When there were statistically significant differences between the three groups, the Steel-Dwass test was used as a multiple comparison test. Categorical variables were evaluated using the Chi-square (χ^2) test of independence. Differences were considered statistically significant when P-value was < 0.05.

Results

Patient characteristics

Patient characteristics, laboratory data, and vancomycin administration data are shown in Table 1. Among the 462 patients included in the study, 97 patients were classified as underweight, 277 as normal weight, and 88 as obese. There were statistically significant differences in age, weight, BMI, Cr, eGFR, and vancomycin dose among the three BMI subgroups. There was no significant difference

in initial trough concentration or AUC between the BMI groups. However, the initial trough concentrations of many patients in Japan did not reach the effective range, and it might be necessary to revise the overall initial dosing regimen.

Impact of BMI on the vancomycin doses to achieve each trough concentration and AUC category

Table 2 presents the vancomycin doses classified according to the vancomycin trough concentration and AUC. There were statistically significant differences in the vancomycin dose required to achieve the target trough concentrations of 10.0–19.9 μg/mL and AUC of 400–600 μg·h/mL among the BMI subgroups. Specifically, the dose required to reach the target trough and AUC range appeared to be inversely related to the BMI, and the required dose in the obesity subgroup was lower than the recommended dose. Vancomycin trough concentrations classified according to the AUC values did not exhibit statistically significant differences among the BMI subgroups, as shown in Figure 1.

Dose-adjusted vancomycin trough concentration and AUC

Since there were significant differences in age and renal function among the BMI subgroups of the eligible patients, to exclude the influence of these background factors, we investigated dose-adjusted vancomycin trough concentrations and AUC according to renal function (normal renal function: eGFR ≥ 90.0 and mild renal dysfunction: eGFR 60.0–89.9 mL/min/1.73 m^2) and age (elderly patient group: age < 65; non-elderly patient group: age ≥ 65). There was no significant difference in eGFR among the BMI subgroups in the normal renal function group and the mild renal dysfunction group. The dose-adjusted vancomycin trough concentration [underweight: 0.601, normal: 0.665 and obesity: 0.896 (μg/mL)/(mg/kg per time)] and AUC [underweight: 22.7, normal: 25.4 and obesity: 31.0 (μg·h/mL)/(mg/kg per time)] in elderly patients with normal renal function appeared to increase significantly with an increase in the BMI (Table 3).

Target vancomycin dose to achieve AUC of 400 μg·h/mL

We calculated the target vancomycin dose to achieve AUC_{400} based on AUC estimated from the actual dose and the trough value (Table 4). Significant differences were present only in the elderly patient group with normal renal function, indicating that AUC_{400} can be achieved with lower doses in individuals with a higher BMI (underweight: 17.7, normal: 15.8, and obesity: 12.9 mg/kg per time).

Discussion

The main objective of this study was to examine the impact of BMI on trough concentration and AUC to design the optimal vancomycin regimen design for BMI subgroups. In recent years, AUC-guided TDM (target AUC ranges: 400–600 μg·h/mL) has been recommended over the traditional trough-guided TDM (target trough ranges: 10–20 μg/mL) [11, 12]. Therefore, vancomycin trough concentration and AUC estimated from the trough concentration was considered in this study.

We found that the vancomycin dose that was required to achieve the target trough concentration and AUC was significantly lower in patients with high BMI than in those with low BMI ($P < 0.05$). Morrill et al. compared the effects of empiric vancomycin dosing regimens on the attainment of optimal target trough concentrations in obese patients (BMI between 30 and 40 kg/m^2) and in extremely obese patients (BMI > 40 kg/m^2) [13]. They reported that in obese patients, the standard daily dose of approximately 30 mg/kg was appropriate for the attainment of the target trough concentration; however, in extremely obese patients, a lower daily dose of 20–25 mg/kg was sufficient. Richardson et al. also showed that the average daily dose of vancomycin in obese patients did not differ significantly from that in non-obese patients (23.9 mg/kg vs 26.0 mg/kg, $P = 0.18$); however, mean vancomycin trough concentrations in obese patients were significantly higher than those in non-obese patients (16.5 mg/L vs 12.1 mg/L, $P = 0.004$) [14]. Thus, previous studies have shown that obese patients require lower doses to achieve the same trough concentration compared to patients with a normal weight. Furthermore, our results agree with those of previous studies that included not only obese patients but also underweight patients (BMI < 18.5 kg/m^2), which found that mean vancomycin doses required to achieve the target trough levels decreased when the BMI increased (underweight, 19.8 mg/kg; normal weight, 16.5 mg/kg; obese: 13.7 mg/kg; $P < 0.01$) [15]. In addition, the vancomycin doses that resulted in the attainment of the target AUC range, newly investigated in this study, were similar to the doses determined using the trough concentration.

