Optimization of Intermittent Vancomycin Dosage Regimens for Thai Critically Ill Population Infected by MRSA in the Era of the "MIC Creep" Phenomenon

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ABSTRAK

Latar belakang: *peningkatan nilai minimum inhibitory concentration (MIC) dari bakteri methicillin-resistant Staphylocuccus aureus (MRSA) dapat menyebabkan perburukan kondisi klinis pasien khususnya pasien yang berada dalam kondisi kritis. Tujuan penelitian ini adalah untuk mengidentifikasi pengaturan dosis vancomycin yang paling tepat untuk mengatasi infeksi yang disebabkan oleh MRSA dengan nilai MIC yang tinggi pada pasien kritis etnis Thailand.* ***Metode:*** *replikasi sebanyak 10.000 kali terhadap beberapa rejimen dosis vancomycin dilakukan dengan menggunakan Monte Carlo simulation. Nilai parameter farmakokinetik vancomycin didapatkan dari penelitian yang dilakukan pada pasien etnis Thailand. Setelah simulasi selesai, dihitung nilai probability of target attainment (PTA) dan cumulative fraction of response (CFR) dari setiap rejimen dosis vancomycin. Risiko terjadinya nefrotoksik juga dihitung dan digunakan sebagai pertimbangan dalam menentukan rejimen dosis vancomycin.* ***Hasil:*** *dosis vancomycin yang lebih tinggi, yakni: 3g/hari dan 4g/hari, dibutuhkan untuk mencapai nilai PTA 80% jika vancomycin digunakan untuk mengatasi MRSA dengan MIC 1,5mg/L dan 2,0 mg/L, secara berturut-turut. Nilai CFR tertinggi, yakni 94,40% dan 93,57%, didapatkan dari rejimen dosis 1g setiap 6 jam dan 2g setiap 12 jam. Dosis standar vancomycin, yakni 1g setiap 12 jam, dan rejimen dosis dengan total 3g/hari dapat mencapai CFR 51% dan 73%. Risiko nefrotoksik yang dihasilkan dari dosis rejimen 1,5g setiap 12 jam dan 2g setiap 12 jam adalah sebesar 26,59% dan 31,20%.* ***Kesimpulan:*** *dosis vancomycin 1,5g setiap 12 jam dan 2g setiap 12 jam yang diberikan secara intermittent seharusnya diimplementasikan sebagai terapi definitif pada pasien yang terinfeksi MRSA dengan MIC 1,5 dan 2,0 mg/dl, secara berturut-turut.*

Kata kunci: *Vancomycin, pasien kritis, Thai population, Monte Carlo simulation, MIC creep.*

ABSTRACT

Background: *the shifting of minimum inhibitory concentration (MIC) of methicillin-resistant Staphylocuccus aureus (MRSA) strains to the higher value has emerged to worsen clinical outcome to the patients particularly critically ill population. The aim of this study was to identify the most appropriate dosage regimen of vancomycin to treat infection caused by MRSA with higher MIC in critically ill Thai population.* ***Methods:*** *10,000 replications of intermittent vancomycin dosage regimens were performed using Monte Carlo simulation. Pharmacokinetic*

parameters were derived from a population pharmacokinetic study conducted specifically in Thai population. The probability of target attainment (PTA) and cumulative fraction of response (CFR) of each dosage regimen were calculated. Risk of nephrotoxicity was also calculated and used as a consideration in determining the most appropriate dosage regimen of vancomycin. ***Results:*** *in order to achieve desired PTA > 80% vancomycin at higher dosing regimens were needed including 3g/day and 4 g/day for MIC 1.5mg/L and 2.0 mg/L, respectively. Highest CFR of 94.40% and 93.57% were from vancomycin 1 g every 6 h and 2 g every 12h. Standard dose of vancomycin and total dose of vancomycin 3 g/day provided approximately 51% and 73% CFR. Risk of nephrotoxicity afforded by giving 1.5g every 12h and 2g every 12h of vancomycin were 26.59% and 31.20%, respectively.* ***Conclusion:*** *the result from this study recommended intermittent dosage regimen 1.5g every 12h and 2g every 12h should be implemented as definite antibiotic treatment when considered infection caused by MRSA with MIC 1.5 and 2.0 mg/L, respectively.*

Keywords: *Vancomycin, critically ill, Thai population, Monte Carlo simulation, MIC creep.*

