EVALUATION OF VANCOMYCIN PHARMACOKINETIC PARAMETERS AMONG CRITICALLY ILL PATIENTS: A SYSTEMATIC REVIEW

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Abstract: *Background:* The use of vancomycin in critically ill patients is always challenging due to the pathophysiological changes among this vulnerable group that may alter the pharmacokinetic and pharmacodynamic of vancomycin. *Objectives:* This study was designed to identify the patient's factors or covariates that might influence the development of vancomycin population pharmacokinetic models and to determine the appropriate dosing regimen for critically ill patients. *Methods:* A literature search was conducted independently between 2 reviewers from PubMed and Ovid databases from its inception until November 2020. The data was extracted by one reviewer and was checked by another reviewer. Quality assessment was evaluated by using ROBINS-I assessment tool while Cronbach's alpha was used for reliability between the 2 reviewers. *Results and discussion:* A total of 7 studies were included with 1 study identified by checking the references of included papers. All studies showed a significant reduction of objective function value (OFV) with $P < 0.05$ when body weight (BW) and creatinine clearance (CrCl) were included in calculating volume of distribution (Vd) and clearance (Cl) of vancomycin respectively in the final model. Loading and maintenance doses were recommended according to the CrCl, BW, age and CSF-albumin of the patients. *Conclusions:* The specific pharmacokinetic parameter of this population should be identified to allow more precise individualisation of vancomycin dosing for better efficacy and safety in the ICU setting. Therefore, therapeutic drug monitoring (TDM) vancomycin should be performed to ensure better patient outcomes as well as to avoid vancomycin-induced nephrotoxicity and ototoxicity.

Keywords: vancomycin; pharmacokinetic models; critically ill patients; dosing regimen

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INTRODUCTION

Vancomycin is categorised as a glycopeptide antibiotic which has been used for more than 65 years. Vancomycin remains as one of the first-line antibiotics for methicillin-resistant coagulase-negative and coagulase-positive staphylococcal infections as well as some serious gram-positive infections in patients who are allergic to penicillin or cephalosporins despite many glycopeptide antibiotics have been developed [1]. In recent years, vancomycin has been widely used in clinical settings due to the increasing prevalence of infections caused by gram-positive bacteria especially methicillin-resistant *staphylococcus aureus* (MRSA) and methicillin-resistant *staphylococcus epidermidis* (MRSE). Unfortunately,

vancomycin possesses resistance towards vancomycin-resistant strains of *staphylococcus aureus* such as glycopeptide-intermediate *staphylococcus aureus* (GISA), vancomycin-intermediate *staphylococcus aureus* (VISA), and vancomycin-resistant enterococci (VRE) infections. Vancomycin exerts its effect by bactericidal killing. It interrupts the proper synthesis of the bacterial cell wall structure called peptidoglycan that coats most bacterial membranes to maintain their shape, integrity and prevent them from swelling and bursting due to high intracellular osmolarity.

Vancomycin has very poor absorption upon oral administration (F<5%) and low volume of distribution (Vd) ranging from 0.4 to 1.0 L/kg. It has also a moderate binding to protein (≤50%) and a half-life of 4-6 hours in normal adults. Vancomycin is primarily eliminated via renal route by glomerular filtration, with > 80-90% remained unchanged in urine within 24 hours after the administration of a single dose. Vancomycin has both time-dependent and concentration-dependent killing which relies upon the maximization of the duration of the drug exposure above the MIC of the pathogen. Many studies have suggested that AUC_{24}/MIC is an important therapeutic target for S. aureus infections. In clinical settings, the use of the measured MIC from an infected patient should first be monitored to identify the individualised AUC_{24}/MIC target for dose adjustment and a target ranging from 400 mg·h/L to 600 mg·h/L is needed in order to optimize the efficacy of vancomycin [2,3]. However, several infusion-related toxicities need to be considered and monitored such as nephrotoxicity,

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ototoxicity, Red-Man syndrome and thrombophlebitis which are usually related to high peak and trough concentration of vancomycin.