However, the previous reports did not consider the effects of renal function and age in detail [13–15]. In addition, renal function and age were significantly different among the BMI subgroups for all subjects in this study. Therefore, the patients were divided into two groups according to renal function (normal renal function: eGFR ≥ 90.0; mild renal dysfunction: eGFR 60.0–89.9 mL/min/1.73 m^2) and two groups according to age (elderly patient group: age ≥ 65; non-elderly patient group: age < 65) to rule out the effects of these factors. Then, the dose-adjusted vancomycin trough concentration and AUC were calculated to demonstrate the effect of BMI clearly. Since this index represents the rate of increase in trough concentrations and AUC per 1 mg/kg dose, it is believed that the effect of BMI can be evaluated [15]. In this study, elderly patients with normal renal function

were the most affected by BMI; dose-adjusted trough concentration and AUC were shown to increase significantly with increasing BMI. Therefore, the target doses for attaining AUC_{400} were lower for elderly patients with high BMI and normal renal function (underweight, 17.7 mg/kg; normal weight, 15.8 mg/kg; obese, 12.9 mg/kg; $P < 0.05$).

Various physiological functions, such as renal function, liver function, and cardiac output, generally decrease with age, resulting in reduced clearance and increased serum concentration of certain drugs. In addition, the serum concentration of water-soluble drugs such as vancomycin tends to increase in the elderly because the water content in the body and the volume of distribution of drugs are generally lower in the elderly than in young people [17]. Indeed, according to previous studies, the volume of distribution (Vd) was associated with BMI, and drug clearance (CL) exhibited a positive correlation with renal function [18, 19]. In a study that evaluated the effect of BMI on the volume of distribution of vancomycin, Hong et al. [20] reported that the mean volume of distribution per weight was significantly higher ($P < 0.0001$) in patients with a BMI of 30–39.9 kg/m^2 (0.736 L/kg) than in those with BMI > 40 kg/m^2 (0.481 L/kg). An earlier study by Bauer et al. [21] indicated that the Vd was higher in the normal weight group (0.68 L/kg) than in the morbidly obese group (0.32 L/kg). Hence, we speculate that BMI may impact vancomycin concentration by affecting the Vd, and decreased renal function due to aging primarily influenced vancomycin concentration by affecting the CL. Therefore, it is possible that the dose-adjusted vancomycin trough concentration and AUC increased with increasing BMI in the elderly patient group with normal renal function because of the effects of these pharmacokinetic parameter changes. However, one reason for the low effect of BMI in elderly patients with mild renal dysfunction might be that the decrease in vancomycin clearance due to decreased renal function was more dominant than the effect of BMI, or the number of subjects in this group was small; further investigation is required to test these hypotheses in the future.

Some limitations of this study need to be considered. First, this was a single-center retrospective study. Second, the doses examined and the conclusions drawn from this study apply only to twice a day dosing. Third, we performed blood sampling only for trough concentrations. Blood sampling for both peak and trough concentrations should be performed for more accurate AUC evaluations in underweight and obese patients. Fourth, the clinical effects and adverse events associated with vancomycin in this study have not been confirmed; therefore, the need for dose-adjustment for underweight or obese patients was not considered.

Conclusion

Our results suggest that elderly patients with normal renal function were the most affected by BMI on vancomycin trough concentration and AUC. For this reason, the vancomycin regimen design in these patients may need to be adjusted carefully, not only based on the patient's renal function but also based on BMI. In the future, prospective controlled trials should be conducted to gain more insight.

