Original Article

Pharmacokinetic and Pharmacodynamic Approach in Adult Critically-Ill Patients Treated with Standard Dose of Vancomycin for MRSA Infection

Eko Setiawan SFarm, MSc, Apt[1], Preecha Montakantikul PharmD, BCP[2]

[1] Center for Medicine Information and Pharmaceutical Care, Faculty of Pharmacy, University of Surabaya, Indonesia
[2] Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

Background: The achievement of vancomycin's pharmacokinetic/pharmacodynamic [PK/PD] index, i.e., AUC_{24}/MIC 400 mg-hour/L or more, is highly determined by pharmacokinetic parameters of different groups of patients.

Objective: To investigate the possibility of standard dose of vancomycin to achieve AUC_{24}/MIC of 400 mg-hour/L or more in critically-ill adult patients.

Materials and Methods: The literature search was conducted in PubMed, Cochrane, and Trip Database from database inception until August 2012 by using MeSH term and combination of several keywords. Studies included in the present review should present population pharmacokinetic equation model. Further analysis would consider mean, minimum, and maximum values of covariates that influenced the pharmacokinetic equation models. The maximum MIC was chosen to be 2 mg/L according to susceptibility breakpoint of *Staphylococcus aureus* to vancomycin.

Results: Four studies were included in the present study. The range of volume distribution, clearance, AUC_{24}, and MIC coverage calculated by using mean value of influential covariates of pharmacokinetic equation model were 59.86 to 149.05 L, 3.03 to 4.15 L/hour, 481.46 to 661.09 mg-hour/L, and 1.20 to 1.65 mg/L, respectively. The minimum and maximum values of influential covariates gave the following results, 36.90 to 306.27 L, 0.18 to 13.22 L/hour, 151.34 to 10,917.03 mg-hour/L, and 0.38 to 27.29 mg/L, respectively.

Conclusion: Not all critically-ill patients infected with vancomycin-susceptible MRSA were effectively treated by standard dose of vancomycin. Drug concentration monitoring and MRSA's MIC testing are needed to be regularly conducted to ensure the effectiveness of vancomycin treatment.

Keywords: Vancomycin, Critically ill, Methicillin-resistant *Staphylococcus aureus*

J Med Assoc Thai 2018; 101 (5): 555-62
Website: http://www.jmatonline.com

Methicillin-resistant *Staphylococcus aureus* [MRSA] is one of the most common virulent pathogen found in the hospital setting[1-3]. Patients with mechanical ventilation, central venous catheter, surgery procedure, history of hospitalization, previous antibiotic utilization, and receiving enteral feeding have higher risk of MRSA infection[4-6]. Therefore, those who are admitted in the intensive care unit [ICU] or other units that also frequently utilize those equipment, such as cardiac care unit [CCU] or neonatal intensive care unit [NICU], have greater propensity to be infected with MRSA compared with those admitted in other wards. MRSA infection affords higher burden in the health care system due to higher mortality rate and total health care cost than methicillin-susceptible *S. aureus* [MSSA] infection[7-10].

Vancomycin has long been used as the first line therapy for MRSA infection. Some of MRSA strains develop further resistant mechanisms, i.e., vancomycin intermediate-resistant *S. aureus* [VISA] and vancomycin resistant *S. aureus* [VRSA], will not be effectively treated with vancomycin. Fortunately, the VISA and VRSA cases were not frequently found in the daily practice[11]. However, another more important issue using vancomycin to treat MRSA infection is higher number of treatment failure when vancomycin is used to treat MRSA strains with higher minimum inhibitory concentration [MIC] values even though they were classified as susceptible strain by the Clinical

Correspondence to:

Montakantikul P. Department of Pharmacy, Faculty of Pharmacy, Mahidol University, 447 Sri Ayuthaya Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: +66-87-1009097
Email: preecha.mon@mahidol.ac.th

How to cite this article: Setiawan E, Montakantikul P. Pharmacokinetic and pharmacodynamic approach in adult critically-ill patients treated with standard dose of vancomycin for MRSA infection. J Med Assoc Thai 2018;101:555-62.