Sepsis, head injury and community-acquired pneumonia were the three most common diagnoses leading to ICU admission in 2017 which have contributed to a total number of 38,196 compared to 37,759 in the year 2016 and 39,595 in the year 2015 [4]. Severe sepsis and septic shock is the major illness of hospital admissions to ICU and is leading to 35-65% of in-hospital mortality rates [5]. Critically ill patients are always susceptible to the life-threatening infections. As such, the optimal antimicrobial dosage regimen is required as early as possible. However, the conventional dosing regimens frequently fail to achieve or maintain the therapeutic exposures in this population. During the critical conditions, it is difficult to maintain the optimal environment between the route of administration and the pharmacokinetics of the drugs which differ significantly from the normal population. These abnormalities, in addition to the alterations in absorption, distribution, metabolism, and elimination may lead to suboptimal drug exposure at the site of action.

MRSA infection is also the cause leading to ICU admission with mortality rates from 15% to 60% due to bacteremia, 30% to 37% due to endocarditis and 80% to 90% due to pneumonia [6]. Appropriate use of vancomycin has been constantly reviewed in order to reduce the risk of resistance to this antibiotic. Vancomycin is used appropriately in 30% to 50% of the cases after the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines were implemented in tertiary care hospitals [7]. The use of vancomycin among critically ill patients is often challenging as this particular population who are vulnerable to toxicity often requires a higher dose of vancomycin. The target levels of vancomycin might be difficult to achieve because of the increased Vd and the presence of augmented renal clearance (ARC) [8]. ARC refers to a phenomenon demonstrated by certain critically ill patients where an enhanced elimination of a medication is found where a patient's CrCL exceeds 130 ml/min [9]. ARC appears to be quite common in this population that can lead to very low concentrations of some renally cleared drugs such as vancomycin. Vancomycin also distributed incompletely and has high variability in critically ill patients with severe sepsis [10]. Therefore, therapeutic drug monitoring (TDM) is very important to ensure ICU patients' safety and drug efficacy.

In conclusion, evaluation of pharmacokinetic parameters of vancomycin is important in order to improve the efficacy of the drug as well as minimising the antibiotic resistance developed in this population. This review aimed to identify different covariates or patients' factors affecting vancomycin pharmacokinetic parameters as well as to review the dosing regimen based on the final pharmacokinetic model among critically ill patients.

MATERIALS AND METHODS

2.1. Eligibility Criteria and Study Selection

Types of Studies: Prospective, cohort & matched-cohort and retrospective, cohort studies studying the administration of IV vancomycin and pharmacokinetic parameters among critically ill patients in hospitals were included in this review.

Types of Participants: All participants receiving vancomycin were aged more than 18 years old admitted to ICU and not requiring renal replacement therapy (RRT). Patients who were pregnant, had acute or chronic renal failure and/or abnormal hepatic function were excluded. The CL and Vd were the primary outcome measures.

Types of Intervention: Non-linear mixed-effects modelling (NONMEM) approach was used by all studies to perform pharmacokinetic analysis of vancomycin. Patient related factors such as age and body weight, as well as vancomycin related factors such as dosage, types of model and total blood samples were extracted.

Types of Outcome Measures: The CL and Vd were the primary outcome measures. The objective function value (OFV) was also used to evaluate the statistical significance of covariates. A difference of 3.84, 6.63 and 10.83 points in the OFV between the base and final models in one parameter was considered significant at the 5%, 1% and 0.1% levels, respectively. Interindividual (IIV) and residual variabilities (RV) were also modelled using exponential, proportional and additive error. The model validation from various studies were also measured to assess the performance of the final population model. Finally, the dosing recommendation for loading dose (LD) and maintenance dose (MD) from each study were reviewed based on the final population pharmacokinetics model.

Study Selection: PubMed and Ovid MEDLINE were the databases used. The eligibility assessment of the included studies was performed independently in an unblinded standardised manner by 2 reviewers from inception until November 2020. The full texts were retrieved according to the inclusion criteria. Any disagreement was resolved by discussion between the two review authors.