Statements

Acknowledgement

This study was awarded the 68th Award in the Category of Clinical Research conferred by the Director of the West Japan Branch of the Japanese Society of Chemotherapy.

Statement of Ethics

This retrospective chart review study involving human participants was carried out in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study received the approval of the ethics review committee of the Osaka City University Hospital (Ethics Committee approval number: 2019-042). As it is a retrospective study, patient consent was not required according to the ethics review committee of the Osaka City University Hospital. Patient information was anonymized and de-identified prior to analysis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by N.S. The first draft of the manuscript was written by N.S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. Vancomycin trough concentration classified according to AUC values.

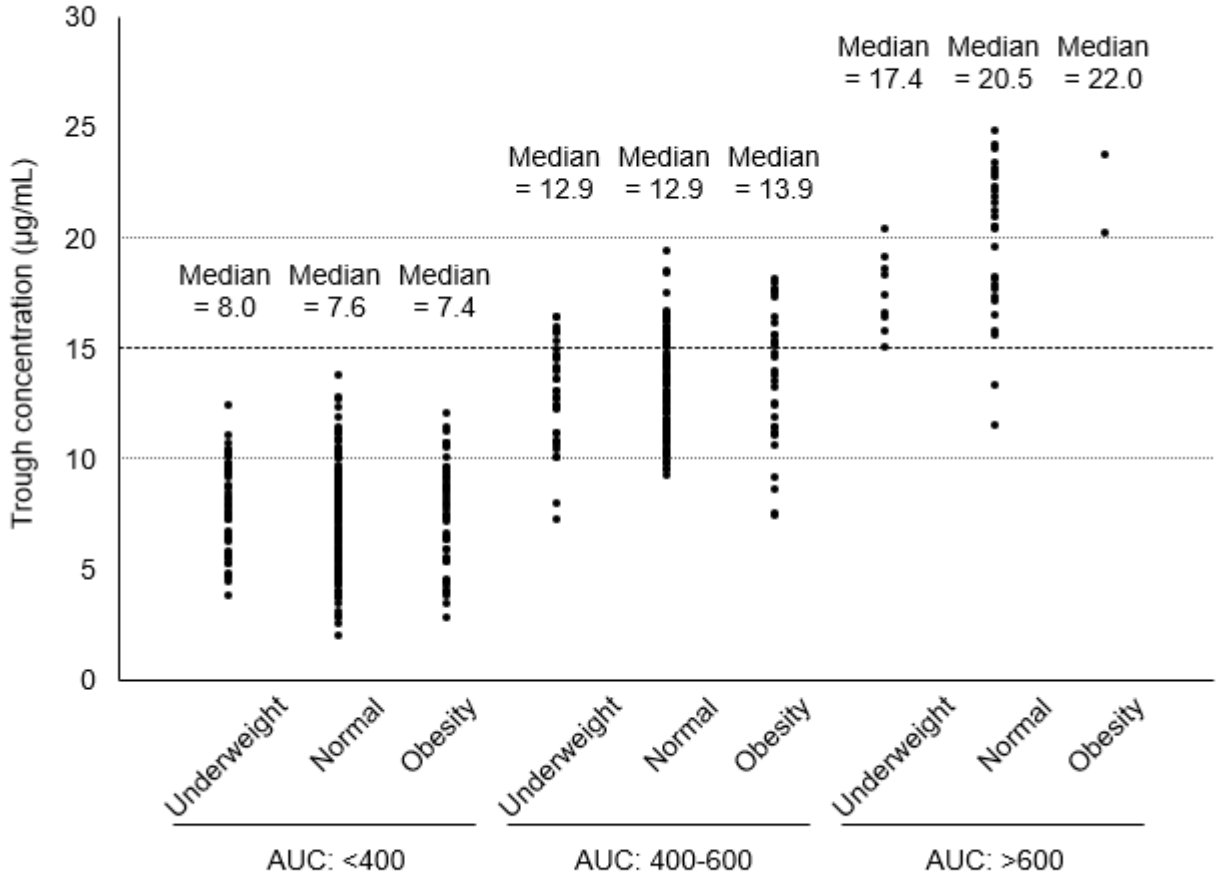

Table 1. Patient characteristics

	Underweight [n = 97]	Normal [n = 277]	Obesity [n = 88]	P-value	Steel-Dwass test
Male / Female	63 / 34	178 / 99	64 / 24	0.333	-
Age (year)	66 [21-87]	61 [19-89]	57 [18-85]	<0.05	a, b
Height (m)	1.64 [1.45-1.90]	1.64 [1.30-1.83]	1.64 [1.26-1.85]	0.924	-
Weight (kg)	44.0 [25.4-59.5]	57.6 [38.5-78.2]	75.0 [44.2-127.8]	<0.05	a, b, c
Body mass index (kg/m^2)	16.7 [12.1-18.4]	21.4 [18.6-24.9]	27.0 [25.0-48.5]	<0.05	a, b, c
Cr (mg/dL)	0.59 [0.35-0.96]	0.63 [0.37-1.01]	0.68 [0.42-1.11]	<0.05	b, c
eGFR ($mL/min/1.73\ m^2$)	97.9 [60.4-129.7]	92.4 [60.0-129.1]	86.8 [60.2-127.2]	<0.05	b
Vancomycin dose (mg/kg per time)	14.9 [7.6-27.1]	15.4 [7.3-24.7]	13.3 [5.3-20.5]	<0.05	b, c
Trough concentration (μg/mL)	10.1 [3.8-20.4]	10.1 [2.0-24.8]	9.1 [2.8-23.7]	0.480	-
The number of patients in trough concentration categories					