and Laboratory Standards Institute [CLSI], i.e., less than 2 mg/L[12-15]. The phenomenon of population shifting in vancomycin MIC against MRSA strains to the higher number over time is also known as the "MIC Creep" MRSA phenomenon[16]. Studies conducted in several institutions indicated the "MIC Creep" phenomenon in their institution[17-19]. Further analysis found that patients who had unfavorable outcomes usually failed to achieve the desired pharmacokinetic-pharmacodynamic [PK/PD] index: area under the plasma drug concentration and time curve for 24 hours [AUC_{24}]/MIC of 400 mg-hour/L or more[15,20].

There are several factors influencing the achievement of this desired PK/PD index, with the most prominent factors being dosage regimen of vancomycin, PK parameters profile of each group of patients, and MIC values of the bacteria. Standard dose of vancomycin, defined as 1 g every 12 hours, has been commonly prescribed to hospitalized MRSA infected patients with normal renal function. Whether this dosage regimen will afford the achievement of the desired PK/PD index for all hospitalized patients is questionable. A greater concern should be given to the critically-ill patients, since they have rapidly changing physiologic conditions that will give an impact to the different PK parameters profile compared with non-critically-ill patients or healthy subjects, a population that usually were recruited in the phase 1, 2, and 3 clinical trials and, in which, their data usually were used as reference values. Different PK parameters, particularly volume distribution [Vd] and creatinine clearance [Cl_{cr}], will change the overall drug concentration profile in the blood that finally will impact the achievement of AUC_{24} and MIC coverage of MRSA strain. The present study was conducted to investigate the differences of PK parameters among adult critically-ill patients by using population PK studies, and its impact on the achievement of AUC_{24} and maximum MIC coverage by giving standard dose of vancomycin in patient with normal renal function.

Materials and Methods

Definition

Critically-ill patient is a patient who requires a higher level of care than that was normally provided on a standard hospital ward[21]. Therefore, in the present study, the authors defined patients who were admitted to the ICU or CCU as the critically ill population. Patients those are 17 years old or older were classified as adult patient. Population PK study is a quantitative assessment of typical PK parameters, and the between individual and residual variability in drug absorption, distribution, metabolism, and excretion[22]. This kind of study presents the equation model of certain PK parameters that consist of several influential covariates.

Criteria for eligible studies

The inclusion criteria for eligible studies were English language published articles that presented the population PK equation model conducted particularly in the adult critically-ill patients.

The following criteria were used to exclude articles from the present study, 1) a review article, 2) recruited subject that are younger than 17 years old and/or non-critically ill patients and/or healthy subjects in the PK equation model building, 3) presented only PK parameters data without any population PK equation model, particularly for Vd and CL, and 4) used non-mixed effect model in their method.

Search strategy

Three databases were used in the present review, i.e. PubMed, Cochrane Database, and Trip Database. Literature search was conducted from the database inception until August 2012 by using Medical Subject Headings [MeSH] terms and combination of the following keywords: "vancomycin" and "population pharmacokinetic"; "vancomycin" and "adult population pharmacokinetic"; "vancomycin" and "critically ill population"; "vancomycin" and "population pharmacokinetic" and "intensive care unit"; "vancomycin" and "population pharmacokinetic" and "ICU"; "vancomycin" and "population pharmacokinetic" and "critically ill"; "vancomycin" and "pharmacokinetic study" and "ICU"; "vancomycin" and "pharmacokinetic study" and "intensive care unit"; "vancomycin" and "critical illness/es"; "vancomycin" and "population pharmacokinetic" and "critical illness/es"; or "vancomycin" and "pharmacokinetic study" and "critical illness/es". Follow-up of the reference lists of relevant articles also had been conducted to extent the searching method of the original article.

