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ORIGINAL PAPER

Initial dosing regimen of vancomycin to achieve early therapeutic plasma concentration in critically ill patients with MRSA infection based on APACHE II score

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Abstract It is essential to assure the efficacy of antimicrobials at the initial phase of therapy. However, increasing the volume of distribution (Vd) of hydrophilic antimicrobials in critically ill patients leads to reduced antimicrobial concentration in plasma and tissue, which may adversely affect the efficacy of that therapy. The aim of the present study was to establish a theoretical methodology for setting an appropriate level for initial vancomycin therapy in individual patients based on Acute Physiology and Chronic Health Evaluation (APACHE) II score. We obtained data from patients who received intravenous vancomycin for a suspected or definitively diagnosed Gram-positive bacterial infection within 72 h after admission to the intensive care unit. The Vd and elimination half-life ($t_{1/2}$) of vancomycin values were calculated using the Bayesian method, and we investigated the relationship between them and APACHE II score. There were significant correlations between APACHE II scores and Vd/actual body weight (ABW), as well as $t_{1/2}$ ($r = 0.58$, $p < 0.05$ and $r = 0.74$, $p < 0.01$, respectively). Our results suggested that the Vd and $t_{1/2}$ of vancomycin could be estimated using the following regression equations using APACHE II score.

$$\text{Vd/ABW} = 0.018 \times \text{APACHE II score} + 0.63$$

$$t_{1/2} = 0.70 \times \text{APACHE II score} + 4.58$$

We found that APACHE II score was a useful index for predicting the Vd and $t_{1/2}$ of vancomycin, and used that to establish an initial vancomycin dosing regimen comprised of initial dose and administration interval for individual patients.

Keywords Vancomycin therapy · Initial dose · Dosage interval · APACHE II score · Volume of distribution

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1 Introduction

When treating critically ill patients, it is important that the efficacy of administered drugs is obtained as rapidly as possible. Notably, approximately 50 % of intensive care unit (ICU) patients have been shown to be affected by catheter-associated bloodstream, ventilator-associated pneumonia, and surgical site infections as well as others, with subsequent increased mortality (Vincent et al. 2009). Therefore, it is essential for antimicrobials given at the initial phase of therapy to be efficacious. However, pathophysiologic changes such as capillary leakage, hypoalbuminemia, and pleural effusion, as well as other factors can occur in critically ill patients, leading to changes in the

pharmacokinetics of administered antimicrobials. Previous reports have shown that the volume of distribution (Vd) of hydrophilic antimicrobials tended to increase (Roberts and Lipman 2006; Petrosillo et al. 2010; Varghese et al. 2011), while antimicrobial concentrations in plasma and tissue did not reach an effective level in critically ill patients with an infection (Joukhadar et al. 2001; Taccone et al. 2010a, b). Moreover, the starting doses for water-soluble antimicrobials have been found to be insufficient, which adversely affects the prognosis of these patients (Kollef et al. 1999; Ibrahim et al. 2000; Kumar et al. 2006). Therefore, it is important that an appropriate initial dose for antimicrobial therapy be set for critically ill patients suffering from infection.

Vancomycin hydrochloride, classified as a glycopeptide and water-soluble antibiotic, is recommended as first-line therapy for a methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The only established criterion for setting the initial dose in critically ill patients is based on actual body weight (ABW) (Liu et al. 2011). However, it is thought that the Vd of vancomycin varies among individuals because of body fluid retention and other conditions. We considered that a more appropriate initial dose could be established by estimating the Vd of vancomycin for individual patients.

In the present study, we utilized the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system (Knaus et al. 1985), a classification method used to determine disease severity in the ICU for prediction of Vd. APACHE II scores are determined from physiological variables including body temperature, blood pressure, heart rate, respiratory rate, and white blood cell count, as well as information about previous health status and other data obtained at admission such as age, organ dysfunction, and immunodeficiency. We speculated that the obtained score reflects body fluid retention induced by systemic inflammatory response syndrome (SIRS) and organ dysfunction, and attempted to predict Vd and the elimination half-life ($t_{1/2}$) of vancomycin using APACHE II scores.