2.2. Data Extraction and Quality Assessment

Information about name of author, year of publication, study design, participant demographics, vancomycin dosage, models, total samples, pharmacokinetic parameters, IIV & RV and dosing regimens for LD and MD were extracted. One review author extracted the data from identified studies using a standardised data extraction form. The second author checked the extracted data. Disagreements were resolved by discussion between the two review authors.

The risk of bias for each included study was independently assessed by pairs of the reviewers using Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) assessment tool developed by (Hinneburg, 2017) [11]. All the answers from each reviewer were analysed using Cronbach Alpha to check the internal consistency or the reliability between the 2 reviewers.

RESULTS

Study Selection

A total of 7 studies involving 5 trials were identified for inclusion in the review. The search of Ovid MEDLINE and PubMed databases provided a total of 513 citations. Following removal of 22 duplicates from the search strategy, a total of 491 articles were screened for inclusion. Of these, 104 were discarded because the full texts of the studies were not

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available. The full texts of the remaining 387 citations were reviewed in more details. Among these, 380 studies did not meet the criteria for various reasons (animal studies, impaired renal disease, irrelevance, neonates/children/geriatric studies, no pharmacokinetics analysis and not using NONMEM approach). Seven articles met the inclusion criteria that were

previously agreed and were included in the systematic review. One additional article was identified by checking the references of included papers and searching for study that has cited this paper. The complete selection process of studies included is shown in Figure 1.
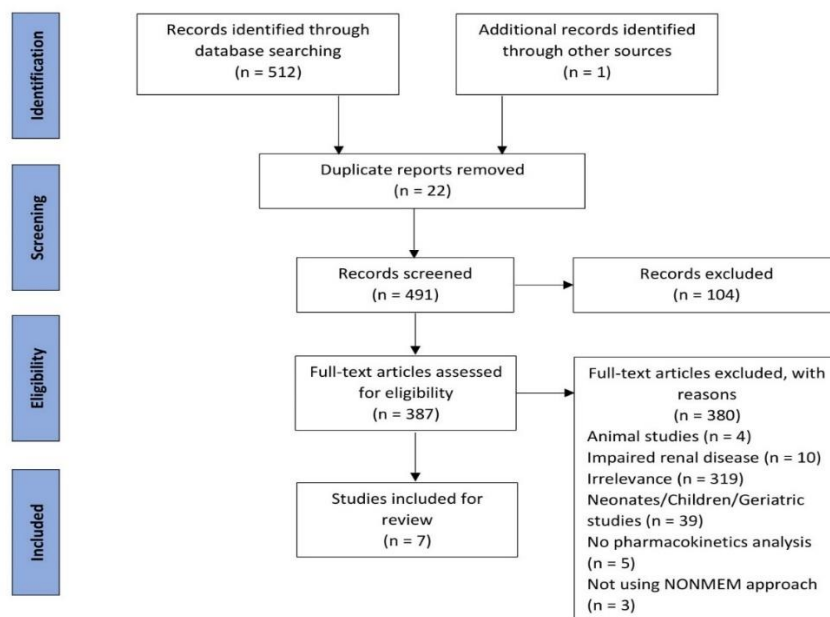

Figure 1. PRISMA flow diagram showing the selection process and criteria of the included studies

Study Characteristics

All 7 studies finally selected for the review contains 3 prospective studies with 2 cohort studies and another 4 studies were retrospective studies with 2 cohort studies. All studies were published in English. The blood samples were collected at least 1 hour after the completion of drug infusion and immediately or up to 30 minutes before the next dose in most of the studies whereas serial blood samples were drawn in 2 studies at the scheduled times. The total blood sample was not provided in Wu et al. (2016) [18] although request email has been sent. Four of the studies were using fluorescence polarization immunoassay to measure the vancomycin plasma

concentration. Two studies were using Cobas analyser, and one study using HPLC method to measure serum vancomycin concentration.