AUC achievement and MIC coverage analysis

First of all, PK parameters, i.e., Vd and CL, were calculated by entering the maximum, mean, and minimum value of covariate that influenced the population PK equation model, such as age, body weight, and Cl_{cr}, in every equation model obtained. The purpose of considering the range of influential covariate was to present the variation characteristics of critically-ill patients and its effect on the AUC_{24}

achievement and MIC coverage. After getting the values of PK parameters, the next step was AUC_{24} calculation using the following equation:

AUC_{24} = total daily dose of vancomycin/CL(1)

CL stands for vancomycin clearance (L/hour). Total daily dose of vancomycin in this analysis was 2 g. Because the authors considered the range values of influential covariate of CL, finally, we presented three different values of AUC_{24} for each study. Each value of AUC_{24} was put in the equation below to get the maximum MIC coverage by giving standard dose of vancomycin to the critically-ill patient.

MIC (mg/L) = AUC_{24}/400(2)

Results

Initial literature search using Pubmed, Cochrane Database, and Trip Database identified 715 articles. There were 356 duplicated articles and 329 irrelevant articles. Studies classified as irrelevant could be a study in the area of in-vitro simulation PK and/or PD, neonates or pediatrics, dosing assessment or determination, therapeutic drug monitoring, review of other drugs, and review of disease. Thirty studies were available for further full-text analysis and 26 among them were excluded because of several reasons, including 1) review articles, 2) recruited subject less than 17 years old, 3) in-vitro PK analysis, 4) presenting only PK data without providing PK equation model, or 5) dosing nomogram validation. Detailed selection of eligible studies is described in Figure 1.

Finally, the authors retained four population PK studies conducted particularly in the critically-ill patients[23-26]. Table 1 and 2 presents the characteristics of the four studies and their population PK equation models for Vd and CL. Three studies were conducted in the ICU department and one study was conducted in the CCU department. All studies used NONMEM® program, a non-linear mixed-effect modelling program, to analyze the drug concentration versus time data. Each study might have some approaches to identify the covariate that would be included in the PK equation model building. However, generalized additive modelling [GAM] was commonly used by most of the studies. The identified covariates were added to the basic PK equation model one by one, and then, the most appropriate final population PK equation model was chosen based on the differences in the objective function value [OFV].

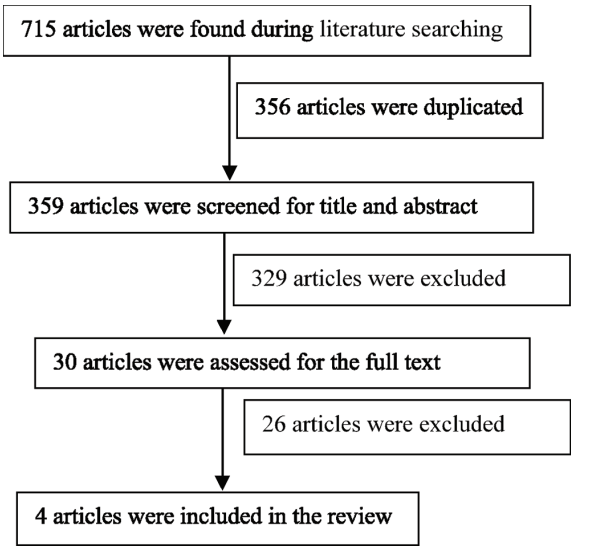

Figure 1. Flow chart for selection eligible study.

Table 1. Characteristics of eligible studies

Study	Number of population	Age (year)	Weight (kg)	CLcr (mL/minute)	Scr (mg/dL)	Vancomycin dosage regimen	Compartment model of vancomycin	Blood concentration per patient
Revilla et al.[23]	191	61.10 (18 to 85)	73.00 (45 to 150)	74.70 (10 to 328)	1.40 (0.6 to 150)	Intermittent and continuous infusion; 18.4±10.3 mg/kg/day	One-compartment	3
Llopis-Salvia and Jimenez-Torres[24]	50	60.00 (18 to 81)	60.61 (40 to 130)	76.28 (16.27 to 120)	-	Mainly (70%) intermittent infusion; 18.51 mg/kg/day (4.9 to 38.7)	Two-compartment	7
Roberts et al.[25]	206	58.10 (18 to 86)*	74.80 (35 to 140)*	90.70 (4 to 263)*	-	Continuous infusion; based on clinician judgement	One-compartment	2
Staatz et al.[26]	102	66.00 (17 to 87)	74.00 (44 to 110)	60.00 (12 to 172)	101.00 (45 to 527)	Intermittent infusion; 1,000 mg (120 to 2,000)	One-compartment	3