In this study, we attempted to establish a theoretical methodology by which the initial dose and administration interval of vancomycin could be established based on APACHE II score for providing an adequate antimicrobial effect from the first administration.

2 Materials and methods

2.1 Patient data

This study was conducted in a retrospective manner. We obtained data from patients admitted to the ICU of Saiseikai Yokohamashi Tobu Hospital from April 2010 to September 2012. All received vancomycin hydrochloride intravenously for 1–2 h, within 72 h after admission to the ICU. The blood sampling for measuring plasma concentration was performed at least once within 1–2 h after the end of the first intravenous infusion. Moreover, the blood samples were taken more than twice between the first and second administration of the drug (Rodvold et al. 1988; Patel et al. 2011; Matsumoto et al. 2013). Exclusion criteria were under the age of 20 years, severe renal impairment with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, and receiving hemodialysis.

2.2 Calculation of APACHE II score

The APACHE II severity of disease classification system is shown in Table 1 in detail. The APACHE II score was consisted of three domains (the Acute Physiology Score, the Age Score and the Chronic Health Score) (Knaus et al. 1985). The score ranged from 0 to 71 and high score was considered to indicate higher risk of death. The Acute Physiology Score point was calculated from 12 routine physiological measurements within the first 24 h after admission to the ICU. The Age Score point was determined by age. The Chronic Health Score point was determined by the previous health status such as a history of severe organ system insufficiency. In the present study, all scores were calculated retrospectively based on data in the patient records.

2.3 Calculation of Vd and $t_{1/2}$ of vancomycin

The pharmacokinetic parameters Vd and $t_{1/2}$ for vancomycin were calculated using the Bayesian method with the VCM-TDM E_edition Ver. 3.00 software package (Shionogi & Co., Ltd. Japan). Patient data (age, gender, ABW, and Scr or creatinine clearance), vancomycin dosing history (administration time and date, dosage, and drip time), and vancomycin concentration history (sampling time and date, and plasma concentration of vancomycin) were extracted from medical records for this calculation. Then, the vancomycin dosing history, and concentration history between the first and second administration were acquired to establish a methodology for setting the initial dosage of vancomycin hydrochloride. Furthermore, the ratio between Vd and ABW was represented as Vd/ABW. The plasma concentration of vancomycin was measured using a particle-enhanced turbidimetric inhibition immunoassay (Dimension Xpand-Plus HM, Siemens Healthcare Diagnostics, Inc., Tokyo, Japan) in the hospital laboratory. Then, the pharmacists provided an optimal individual vancomycin dosage regimen based on the data of each patient to the physicians.

Table 1 The APACHE II severity of disease classification system (Knaus et al. 1985)

Acute Physiology Score points (sum of the 12 individual variable points)										
Physiologic variable		High abnormal range				Low abnormal range				
		+4	+3	+2	+1	+0	+1	+2	+3	+4
1	Rectal temperature (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
2	Mean arterial pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
3	Heart rate (ventricular response)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
4	Respiratory rate (non-ventilated or ventilated)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
5	Oxygenation: A-aDO_2 or PaO_2	≥500	350–499	200–349		<200				
	(a) $FiO_2 \geq 0.5$ record A-aDO_2									
	(b) $FiO_2 < 0.5$ record only A-aDO_2					PO_2 >70	PO_2 61–70		PO_2 55–60	PO_2 <55
6	Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
7	Serum sodium (mMol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
8	Serum potassium (mMol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
9	Serum creatinine (mg/100 mL) (double point score for acute renal failure)	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
10	Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
11	White blood count (total/mm^3) (in 1,000 s)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
12	Glasgow coma score (GCS)									
	Score = 15 minus actual GCS									
	Serum HCO_3 (venous mMol/L) [not preferred, use if no ABGs]	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15
Age Score points		+0	+2		+3		+5		+6	
Age (years)		≤44	45–54		55–64		65–74		≥75	
Chronic Health Score points										
+2 points: for elective postoperative patient with a history of severe organ system insufficiency or immunocompromised[a]										
+5 points: for nonoperative patient or emergency postoperative patient with a history of severe organ system insufficiency or immunocompromised[a]										
APACHE II score = Acute Physiology Score points + Age Score points + Chronic Health Score points										