3.2.1. Patient Population

The included studies involved 782 critically ill patients with 649 as internal validation and 133 as external validation. The studies from Roberts et al. (2011) [16] & Kovacevic et al. (2020) [12] did not perform external validation. The main inclusion criteria entailed adults (18 years and older), not requiring renal replacement therapy, normal hepatic function, and non-pregnancy. The age and body weight of the included studies are tabulated (Table 1).

Table 1. Characteristics of the studies included

Author, year	Study design	Population				Vancomycin Dosage	Models	Total Blood Samples	
		n		Age (years)	Body Weight (kg)			In	Ex
		In	Ex						
Kovacevic et al. (2020) [12]	Prospective	73	-	56.9 ± 17.0	78.2 ± 14.2	LD: 2000 mg/d (16 pts) LD: 1000 mg/d (57 pts) MD: 1000 mg/12h	One-Compartment	146	-
Revilla et al. (2010) [13]	Retrospective, cohort	191	46	61.1 ± 16.3	73.0 ± 13.3	1000 mg/12h (42%) 1000 mg/24h (20%)	One-Compartment	569	73
(Medellín-Garibay et al., 2016) [14]	Retrospective, cohort	118	40	74.3 ± 14.0	72.0 ± 15.0	1000 mg/12h (74.6%) 500 mg/12h (19.5%) 25.3 ± 7.8 mg/kg/d	Two-Compartment	392	119

(Li et al., 2016) [15]	Prospective, cohort	20	16	45.25 ± 15.96	68.90 ± 12.07	Low dose LD: 500 mg/d MD: 2000 mg/24h High dose LD: 1000 mg/d MD: 3000 mg/24h	Three-Compartment	389	284
(Roberts et al., 2011) [16]	Retrospective	206	-	58.1 ± 14.8	74.8 ± 15.8	TBW <70 kg LD: 750 mg/d MD: 2000 mg/24h TBW >70 kg LD: 1000 mg/d MD: 3000 mg/24h	One-Compartment	582	-
Llopis-Salvia & Jiménez-Torres, (2006) [17]	Retrospective, cohort	30	20	60 (18-81)	60.61 (40-130)	18.51 mg/kg/d	Two-Compartment	234	103
(Wu et al., 2016) [18]	Prospective, matched cohort	11	11	47.18 (16.85)	66.57 (17.53)	LD: 15-25 mg/kg MD: PK dosing method	One-Compartment	Not reported	
n, study population; In, internal validation; Ex, external validation; LD, loading dose; MD, maintenance dose; TBW, total body weight.									

Interventions

The majority of the studies were conducted in Europe (Spain, Belgium, Bosnia & Herzegovina) whereas 2 of the studies were conducted in Asia (China & Taiwan). Vancomycin doses was administered as either continuous or intermittent infusions in the included studies. Different dosing regimens are tabulated in Table 1.

Outcomes: A one-compartmental model with zero-order output and first-order elimination was used as a base model in 4 studies, two-compartmental model in 2 studies and three-compartmental model in 1 study to develop the final vancomycin pharmacokinetic model. These models were further assessed with the inclusion of the covariates. All studies showed a significant reduction of OFV ($P < 0.05$) when BW and CrCl were included in Vd and Cl of vancomycin respectively in the base model. In Li et al. (2016) [15], CSF albumin was also significantly influenced the intercompartmental clearance (Q). The inclusion of these covariates had also reduced the IIV and RV in the development of the final model as shown in Table 2. However, the IIV of Vd in Kovacevic et al. (2020) [12] was not provided. Five studies have performed external validation to evaluate the predictive performance of the final population model whereas 2 studies evaluated their final model internally. Lastly, the different LD and MD developed based on their final population models provided by 5 studies have also been tabulated in Table 3. The covariates used in determining the dosing regimens were TBW, CrCL, age, CSF-albumin, and concomitant use of drug (frusemide).

Results of Individual Studies

Table 2. Pharmacokinetic parameters described in individual studies.