INTRODUCTION

Nowadays, there is a greater interest in using vancomycin to treat Methicillin Resistant Staphylococcus aureus (MRSA) infected patients. Several published studies found higher risk of treatment failure when vancomycin was used to treat susceptible strains with higher vancomycin minimum inhibitory concentration (MIC) value.[1-4] Moreover, there is phenomenon called "MIC creep" which is the concern of shifting of vancomycin MICs within the susceptibility range to MRSA.[3] Vancomycin dosage adjustment is ultimately needed to achieve the desired target of treatment of vancomycin, i.e area under the plasma drug concentration and time curve at steady-state over 24 hours (AUC0-24) over MIC (AUC0-24/MIC) of ≥400mg. hr/L unless otherwise stated.[5] Achievement of desired target of treatment provided good clinical outcome for patients. Moreover, results that were derived from in vitro studies revealed that achievement to desired AUC0-24/MIC value would prevent the development of further resistant strains.[6,7] However, it is very challenging to ensure the achievement of the desired target of treatment particularly in the era of "MIC Creep" phenomenon because higher AUC0-24 is needed to compensate higher value of MIC. The most important question is how vancomycin dosage regimens should be applied in the era of "MIC Creep" phenomenon which is ultimately determined by pharmacokinetics (PK) parameters of particular population.[8-10]

One population with deviated vancomycin PK parameters is the critically ill patients.[11,12] Critically ill population tend to have larger volume of distribution (Vd) and faster clearance creatinine (CLcr) compared with non-critically ill population.[8-12] The different PK parameters might be caused by different physiologic condition compared with non-critically ill populations and/or the treatment given to critically ill, such as massive fluid treatment.[11] Since vancomycin is classified as the hydrophilic drug with majority elimination process by glomerular filtration rate (GFR), thus, the Vd and CLcr are the most important PK parameters in determining the achievement of desired AUC0-24/MIC. It is expected that determining proper vancomycin dosing regimen in critical care service becomes more challenging for MRSA infection which is also proven to be one of the most virulent pathogens in intensive care unit (ICU).[13,14]

Generally, there will be a great risk of treatment failure and/or adverse drug reaction (ADR) in critically ill patients. Likewise, vancomycin has several adverse drug reaction profiles, including "Red-man syndrome", thrombocytopenia, neutropenia, ototoxicity, and nephrotoxicity. Compared with other adverse drug reactions, nephrotoxicity is known as one of the most concerning adverse drug reactions since it is associated with higher financial burden.[15] In order to minimize nephrotoxicity from vancomycin, the trough concentration ≥15 mg/L was mostly recommended as the threshold to

determine risk of nephrotoxicity for intermittent regimens.[16-19]

In the era of anti-MRSA limitation especially in developing countries, the role of vancomycin as a first-line therapy in the management of "MIC Creep" MRSA becomes more important. In Thailand, the limited antibiotics alternative for MRSA is a major concern due to none of them has been proven to be more effective than vancomycin. Additionally, safety profiles also limit its use in some patients. This study aimed to determine the most appropriate dosage regimen of intermittent vancomycin to treat "MIC Creep" MRSA infection in critically ill Thai population.

METHODS

Model Construction

A 10,000 trial Monte Carlo simulation was performed for each vancomycin regimen (Crystal Ball® 2000; Decisioneering Inc., Denver, CO). The ratio of AUC0-24/MIC of 400 mg.hr/L was set as the target of vancomycin treatment. Age was assumed to be a log-Gaussian distribution. However, CLcr had been set as uniform distribution with defined CLcr value of 60-120 mL/min. The simulated vancomycin dosage regimens were: 1 g every 12 h; 1 g every 8 h; 1 g every 6 h; that should be infused in 1 h; and 1.5 g every 12 h; 2 g every 12 h that should be infused in 2 h.

The complete final population PK equation models of vancomycin for Thai population used in present study was derived from a published PK vancomycin model among Thai population.[20] It is estimated that more than 30% of critically ill patients were recruited to the referenced study. The PK models were presented in **Table 1** which revealed good predictive performance for critically ill population with the mean prediction error of -1.43 (95% CI -5.82 to -2.99) and root mean squared prediction error of 12.28 (95% CI -1.60 to -26.16). Two compartment model has been proven as the best compartment model by that PK equation model.

Vancomycin plasma concentration-time profile was calculated in 0.25-h time incremental until steady state condition had been achieved using Oracle Crystall Ball® that was already added in the Microsoft Office Excel 2007 edition (Microsoft Corporation, Redmond, Washington). Concentration of vancomycin at the third day was used to calculate AUC0-12 using trapezoidal method.

Table 1. Final population PK equation models for Thai population.