[a] A history of severe organ system insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

Liver Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

Cardiovascular New York Heart Association Class IV

Respiratory Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (≥40 mmHg), or respiratory dependency

Renal Receiving chronic dialysis

Immunocompromised The patient has received therapy that suppresses resistance to infection, e.g., immune-suppression, chemotherapy, radiation, long-term or recent high-dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS

2.4 Relationship between initial dose and peak plasma concentration (C_{peak}) of vancomycin

Presently, the initial dose of vancomycin for critically ill patients with an MRSA infection is calculated based only on ABW (Liu et al. 2011). To examine the adequacy of that method, we investigated the relationship between the initial dose and C_{peak} value of vancomycin at 2 h after the end of the first intravenous infusion in patients in whom C_{peak} value was measured.

2.5 Relationship of APACHE II score with Vd and $t_{1/2}$ of vancomycin

We calculated the relationship of APACHE II score with Vd and $t_{1/2}$ of vancomycin for each patient. Based on those

results, we examined the best prediction method for estimating the Vd and $t_{1/2}$ of vancomycin based on APACHE II score.

2.6 Relationship between predicted and observed plasma concentration of vancomycin

The prediction method used for estimating the Vd and $t_{1/2}$ of vancomycin based on APACHE II score as noted above was validated. Those values were calculated using a regression equation for data from each patient, and then the plasma concentration of vancomycin at t hours after the end of intravenous infusion of vancomycin hydrochloride was predicted using the values. The predicted value (C_t), plasma concentration at 0 h after the end of the infusion (C_0), and elimination rate constant (k_e) were obtained using the following formulas.

$$C_t = C_0 \times e^{-k_e \times t},\ C_0 = \text{Dose/Vd}$$

$$k_e = 0.693/t_{1/2}$$

Finally, we investigated the relationship between predicted and observed plasma concentration.

2.7 Ethical approval

The present study protocol was approved by the institutional review board of Saiseikai Yokohamashi Tobu Hospital. Patients were notified of this retrospective study with posters displayed in the hospital.

3 Results

3.1 Patients

Twenty-eight patients received intravenous vancomycin within 72 h of admittance to the ICU, of whom 13 were excluded based on the exclusion criteria. Consequently, 15 patients were enrolled (12 males, 3 females; 71 ± 8 years old; ABW 64 ± 12 kg) and their data are shown in Table 2. For all patients, Scr was 1.1 ± 0.4 mg/dL and eGFR was 53.0 ± 22.3 mL/min/1.73 m^2, while the timing of the first administration of vancomycin after admission to the ICU was 29.3 ± 19.0 h.

3.2 Relationship between initial dose and C_{peak} of vancomycin

The relationship between the initial dose of vancomycin based on ABW and C_{peak} value is shown in Fig. 1. C_{peak} was measured in 14 of the 15 patients. The initial doses and values for C_{peak} were 26.1 ± 1.8 mg/kg (range 23.1–29.2 mg/kg) and 24.4 ± 3.7 mg/L (range 17.1–29.9 mg/L), respectively. There was no correlation between initial vancomycin dose based on ABW and C_{peak} value.