<10.0, n	45 [46.4%]	130 [46.9%]	49 [55.7%]		
10.0-14.9, n	37 [38.1%]	98 [35.4%]	24 [27.3%]		
15.0-19.9, n	14 [14.4%]	33 [11.9%]	13 [14.8%]		
≥20.0, n	1 [1.0%]	16 [5.8%]	2 [2.3%]		
AUC (μg·h/mL)	380.3 [193.1-853.1]	388.2 [125.3-865.1]	372.0 [148.9-780.4]	0.470	-
The number of patients in AUC categories					
<400, n	54 [55.7%]	152 [54.9%]	54 [61.4%]		
400-600, n	34 [35.1%]	97 [35.0%]	32 [36.4%]		
>600, n	9 [9.3%]	28 [10.1%]	2 [2.3%]		
Day of TDM (day)	3 [3-7]	3 [3-7]	3 [3-6]	0.732	-

Data are presented as the number of patients [percentage] or the median [range].

Statistical analysis was performed using the Kruskal-Wallis test, and a multiple comparison test was performed using the Steel-Dwass test for determining significance.

$P < 0.05$: a, underweight vs normal; b, underweight vs obesity; c, normal vs obesity.

Abbreviations: eGFR, estimated glomerular filtration rate; AUC, area under the curve; TDM, therapeutic drug monitoring.

Table 2. Vancomycin doses classified according to vancomycin trough concentrations and AUC values

Trough level (μg/mL)	Vancomycin dose (mg/kg per time)			P-value	Steel–Dwass test	AUC (μg·h/mL)	Vancomycin dose (mg/kg per time)			P-value	Steel–Dwass test
	Underweight	Normal	Obesity				Underweight	Normal	Obesity		
<10.0	13.4 [7.6-24.4]	14.5 [7.3-21.7]	12.9 [5.3-18.3]	<0.05	c	<400	12.8 [7.6-24.1]	14.4 [7.3-21.7]	12.7 [5.3-18.3]	<0.05	c
10.0-19.9	17.3 [10.1-27.1]	16.5 [8.7-24.4]	13.8 [5.9-20.5]	<0.05	b, c	400-600	18.4 [10.1-24.4]	16.8 [8.7-24.4]	14.2 [9.2-20.5]	<0.05	b, c
≥20.0	23.5 [23.5-23.5]	18.6 [15.1-24.7]	16.3 [14.8-17.8]	0.165	-	>600	21.5 [14.9-27.1]	18.3 [13.3-24.7]	16.3 [14.8-17.8]	0.076	-

Data are presented as the median [range].

Statistical analysis was performed using the Kruskal-Wallis test, and a multiple comparison test was performed using the Steel-Dwass test for determining significance.