CLcr = creatinine clearance; Scr = serum creatinine

* The range value was derived from personal communication with Roberts et al(25)

The value of each characteristic represented the mean value. Value in the parenthesis represented the range value.

Table 2. Population pharmacokinetic equation model

Study	Population PK model							
	Vd peripheral	Vd central	CL	RV	θ_1	θ_2	θ_3	θ_4
Revilla et al.[23]	-	θ_3 x θ_4[A] IIV 22.83%	(θ_1 x CL_{cr}) + ageθ_2 IIV 30.13%	4.23%	0.67 (95% CI 0.58 to 0.76)	-0.24 (95% CI -0.27 to -0.21)	0.82 (95% CI 0.7 to 0.94)	2.49 (95% CI 2.00 to 2.98)
Llopis-Salvia and Jimenez-Torres[24]	θ_4 x TBW IIV = 36.4%	θ_3 x TBW IIV 36.4%	(θ_1 x CL_{cr}) + (θ_2 x TBW) IIV 29.2%	23.9%, 18.5%	0.034 (95% CI 0.01 to 0.056)	0.015 (95% CI -0.001 to 0.039)	0.414 (95% CI 0.356 to 0.471)	1.32 (95% CI 0.785 to 1.855)
Roberts et al.[25]	-	θ_1 x TBW IIV 37.4%	θ_2 x CL_{cr}/100 IIV 38.9%	19.9%	1.53	4.58	-	-
Staatz et al.[26]	-	θ_3 x TBW IIV 36%	θ_1 x [1 + θ_2 x (CL_{cr} - 57)] IIV 27%	15%, 1.6%	2.97	0.0205	1.24	-

Vd = volume distribution; CL = vancomycin clearance; CL_{cr} = creatinine clearance; TBW = total body weight; IIV = interindividual variability; RV = residual variability

Three studies that were conducted by Llopis-Salvia and Jimenez-Torres[24]; Roberts et al[25]; and Staatz et al[26], found body weight as a significant covariate determining the final equation model of Vd. The study conducted by Revilla et al, was the only study that found renal function, presenting as serum creatinine [S_{cr}], as a determinant factor for Vd[23]. Calculation using the mean value of body weight for the first three studies afforded the Vd values of 105.094 L, 114.44 L, and 91.76 L, respectively. With the assumption of S_{cr} greater than 1 mg/dL and 1 mg/L or less, the result of calculation from study conducted by Revilla et al, using mean value of body weight resulted in Vd values of 149.05 L and 59.86 L, respectively. While considering the minimum and maximum ranges of all influential covariates for all studies, the range of Vd for critically-ill patients was 36.90 to 306.27 L. The detail value of Vd can be found in Table 3. The range of interindividual variability [IIV] for Vd from all studies was 22.83% to 37.40%.

All studies described that Cl_{cr} was the most influential covariate for CL. Study conducted by Revilla et al[23], found another additional covariate for CL, i.e., age. While, study conducted by Llopis-Salvia and Jimenez-Torres[24], found body weight as another additional covariate for CL. Calculation using mean value of Cl_{cr}, age, body weight for all studies afforded the CL value of 3.03 L/hour, 3.15 L/hour, 3.50 L/hour, and 4.15 L/hour for studies conducted by Revilla et al[23], Staatz et al[26], Llopis-Salvia and Jimenez-Torres[24], and Roberts et al[25], respectively. By using these mean values of CL, the range value of AUC_{24} was 481.46 to 661.09 mg-hour/L and the maximum MIC coverage was 1.20 to 1.65 mg/L. While considering the minimum and maximum values of all influential covariates for all studies, the value of CL, AUC_{24}, and maximum MIC coverage were 0.18 to 13.22 L/hour, 151.34 to 10,917.03 mg-hour/L, and 0.38 to 27.29 mg/L, respectively. The IIV for CL for all studies was 27% to 38.90%. The impact of different values of