Author, year	Study design	CL (L/h)			Vd (L)			IIV (%)		RV (%)
		Formula	Parameter	Value	Formula	Parameter	Value	CL	Vd	
Kovacevic et al. (2020) [12]	Prospective	θ_{CLCrCl} x CrCL + θ_{CLRES}	θ_{CLCrCl} θ_{CLRES}	0.024 1.93	θ_V x TBW	θ_V	0.511	56.6		34.5
Revilla et al. (2010) [13]	Retrospective, cohort	θ_1 x CL_{CR} + $AGE^{\theta 2}$	θ_1 θ_2	0.67 -0.24	θ_3 x θ_4^A	θ_3 θ_4^A	0.82 2.49	30.1	22.8	35.0
(Medellín-Garibay et al., 2016) [14]	Retrospective, cohort	θ_1 x CL_{CR} θ_2 x CL_{CR} (if furosemide)	θ_1 θ_2	0.49 0.35	θ_3 x TBW (>65 yrs) θ_4 x TBW (≤65 yrs)	θ_3 θ_4	1.07 0.74	37.0	40.0	19.2
(Li et al., 2016) [15]	Prospective, cohort	θ_{CSF} + $\theta_{CSF-albumin}$ x (CSF albumin - 279)	θ_{CSF} $\theta_{CSF-albumin}$	0.0049 0.000021	θ_c + θ_{TBW} x (TBW - 69)	θ_c θ_{TBW}	27.84 0.96	28.63	21.58	0.55
(Roberts et al., 2011) [16]	Retrospective	θ_1 x CrCL/100	θ_1	4.58	θ_2 x TBW	θ_2	1.53	38.9	37.4	19.9
Llopis-Salvia & Jiménez-Torres, (2006) [17]	Retrospective, cohort	θ_1 x CL_{CR} + θ_2 x TBW	θ_1 θ_2	0.034 0.015	θ_3 x TBW	θ_3	0.414	29.2	36.4	18.5

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(Wu et al., 2016) [18]	Prospective, matched-cohort	θ_1 x CL_{CR}	θ_1	0.0145	θ_2 (Age/47.9)$^{\theta_3}$ x	θ_2 θ_3	0.83 0.44	38.3	21.2	16.3
CL, clearance of vancomycin; Vd, volume of distribution of vancomycin; IIV, interindividual variability; RV, residual variability; θ, typical value; CLCrCl, creatinine clearance-dependent fraction of CL; CLRES, non-creatinine clearance-dependent fraction of CL; CL_{CR}, creatinine clearance; A, dichotomous covariate for serum creatinine, A = 0 if SrCr ≤ 1 mg/dL and A = 1 if SrCr > 1 mg/dL; C, central volume.										

Table 3. Dosing recommendation from 5 included studies.

Author, year	Covariate or patient's factor that are used to determine the dosing regimen	Dosing Regimens	
		LD	**MD**
Revilla et al. (2010) [13]	Age & CrCL	-	For patients ≤65 years CrCL <60 ml/min: 2,000 mg/24h CrCL >120 ml/min: 4,000 mg/24h <u>For patients >65 years</u> CrCL <60 ml/min: 1,750 mg/24h CrCL >120 ml/min: 3,000 mg/24h
Medellín-Garibay et al. (2016) [14]	CrCL & Frusemide	-	<u>Without Frusemide</u> CrCL <55 ml/min: 500 mg/12h CrCL >130 ml/min: 1,500 mg/12h <u>With Frusemide</u> CrCL <55 ml/min: 1,000 mg/24h CrCL >130 ml/min: 1,000 mg/12h
Li et al. (2016) [15]	TBW & CSF-albumin	<u>TBW ≤60 kg</u> CSF-albumin 100-200 mg/dL: 1,000 mg CSF-albumin 200-500 mg/dL: 500 mg <u>TBW ≥80 kg</u> CSF-albumin 100-400 mg/dL: 1,000 mg CSF-albumin 400-500 mg/dL: 500 mg	<u>CSF-albumin</u> 100-200 mg/dL: 12,000 mg/24h 200-300 mg/dL: 7,000 mg/24h 300-400 mg/dL: 5,000 mg/24h 400-500 mg/dL: 4,000 mg/24h
Roberts et al. (2011) [16]	TBW & CrCL	35 mg/kg infused over 180 mins	CrCL ≥100 ml/min: 35-40 mg/kg CrCL ≥50 ml/min: 25 mg/kg CrCL ≥40 ml/min: 14 mg/kg CrCL ≥30 ml/min: 10 mg/kg
Wu et al. (2016) [18]	TBW & CrCL	-	<u>For CrCL 80 ml/min</u> 500 mg/6h 750 mg/8h 1,000 mg/12h *MD = 0.684 x CrCL – 6.408*