$P < 0.05$: a, underweight vs normal; b, underweight vs obesity; c, normal vs obesity.

Table 3. Vancomycin dose-adjusted trough concentration and AUC classified according to renal function and age

A. eGFR≥90.0 mL/min/1.73m^2 group

	Age < 65			P-value	Steel–Dwass test	Age ≥ 65			P-value	Steel–Dwass test
	Underweight [n = 31]	Normal [n = 106]	Obesity [n = 28]			Underweight [n = 34]	Normal [n = 47]	Obesity [n = 10]		
eGFR (mL/min/1.73m^2)	112.4 [90.5-129.7]	106.4 [90.1-129.1]	109.9 [91.8-127.2]	0.614	-	102.1 [90.0-129.5]	100.8 [90.3-128.4]	100.2 [90.3-120.7]	0.480	-
Trough concentration/Vancomycin dose (μg/mL)/(mg/kg per time)	0.541 [0.285-0.940]	0.489 [0.178-1.346]	0.534 [0.280-1.330]	0.429	-	0.601 [0.326-1.227]	0.665 [0.331-1.538]	0.896 [0.624-1.252]	<0.05	b, c
AUC/Vancomycin dose (μg·h/mL)/(mg/kg per time)	20.4 [13.7-31.3]	21.0 [12.3-47.5]	23.1 [16.6-41.2]	0.072	-	22.7 [14.7-44.3]	25.4 [15.7-45.6]	31.0 [25.0-38.7]	<0.05	a, b, c

B. eGFR: 60.0-89.9 mL/min/1.73m^2 group

	Age < 65			P-value	Steel–Dwass test	Age ≥ 65			P-value	Steel–Dwass test
	Underweight [n = 12]	Normal [n = 55]	Obesity [n = 24]			Underweight [n = 20]	Normal [n = 69]	Obesity [n = 26]		
eGFR (mL/min/1.73m2)	80.7 [61.8-86.5]	78.9 [60.8-89.6]	78.9 [60.9-89.7]	0.699	-	76.4 [60.4-89.3]	76.8 [60.0-90.0]	79.2 [60.2-88.1]	0.634	-
Trough concentration/Vancomycin dose (μg/mL)/(mg/kg per time)	0.804 [0.383-1.297]	0.689 [0.350-1.481]	0.730 [0.241-1.440]	0.478	-	0.857 [0.414-1.457]	0.852 [0.259-1.499]	0.866 [0.435-2.040]	0.573	-
AUC/Vancomycin dose (μg·h/mL)/(mg/kg per time)	30.1 [17.9-50.1]	26.7 [18.6-47.7]	29.7 [19.4-55.2]	0.480	-	31.4 [20.5-47.5]	32.1 [18.5-52.2]	32.8 [22.9-62.6]	0.530	-

Data are presented as the median [range].

Statistical analysis was performed using the Kruskal–Wallis test, and multiple comparison test was performed using the Steel–Dwass test for determining significance.

P < 0.05: a, underweight vs normal; b, underweight vs obesity; c, normal vs obesity.

Table 4. Target vancomycin dose (mg/kg per time) to achieve AUC_{400} classified according to renal function and age

eGFR category (mL/min/1.73 m^2)	Underweight	Normal	Obesity	P-Value	Steel-Dwass test	Underweight	Normal	Obesity	P-Value	Steel-Dwass test
	age < 65					age≥65				
≥90.0	19.6 [12.8-29.3]	19.1 [8.4-32.6]	17.3 [9.7-24.1]	0.072	-	17.7 [9.0-27.2]	15.8 [8.8-25.4]	12.9 [10.3-16.0]	< 0.05	a, b, c
60.0-89.9	13.3 [8.0-22.4]	15.0 [8.4-21.5]	13.5 [7.2-20.7]	0.480	-	12.7 [8.4-19.5]	12.5 [7.7-21.6]	12.2 [6.4-17.5]	0.530	-

Data are presented as the median [range].

Statistical analysis was performed using the Kruskal-Wallis test, and multiple comparison test was performed using the Steel-Dwass test for determining significance.

$P < 0.05$: a, underweight vs normal; b, underweight vs obesity; c, normal vs obesity.