Table 3. MIC coverage analysis

Study	Value of covariate	Vd peripheral (L)	Vd Central (L)	CL (L/hour)	AUC (mg-hr/L)	MIC coverage (mg/L)
Revilla et al.[23]	Max[a]	-	306.27[a,c], 123.00[a,d]	13.22	151.34	0.38
	Average	-	149.05[c], 59.86[d]	3.03	661.09	1.65
	Min[b]	-	91.88[b,c], 36.90[b,d]	0.42	4,731.94	11.83
Llopis-Salvia and Jimenez-Torres[24]	Max	171.6	53.82	6.03	331.68	0.82
	Average	80.00	25.09	3.50	570.99	1.42
	Min	52.80	16.56	1.15	1,734.34	4.33
Roberts et al.[25]	Max	-	214.20	12.05	166.04	0.42
	Average	-	114.44	4.15	481.46	1.20
	Min	-	53.55	0.18	10,917.03	27.29
Staatz et al.[26]	Max	-	136.40	9.97	200.57	0.50
	Average	-	91.76	3.15	634.39	1.58
	Min	-	54.56	0.23	8,689.04	21.72

Vd = volume distribution; CL = vancomycin clearance; AUC = area under the curve; MIC = minimuminhibitory concentration; CL_{cr} = creatinine clearance; S_{cr} = serum creatinine

[a] Maximum value CL was calculated by using maximum value of age and minimum value of CL_{cr}

[b] Minimum value CL was calculated by using minimum value of age and maximum value of CL_{cr}

[c] For patients with S_{cr} >1 mg/dL

[d] For patients with S_{cr} ≤1 mg/dL

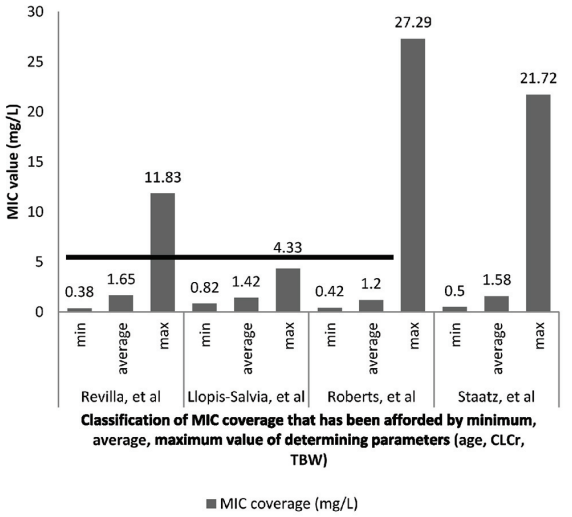

Figure 2. The maximum MIC coverage by considering the range value of covariate, CLCr = creatinine clearance; TBW = total body weight. Black horizontal line represented the maximum limit of susceptible strain of MRSA, i.e., MIC 2.0 mg/L. It was clearly shown that standard dosage regimen of vancomycin could not covered all MRSA susceptible strain for every single critically ill patient.

CL to the achievement of AUC_{24} and maximum MIC coverage can be found in Table 3 and Figure 2.

Discussion

The result of the present study clearly described the different PK profiles that would provide different achievement of AUC_{24} and MIC coverage of MRSA strain for the same dosage regimen of vancomycin. To our knowledge, the present study is the first study that describe the population PK profile of vancomycin particularly among critically-ill patient and correlated them with the achievement of AUC_{24} and maximum MIC coverage by giving standard dose of vancomycin. There was another vancomycin population PK review conducted by Marsot et al[27]. They reviewed the population PK of vancomycin for all population, not only in the adult but also in pediatric population. The most important difference with the present review is that they did not present the impact of different PK parameters profile to the achievement of AUC_{24} and maximum MIC coverage of MRSA strain.