3.3 Relationship of APACHE II score with Vd and $t_{1/2}$ of vancomycin

The APACHE II scores, and values for Vd/ABW and $t_{1/2}$ were 22 ± 6 pts, 1.03 ± 0.20 L/kg, and 20.1 ± 6.1 h, respectively (Table 3). The relationship between APACHE II score and Vd/ABW is shown in Fig. 2, while that between APACHE II score and $t_{1/2}$ is shown in Fig. 3. There was a significant correlation between APACHE II score and Vd/ABW ($r = 0.58$, $p < 0.05$), and between APACHE II score and $t_{1/2}$ ($r = 0.74$, $p < 0.01$). Furthermore, the Vd and $t_{1/2}$ of vancomycin could be estimated using the regression Eqs. (1) and (2), respectively.

$$\text{Vd/ABW} = 0.018 \times \text{APACHE II score} + 0.63 \quad (1)$$

$$t_{1/2} = 0.70 \times \text{APACHE II score} + 4.58 \quad (2)$$

3.4 Relationship between predicted and observed plasma concentration of vancomycin

The relationship between predicted and observed plasma concentration of vancomycin at t hours after the end of infusion is shown in Fig. 4, with a significant correlation found ($r = 0.71$, $p < 0.01$). Consequently, we concluded that our results established a theoretical methodology for setting both appropriate initial dosage and dosage interval for vancomycin therapy based on APACHE II score (Fig. 5).

4 Discussion

It is essential to establish the effects of antimicrobial drugs from the time of initial therapy in critically ill patients with an infection. However, since the degree of body fluid retention such as edema, pleural effusion, and peritoneal effusion vary greatly in those patients, the Vd of hydrophilic antimicrobials also varies, making it difficult to set an appropriate initial dose. In the present study, we attempted to establish a theoretical methodology to establish an initial dosage and dosage interval to provide an adequate antimicrobial effect with the initial administration of vancomycin hydrochloride, a water-soluble antibiotic.

There was no correlation between initial dose based on ABW and the C_{peak} value of vancomycin, indicating that it is difficult to set the initial dosage in individual patients

Table 2 Patient characteristics

Characteristic	*n* (Total 15)
Underlying disease	
Sepsis	9
Pneumonia	5
Cholecystitis	1
Gender male:female	12:3
Age (years)	71 ± 8[a]
ABW (kg)	64 ± 12[a]
WBC ($\times 10^3/\mu L$)	13.3 ± 9.6[a]
CRP (mg/dL)	17.5 ± 10.3[a]
Alb (g/dL)	1.9 ± 0.3[a]
Scr (mg/dL)	1.1 ± 0.4[a]
eGFR (mL/min/1.73 m^2)	53.0 ± 22.3[a]
Timing of first administration of vancomycin after admission to ICU (h)	29.3 ± 19.0[a]

ABW actual body weight, *WBC* white blood cell count, *CRP* serum level of C-reactive protein, *Alb* serum albumin, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *ICU* intensive care unit

[a] Mean ± SD

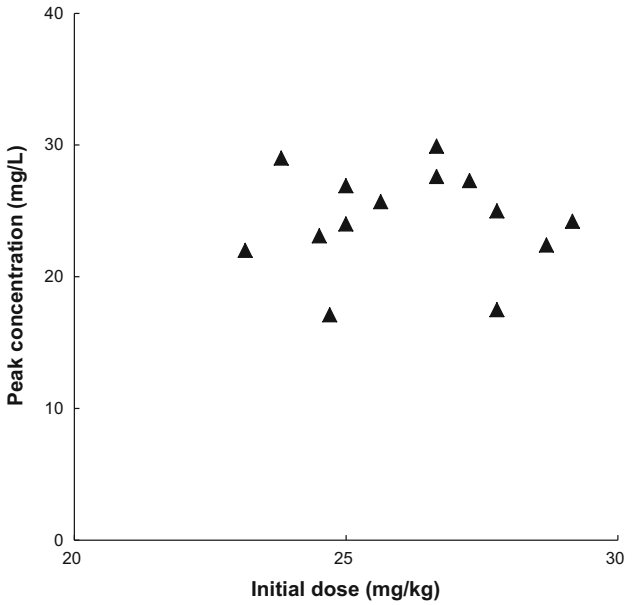

Fig. 1 Relationship between initial dose and peak plasma concentration of vancomycin

based on ABW, because the Vd of vancomycin varies greatly. Therefore, we considered that it is necessary to predict Vd and $t_{1/2}$ prior to administration for establishing an appropriate therapeutic strategy.