PK parameters	Model equation	Interindividual variability
Vancomycin clearance (CL; in L/h)	0.0444 x CLCr (mL/min)	35.78%
Volume of central compartment (V1; in L)	0.542 x Age (years old)	20.93%
Intercompartmental clearance (Q; in L/h)	6.95	39.50%
Volume of peripheral compartment (V2; in L)	44.20	57.27%

Bacterial Isolates and Susceptibility Testings

The MIC distribution data of vancomycin susceptible MRSA strain (MIC $\leq$2.0 mg/L) in this study was derived from European Committee on Antimicrobial Susceptibility Testing (EUCAST) database.[21] Data from EUCAST database clearly indicated that MIC distribution has been shifted to the higher value. There were 0.24%, 60.35%, 39.11% of MRSA strains with MIC 0.5 mg/L, 1 mg/L, and 2 mg/L, consecutively, while the rest had MIC 4.0 mg/L.

In order to represent the real MRSA MIC distribution from hospital in Thailand, this study conducted sensitivity analysis by changing the proportional of MRSA strains at a certain MIC. The best scenario was assumed that all (100%) of MRSA strains had MIC 0.5 mg/L. The worst scenario was assumed that all (100%) of MRSA strains had MIC 2.0 mg/L. There were some scenarios implemented in between the best and the worst scenario by changing the percentage of MRSA strains in particular MIC value.

Model Simulation and Analysis

Result of 10,000 simulation was recorded and further analyzed for the achievement of probability of target attainment (PTA) and cumulative fraction of response (CFR). The percentage of PTA was claculated for each MIC of 0.5 mg/L, 1.0 mg/L, 1.5 mg/L, and 2.0 mg/L. The percentage of PTA in each regimen dosage

multiplied by fraction of bacteria in the MIC distribution derived from EUCAST database and also the case of simulation represented the value of CFR.[22] This study used the value of PTA and CFR>80% as the threshold to define efficacy of particular dosage regimen for each MIC value of MRSA.

Model Simulation on Renal Function Effect

Each simulated vancomycin dosage regimen provided particular trough concentration that was used to calculate the risk of nephrotoxicity. The trough concentration had been classified into several groups based on the referenced study which are trough concentration at <10 mg/L, 10 – 15 mg/L, 15 – 20 mg/L, >20 mg/L.17 The nephrotoxicity occurrences were 5%, 21%, 20%, and 33%, respectively. In order to get more detailed figure of trough concentration, the present study further classified the trough concentration >20 mg/L into 20-35 mg/L and >35 mg/L.

Risk of nephrotoxicity in each group was calculated by multiplying the proportion of achievement of each trough range or the plateau concentration with the occurrence of nephrotoxicity in that same range. The total risk of nephrotoxicity was determined by adding the risk of nephrotoxicity in each range of trough or plateau concentration.

RESULTS

Our study demonstrated that at MIC of 0.5 mg/L, any vancomycin intermittent dosage regimens provided 100.00% PTA. However, MIC of 1.0 mg/L only provided 84.41% PTA when administered standard dose of vancomycin, defined as 1 g every 12 hours or total dose of vancomycin 2 g/day. Likewise, vancomycin 3 g/day and 4 g/day were needed to achieve PTA of >80% for higher MIC of 1.5 mg/L and 2 mg/L, respectively. **Figure 1** presented the PTA of several vancomycin intermittent dosage regimens against each MIC value of MRSA. **Figure 2** portrayed the comparison between percentage of PTA of each intermittent dosage regimen and the cumulative percentage of MIC distribution of MRSA strain. Our finding also indicated that at MIC of 2 mg/L, we needed the intermittent dosage regimen of 4 g/day, either given as 1 g every 6 hours or 2 g every 12 hours, to achieve MIC90.

Results from the PTA calculation were used to calculate the CFR. Highest CFR of 94.40% and 93.57% were from vancomycin 1 g every 6 h and 2 g every 12h, respectively while standard dose of vancomycin and total dose of vancomycin 3 g/day provided approximately 51% and 73% CFR, respectively (**Figure 3**). **Table 2** presented the sensitivity analysis of intermittent dosage regimens of vancomycin. The analysis showed that, if 50% of MRSA population had MIC value >1.0 mg/L, the standard dosage regimen will only grant CFR <50 %. Intermittent infusion with dosage regimen of 3 g/day was not optimal when used with MIC 2.0 mg/L while the intermittent dosage regimen 4 g/day could maintain CFR >80% for all population at the same MIC.

Trough concentrations of each dosing regimen were presented in **Figure 4**. Approximately 17% of standard dose regimen confered trough at 5-10

Table 2. The percentage of CFR achievement for intermittent dosage regimens with different proportion of MIC distribution.