Calculation of Vd using population PK equation model from critically-ill population afforded larger Vd value compared with commonly used reference value of Vd. Without including the Vd calculated using equation model from Revilla et al[23], in which did not only consider body weight as a determinant factor for Vd but also renal function, the range of Vd was 1.24 to 1.734 L/kg. While, the commonly used reference value of Vd is 0.4 to 1 L/kg[28]. The highest value of Vd was derived from the study conducted by Llopis-Salvia and Jimenez-Torres[24], that used two-compartment model in their study. By using two-compartment model, the present study would consider the Vd from both peripheral and central compartments, therefore, afforded the highest value of Vd. As a hydrophilic antibiotic agent with high molecular weight, vancomycin will mostly distribute into the intravascular fluid and interstitial space rather than further penetrate to the intracellular compartment. Therefore, any condition or treatment that influencing these two compartments will impact Vd of vancomycin. There are several reasons why critically-ill patients had larger Vd value, including 1) endothelial dysfunction leading to the increase of capillary permeability and fluid shift to the interstitial space, 2) hypoalbuminemia that would lower the intravascular oncotic pressure leading to fluid shift to the interstitial space, 3) aggressive fluid treatment used to overcome some symptoms, 4) using special medical services like mechanical ventilation or extracorporeal membrane oxigenase, and 5) post-surgical drainages[29-31]. The study conducted by Revilla et al[23] was the only study that emphasized the renal function as an important covariate for Vd. Different renal function will afford different values of Vd. Critically-ill patient with S_{cr} of 1 mg/dL or less will have Vd similar to the reference Vd value, i.e., 0.82 L/kg. Patients with S_{cr} greater than 1 mg/dL, which usually indicate decreased renal function, will have Vd larger than the commonly used reference Vd value, i.e., 2.042 L/kg. This finding was in accordance with one of the renal function that maintain the fluid balance. Whenever the patients have decreased renal function, they will have fluid accumulation that finally will expand the Vd. Therefore, Vd will play an important role in the early phase of treatment, i.e., loading dose determination. Thus, loading dose may be needed for critically-ill patient. Inadequate antibiotic treatment at the early phase of treatment will contribute to unfavorable outcome[32,33].

All the studies showed Cl_{cr} as the most influential covariate for the CL with or without additional covariates. There is linear correlation between Cl_{cr} and CL. Patient who has worsening renal function, will have slower CL value, and vice versa. The linear correlation between these two parameters is in accordance with the basic characteristics of vancomycin that has main elimination process through glomerular filtration[28].

Most of hydrophilic drugs usually undergo glomerular filtration as the main elimination process. Population PK study of another hydrophilic antibiotics, such as beta-lactams, also found the relationship between Cl_{cr} and the clearance of beta-lactams[34,35]. Since the calculation of AUC_{24} in the present study was based on the equation that assumed steady state condition, CL will be a determinant factor the achievement of AUC_{24}. Therefore, the faster CL will afford lower AUC_{24} value, and vice versa. For patients with worsening renal function, giving 1 g of vancomycin every 12 hours will afford coverage to all susceptible MRSA strain classified by CLSI, and even seems to be able to cover VISA and VRSA strain with the MIC classification of 4 to 8 mg/L and more than 16 mg/L, respectively. Unfortunately, it will not happen in the daily practice for some reasons, including 1) vancomycin will never be effectively used in the VISA, which has thicker cell wall and burden of D-Ala-D-Ala terminal, and VRSA strain, which changed the vancomycin site of action (D-Ala-D-Ala) with D-Ala-D-Lac or D-Ala-D-Ser, and 2) the vancomycin dose for patient with bad renal function will not follow standard regimen dose that is usually given to patients with normal renal function[36,37]. Modification of dosage regimen usually apply in patient with bad renal function, either decrease the dose or give at alternate day to avoid drug accumulation and further nephrotoxicity.