Quality Assessment

All the 7 included studies were shown to have moderate risk of bias when assessed using ROBINS-I assessment tool as shown in Table 4. Confounding and missing data were the 2 major biases present in 4 of the studies. The rest were due to selection bias, deviations from intended interventions and selective reporting. A total of 56 answers were analysed and the value for Cronbach's Alpha for the 7 studies was α = .836 indicating that the result had good internal consistency (Table 5).

Table 4. Quality of the included studies

Author, year	Domain of bias in ROBINS-I assessment tool							Overall risk of bias
	A	**B**	**C**	**D**	**E**	**F**	**G**	
Kovacevic et al. (2020) [12]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Revilla et al. (2010) [13]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
(Medellín-Garibay et al., 2016) [14]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
(Li et al., 2016) [15]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
(Roberts et al., 2011) [16]	Low	Low	Low	Moderate	Low	Low	Low	Moderate

Llopis-Salvia & Jiménez-Torres, (2006) [17]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
(Wu et al., 2016) [18]	Low	Low	Low	Low	Moderate	Low	Low	Moderate

A = Bias due to confounding; B = Bias in selection of participants into the study; C = Bias in classification of interventions; D = Bias due to deviations from intended interventions; E = Bias due to missing data; F = Bias in measurement of outcomes; G = Bias in selection of the reported result

Table 5. Reliability statistics

Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items	N of Items
.836	.810	56

DISCUSSION

Identifying the different covariates or patient's factors that can influence the population pharmacokinetic parameters is very important in determining and optimising vancomycin dosing regimen and practices in critically ill patients. Many factors such as age, body weight, height, gender, comorbidities, renal, and hepatic functions are believed to influence the pharmacokinetic parameters of vancomycin in this population. In this review, all the included studies have successfully determined the important covariates affecting the development of final vancomycin pharmacokinetic models using the NONMEM software. The patient's covariates, including TBW, age & CrCl have demonstrated significant reduction of OFV when they were added in the basic population model of all the studies. This was done by using the method of "stepwise inclusion and backward elimination method". A basic model was first selected, and each factor was then added individually into the basic pharmacokinetic model. A significant reduction of OFV was obtained when individual covariate was included into the model. This is called a stepwise inclusion. The backward elimination was performed by removing each covariate independently from the model. This approach will ensure the most meaningful covariates that has resulted in statistical significance in the development of final population model. Overall, the inclusion of TBW and CrCL into the pharmacokinetic model has demonstrated for a significant reduction of OFV in Vd and CL, respectively.

A study of vancomycin pharmacokinetics in postoperative neurosurgical patients [15] has shown that CSF compartment was also one of the covariates that affect the clearance of central compartment. They found that the vancomycin pharmacokinetics in CSF were not similar to those in the peripheral tissues. A "combined 2-compartment/effect compartmental model" was labelled in which the effect compartment is referred to the CSF compartment. This was similar to the parameters obtained from the 3-compartment model which was closer to the drug movement in their patients, therefore, they finally selected the 3-compartment model as their base population model. In addition, Medellín-Garibay et al. (2016) [14] has demonstrated that the concomitant use of a loop diuretic, frusemide reduced the clearance of vancomycin by 30%. The use of frusemide with vancomycin may enhance nephrotoxicity in elderly patients due to its diuretic effects. Therefore, frusemide has to be used cautiously in critically ill elderly patient receiving vancomycin treatment.