In the present study, we focused on the APACHE II scoring system (Knaus et al. 1985), a system for disease severity classification of patients in the ICU, and investigated the relationships of APACHE II score with Vd/ABW and $t_{1/2}$ of vancomycin, which showed significant correlations ($r = 0.58$, $p < 0.05$ and $r = 0.74$, $p < 0.01$, respectively). Furthermore, our results showed that the Vd and $t_{1/2}$ of vancomycin can be predicted prior to administration using the following regression Eqs. (1) and (2). However, there were few adult patients (<65 years) in the present study. When the APACHE II score is 0 in a patient at the age of 44 or younger with low severity, the estimated values of Vd/ABW and $t_{1/2}$ using those equations indicate 0.63 L/kg and 4.58 h, respectively. These values were within 0.39–0.92 L/kg and 2.9–9.1 h which

Table 3 APACHE II scores, volume of distribution, and elimination half-life of vancomycin in the present patients

Patient no.	APACHE II score (pt)	Vd/ABW (L/kg)	$t_{1/2}$ (h)
1	16	0.81	17.3
2	31	1.58	22.8
3	22	0.95	27.8
4	23	0.82	13.2
5	15	1.05	18.3
6	30	1.15	31.2
7	15	0.91	15.8
8	27	1.10	25.6
9	19	0.90	12.5
10	17	1.17	11.0
11	29	1.17	25.0
12	33	1.18	26.8
13	20	0.76	17.6
14	12	1.00	14.4
15	22	0.88	22.4
Mean ± SD	22 ± 6	1.03 ± 0.20	20.1 ± 6.1

APACHE II Acute Physiology and Chronic Health Evaluation II, *Vd* volume of distribution, *ABW* actual body weight, $t_{1/2}$ elimination half-life

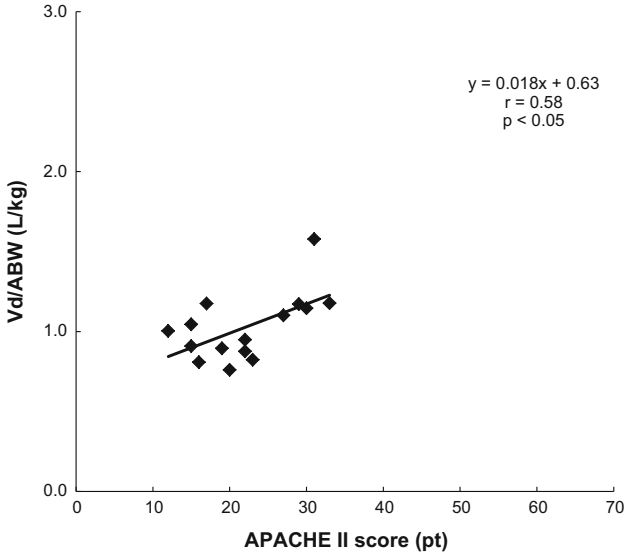

Fig. 2 Relationship between APACHE II score and Vd/ABW. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *Vd* volume of distribution, *ABW* actual body weight