Analyzing the impact of different PK profile on the maximum MIC coverage of MRSA using mean value of influential covariate provided similar pattern, i.e., standard dose of vancomycin could not cover all susceptible strain of MRSA. It will not only place the critically-ill patient on the higher risk of treatment failure, but this condition will also lead to the development of further resistance to MRSA strain that will increase the complexity of the management. Several in vitro studies indicated AUC_{24}/MIC of less than 400 mg-hour/L would make strain with higher MIC and thicker cell wall at the end of their studies[38,39]. Higher MIC value and thicker cell wall are some characteristics of strain that developed further resistant mechanism.

The present study had several limitations. The authors realized that the studies found in this review might not be all population PK studies available since we could not access all database, such as EMBASE database. The authors also did not search the grey literature. The authors assessed the impact of different PK parameters profile on the achievement of AUC_{24} using equation that assumed steady state condition. The most accurate method to calculate AUC_{24} is the trapezoidal method and the calculation should be done after the first dose is given and the patient reach steady state condition. The different methods of calculation might afford some deviation, either under- and over-estimation values of AUC_{24}. Lastly, the authors did not emphasize the impact of some medical equipment, such as dialysis and extracorporeal membrane oxygenation that play an important role in determining vancomycin concentration.

Conclusion

Variation PK parameters found among critically-ill patient present a great challenge in the management of MRSA infection. Not all critically-ill patients will be effectively treated with standard dose of vancomycin, though they are infected with vancomycin susceptible strain. Challenges will arise in the era of "MIC Creep" phenomenon, since higher AUC_{24} value should be achieved as a compensation of higher value of MIC infected strain. Drug concentration monitoring and MRSA's MIC testing is ultimately needed to be regularly conducted to ensure the achievement of desired target of treatment for all MIC of MRSA strains. Dosage regimen determination considering the variation of pharmacokinetic parameters among critically-ill patient and the local MIC distribution of MRSA strains are needed to be conducted to ensure the efficacy of vancomycin while minimizing the risk of adverse drug reaction.

What is already known on this topic?

Several published articles revealed that MRSA infection caused by high vancomycin MIC values (MIC greater than 1 mg/L) gave significant risk to worsen clinical outcomes than ones with lower values. Critically-ill condition is known as one of strong risk factors to be infected with high vancomycin MIC value. It has been proposed that critically-ill patients have different physiology conditions that affect vancomycin's pharmacokinetic profile. Little is known about the impact of deviated pharmacokinetics profile among critically-ill patients to the maximum value of MIC coverage by giving standard dosage regimen of vancomycin.

What this study adds?

This study reported the maximum MIC value that cannot be covered by giving standard dosage regimen of vancomycin (1 g every 12 hours in patient with normal renal function) in critically-ill patients with

high vancomycin MIC value. Drug concentration monitoring and MRSA's MIC testing in critically-ill patients are needed to ensure the effectiveness of vancomycin treatment.

Potential conflicts of interest

The authors declare no conflict of interest. This study had been conducted independently without any financial and grant support from any institution.

References

1. Zhanel GG, DeCorby M, Laing N, Weshnoweski B, Vashisht R, Tailor F, et al. Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. Antimicrob Agents Chemother 2008;52:1430-7.
2. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 2008;29:996-1011.
3. Fluit AC, Verhoef J, Schmitz FJ. Frequency of isolation and antimicrobial resistance of gram-negative and gram-positive bacteria from patients in intensive care units of 25 European university hospitals participating in the European arm of the SENTRY Antimicrobial Surveillance Program 1997-1998. Eur J Clin Microbiol Infect Dis 2001; 20:617-25.
4. Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. J Antimicrob Chemother 2008;61:26-38.
5. Graffunder EM, Venezia RA. Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother 2002;49:999-1005.
6. Wang FD, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial *Staphylococcus aureus* bacteremia. Am J Infect Control 2008;36:118-22.
7. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53-9.
8. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. Med J Aust 2001; 175:264-7.
9. Filice GA, Nyman JA, Lexau C, Lees CH, Bockstedt LA, Como-Sabetti K, et al. Excess costs and utilization associated with methicillin resistance for patients with *Staphylococcus aureus* infection. Infect Control Hosp Epidemiol 2010; 31:365-73.
10. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166-74.
11. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clin Microbiol Rev 2010;23:99-139.
12. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; Twenty-first informational supplement M 100-S21. Vol.31 No.1. Wayne, PA: CLSI; 2011.
13. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 2008;46:193-200.
14. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Jr., Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 2004;42:2398-402.
15. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 2011;52:975-81.
16. Gould IM. Clinical relevance of increasing glycopeptide MICs against *Staphylococcus aureus*. Int J Antimicrob Agents 2008;31 Suppl 2:1-9.
17. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate

Staphylococcus aureus (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001-05. J Antimicrob Chemother 2007;60:788-94.
18. Robert J, Bismuth R, Jarlier V. Decreased susceptibility to glycopeptides in methicillin-resistant *Staphylococcus aureus*: a 20 year study in a large French teaching hospital, 1983-2002. J Antimicrob Chemother 2006;57:506-10.
19. Musta AC, Riederer K, Shemes S, Chase P, Jose J, Johnson LB, et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. J Clin Microbiol 2009;47:1640-4.
20. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet 2004;43:925-42.
21. Subbe C. Recognition and assessment of critical illness. Anaesth Intensive Care Med 2007;8: 21-3.
22. Ette EI, Williams PJ, Lane JR. Population pharmacokinetics III: design, analysis, and application of population pharmacokinetic Studies. Ann Pharmacother 2004;38:2136-44.
23. Revilla N, Martín-Suárez A, Pérez MP, González FM, Fernández de Gatta Mdel M. Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/pharmacodynamic simulation. Br J Clin Pharmacol 2010; 70:201-12.
24. Llopis-Salvia P, Jimenez-Torres NV. Population pharmacokinetic parameters of vancomycin in critically ill patients. J Clin Pharm Ther 2006;31: 447-54.
25. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 2011;55:2704-9.
26. Staatz CE, Byrne C, Thomson AH. Population pharmacokinetic modelling of gentamicin and vancomycin in patients with unstable renal function following cardiothoracic surgery. Br J Clin Pharmacol 2006;61:164-76.
27. Marsot A, Boulamery A, Bruguerolle B, Simon N. Vancomycin: a review of population pharmacokinetic analyses. Clin Pharmacokinet 2012;51: 1-13.
28. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006;42(Suppl 1):S35-9.
29. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005;44:1009-34.
30. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006;22:255-71.
31. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840-51.
32. Paul M, Kariv G, Goldberg E, Raskin M, Shaked H, Hazzan R, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2010;65:2658-65.
33. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.
34. Roos JF, Bulitta J, Lipman J, Kirkpatrick CM. Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. J Antimicrob Chemother 2006;58:987-93.
35. Roos JF, Lipman J, Kirkpatrick CM. Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against gram-negative bacteria. Intensive Care Med 2007;33: 781-8.
36. Sakoulas G, Moellering RC Jr. Increasing antibiotic resistance among methicillin-resistant *Staphylococcus aureus* strains. Clin Infect Dis 2008;46(Suppl 5):S360-7.
37. Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. J Clin Invest 2003;111: 1265-73.
38. Zelenitsky S, Alkurdi N, Weber Z, Ariano R, Zhanel G. Preferential emergence of reduced vancomycin susceptibility in health care-associated methicillin-resistant *Staphylococcus aureus* isolates during continuous-infusion vancomycin therapy in an in vitro dynamic model. Antimicrob Agents Chemother 2011;55:3627-30.
39. Rose WE, Knier RM, Hutson PR. Pharmacodynamic effect of clinical vancomycin exposures on cell wall thickness in heterogeneous vancomycin-intermediate *Staphylococcus aureus*. J Antimicrob Chemother 2010;65:2149-54.