The addition of TBW and CrCL in the basic model has reduced the IIV and RV in the CL and Vd of the final model respectively. All studies have shown a 10% to 50% reduction when these factors were included. The lower the values of IIV and RV, the better the models fit the population. These ranges were not considered high among ICU patients due to their broad inter- and intra-patient variability. These values were usually reported higher in this population compared to those who were not critically ill. In the study of Kovacevic et al. (2020) [12], IIV of CL were higher as compared to other studies. This might be due to the CrCL estimated using the Cockcroft-Gault equation in which a lower serum creatinine (SrCr) was used. Wu et al. (2016) [17] mentioned that a SrCr of <0.8 mg/dL would lead to an unrealiable vancomycin CL as those levels, when they were inserted into Cockcroft-Gault equation, would overestimate the patient's renal function and that CrCL did not correlate with vancomycin CL. Hence, the impact of this covariate results in higher IIV value than the others.

An external validation is usually more reliable, precise and robust as compared to an internal validation in evaluating the predictive performance of the final vancomycin pharmacokinectic model as well as developing the dosing regimens appropriately. Both of the validations were using the similar patient characteristics such as age, TBW, CrCL, and others but with different sets of study population. The external validation was demonstrated in comparing the observed values and predicted values of the vancomycin concentrations. The predicted value is obtained from the NONMEM software by keying in all the relevant parameters such as population variability (IIV & RV) and patient's factors. The values were then be plotted in a 'goodness-of-fit' scatter plot of the predicted concentrations against the observed concentrations. A linear regression line was then drawn in the scatter plot showing the relationship between these values. The plots from all the studies have shown that the predicted concentrations fit the observed concentration well, suggesting the final population pharmacokinetic model describes the measured vancomycin concentration adequately.

AUC_{24}/MIC ratio of ≥ 400 is a guaranteed approach for C_{min} to maintain between 15-20 mg/L to optimise the clinical efficacy of vancomycin in the ICU population for a pathogen with a MIC of 1 mg/L. However, not all the 5 included studies were using this approach in determining the dosing regimens. For instance, Revilla et al. (2010) [13] did not use the MIC value because it is unknown in their usual clinical practice and cannot be assumed. Nevertheless, their suggested dosing regimens were reliable because of their large study population.

Among the 5 studies with dosing recommendations, only 2 of them have suggested the use of LD based on the TBW in achieving the vancomycin concentration of > 20 mg/L rapidly in the treatment of ICU patients. The infustion time of LD suggested in Li et al. (2016) [15] was 1 hour versus 3 hours in

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Roberts et al. (2011) [16]. This may be due to the different study population used where postoperative neurosurgical patients and treatment for ICU-acquired MRSA infection are studied in Li et al. (2016) [15] and Roberts et al. (2011) [16] respectively. It is well-known that vancomycin is poorly distributed across the blood-brain barrier (BBB) and requires higher doses in order to achieve the desired concentration. However, this study has shown that the neurosurgical operation would disrupt the structure of BBB and thus the penetration of vancomycin into the CSF would be easier. Therefore, the LD required was lower in this population as compared to other ICU patients.