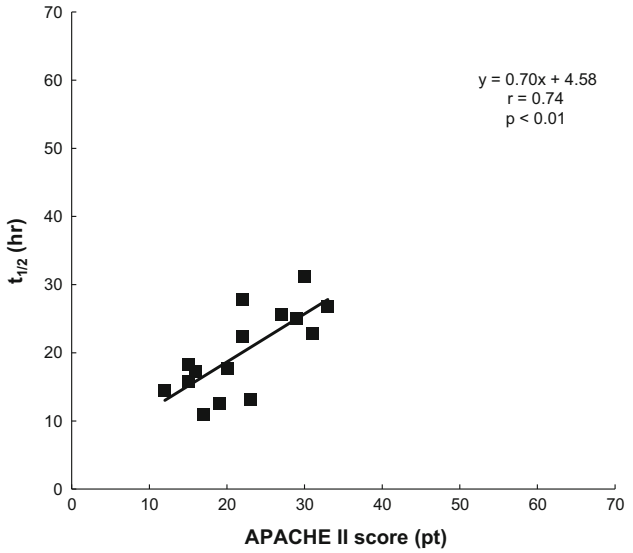

Fig. 3 Relationship between APACHE II score and $t_{1/2}$. *APACHE II* Acute Physiology and Chronic Health Evaluation II, $t_{1/2}$ elimination half-life

were reported in healthy subjects, respectively (Matzke et al. 1986). Consequently, we concluded that this methodology was effective and suitable for all ages except children.

In critically ill patients with an infection, the variable factors related to the Vd of hydrophilic antimicrobials are capillary leakage due to SIRS caused by inflammatory cytokines and body fluid retention due to organ dysfunction such as heart, hepatic, or renal failure (Roberts and Lipman

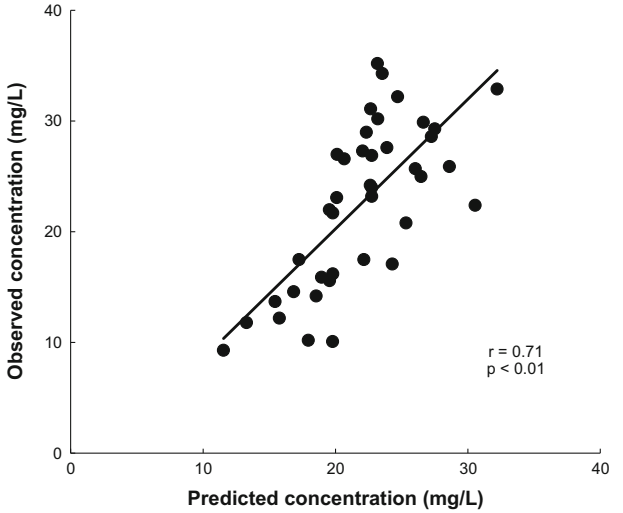

Fig. 4 Relationship between predicted and observed plasma concentrations of vancomycin

2006; Petrosillo et al. 2010; Varghese et al. 2011). APACHE II scores are calculated from the Acute Physiology Score including values for body temperature, heart rate, respiratory rate, and white blood cell count, which are required for diagnosis of SIRS (Bone et al. 1992), as well as the Age Score and the Chronic Health Score including information about organ dysfunction. Therefore, APACHE II score may reflect the degree of capillary leakage, body fluid retention, and total body clearance of drugs due to various clinical conditions. We found significant correlations between APACHE II score and the Vd and $t_{1/2}$ of vancomycin. As for related factors, patients with higher APACHE II scores had higher blood levels of inflammatory cytokines such as tumor necrosis factor and interleukin-6 (Damas et al. 1997), which cause an increase in capillary permeability and fluid shift from the intravascular compartment to interstitial space (Lee and Slutsky 2010), resulting in leakage of vancomycin. Moreover, patients with higher APACHE II scores have a potential for decreased glomerular filtration rate due to renal impairment, thus increasing body fluid retention from edema and vascular permeability. Therefore, we concluded that an increase in Vd and prolongation of $t_{1/2}$ easily occur following vancomycin administration.

Pathophysiologic changes due to various clinical conditions lead to alterations in the Vd of hydrophilic antimicrobials in critically ill patients, making it difficult to set an appropriate initial dose. In the present study, we found that the Vd and $t_{1/2}$ of vancomycin could be estimated based on APACHE II score, and established a theoretical methodology for vancomycin therapy regarding initial dose and administration interval in individual patients (Fig. 5).

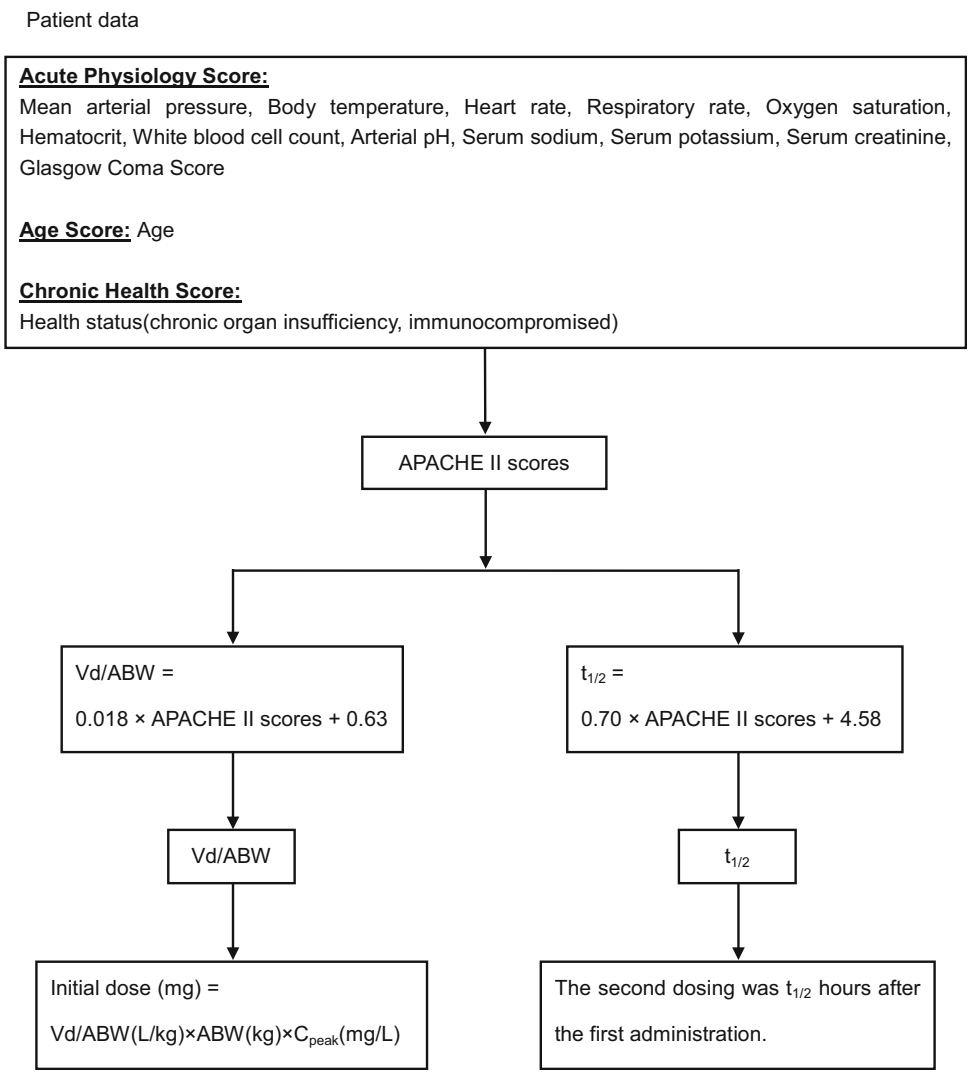

Fig. 5 Predicted method for initial vancomycin dosing regimen. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *Vd* volume of distribution, *ABW* actual body weight, $t_{1/2}$ elimination half-life, C_{peak} peak plasma concentration of vancomycin

In the future, to confirm whether this methodology is suitable, the study should be performed at all ages.

Conflict of interest None of the authors has any conflict of interest to disclosure.

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