CrCL is the main influential factor on the determination of MD is CrCL in all the included studies. The others are age, concomitant use of frusemide and CSF-albumin. Wu et al. (2016) [18] has performed their dosing simulation only in a 50 year-old patient with a body weight of 70kg and CrCL of 80 ml/min and have concluded that 1,000 mg BD is the most suitable regimen in this particular CrCL. However, it may not be accurate as not all ICU patients have the same renal function. As such, an equation has been derived by utilizing the correlation between the vancomycin CL and CrCL. Unfortunately, their study population was too small (which was only 11 study group with 11 control group), hence they might not be able to detect the true differences between the groups and thus the appropriateness of their equation. In contrast, Roberts et al. (2011) [16] performed their dosing simulation with various CrCL. They suggested that a daily dose of 35 mg/kg is necessary for patients with a CrCL of 100 ml/min and a larger dose is required for CrCL of $\geq$ 100 ml/min. It should also be administered by continuous infusion in order to maintain the target SS concentration of $\geq$ 20 mg/L. However, an external validation should be done in this study as their simulations suggested very high doses as compared to those that were usually prescribed so that the potential vancomycin toxicity can be avoided. Besides, continuous infusion of vancomycin was not recommended by Li et al. (2016) [15] in their study population of neurosurgical patients due to potential nephrotoxicity and ototoxicity. This is because their dosing regimens simulated mainly focus on CSF-albumin levels of less than 500 mg/dL.

On the other hand, both Revilla et al. (2010) [13] & Medellín-Garibay et al. (2016) [14] suggested that it was appropriate to use vancomycin without the LD in critically ill patients. Both the studies suggested daily dosing of 1 g to 2 g for patients with CrCL $\leq$ 60 ml/min and 3 g to 4 g for patients with CrCL $\geq$ 130 ml/min. Medellín-Garibay et al. (2016) [14] has suggested that it should be given in 2 divided doses. This is to ensure the C_{trough} is maintained between 15 mg/L to 20 mg/L as well as to avoid the development of antibiotic resistance and to improve clinical outcomes. However, the cohort study by Revilla et al. (2010) [13] demonstrated that daily dosing could also achieve therapeutic success without developing the toxicity. In addtion, vancomycin dose should be slightly reduced when administered with frusemide (Medellín-Garibay et al., 2016) [14]. The patient's age is also one of the factors that determined the dosing recommendation of ICU patients. Young patients may receive higher doses than elderly due to their better renal function. The elder ICU population studied by Revilla et al. (2010) [13] may have better renal function as well (CrCl >120 ml/min). Thus, different dosing regimens are developed between the age groups. However, the overall recommended

dosages for various CrCL in elderly in this study were lower than those suggested in young patients.

There are several limitatiions in this study. Initially, this study was carried out to develop the population pharmacokinetic parameters of vancomycin in ICU patients only. However, due to the lack of studies available, the scope of the study was widened to evaluate the dosing recommendation simulated by included studies. Furthermore, we excluded the renally impaired patients who require renal replacement therapy for the development of population model and dosing regimen although it is well-known that vancomycin would cause nephrotoxocity in patients with poor renal clearance when higher doses are needed. Hence, the population model and dosing regimen included in this study are not suitable for patients requiring RRT.

CONCLUSION

The TBW and CrCL are the most common covariates and factors that influence the Vd and CL of vancomycin among critically ill patients. Other factors may include age, concomitant use of frusemide and CSF are also affecting the development of vancomycin pharmacokinetic models. The higher Vd and Cl of vancomycin in critically ill patients would lead to a subtherapeutic exposure of vancomycin if a standard dosage regimen is used. The specific pharmacokinetic parameter of this population should be identified to allow more precise individualisation of vancomycin dosing so that effective antibiotic use can be achieved in the ICU setting. The initial approach of the dosing recommendation in this study could be implemented. More specifically, TBW should be used for initial dosing as it is an accurate indicator of Vd of vancomycin. Maintenance dose can then be guided by CrCL. Therefore, TDM should still be performed to ensure safety and efficacy as well as reduce risk of toxicity.

The high intra- and inter-patient variability in this vulnerable population increase the challenges in developing patient-specific dosing practices. Therefore, more studies should be done and published on population pharmacokinetic parameters of vancomycin in ICU patients to understand more on the specific patient's individual factors and allow more individualised dosing to be administered. The vancomycin-induced nephrotoxicity should also be studied in this population to ensure the effectiveness of this drug for better patient outcomes.

Conflicts of Interest: The authors declare no conflict of interest.

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