Proportion of MRSA with particular MIC value (%)				Van 1g every 12h	Van 1g every 8h	Van 1g every 6h	Van 1.5g every 12h	Van 2g every 12h
0.5	1.0	1.5	2.0	CFR (%)	CFR (%)	CFR (%)	CFR (%)	CFR (%)
100	0	0	0	100.00	100.00	100.00	100.00	100.00
50	50	0	0	92.20	100.00	100.00	100.00	100.00
0	100	0	0	84.41	100.00	100.00	100.00	100.00
0	50	50	0	49.90	92.66	100.00	92.16	100.00
0	50	25	25	46.05	79.75	96.61	79.28	96.08
0	50	0	50	42.20	66.84	93.22	66.39	92.16
0	0	100	0	15.39	85.33	100.00	84.33	100.00
0	0	50	50	7.69	59.50	93.22	58.56	92.17
0	0	0	100	0.00	33.68	86.44	32.79	84.33

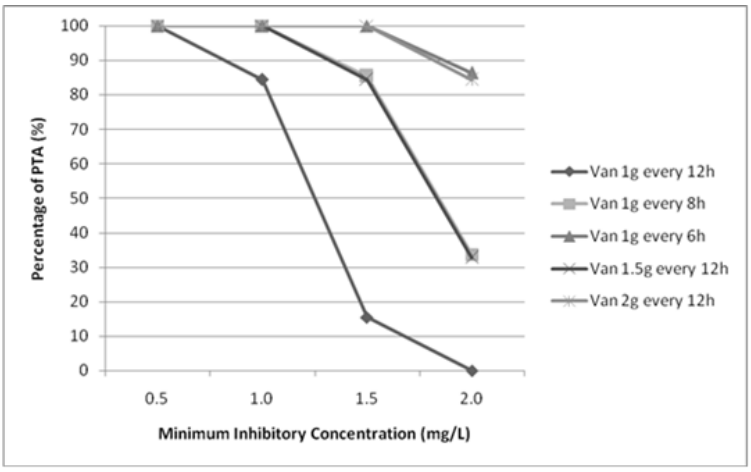

Figure 1. Percentage of PTA achievement of intermittent dosage regimens.

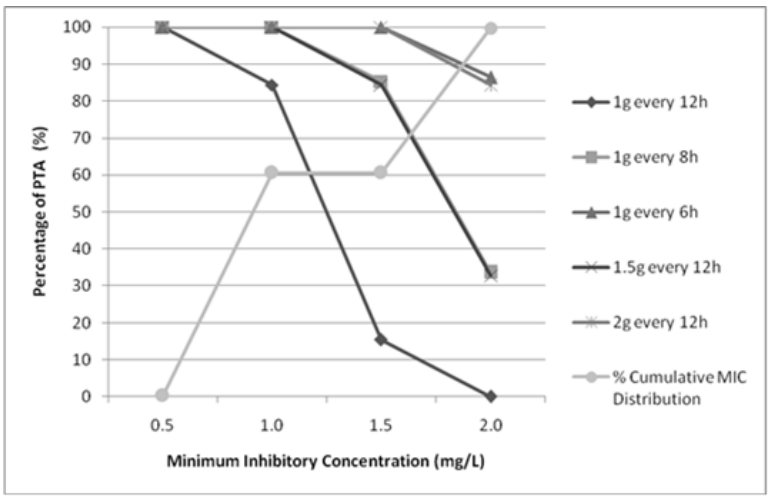

Figure 2. Comparison of percentage PTA achievement of intermittent dosage regimens and cumulative MIC distribution of MRSA strain.

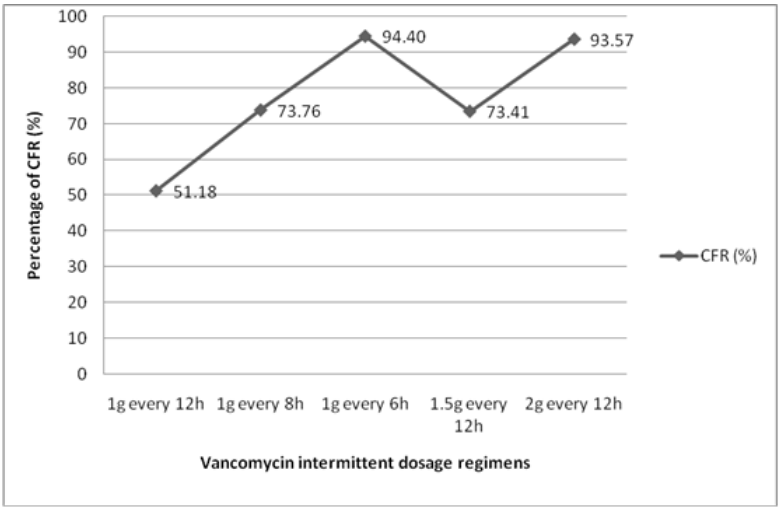

Figure 3. Percentage of CFR achievement of intermittent dosage regimens.

mg/L, while the highest trough concentration, i.e:>35 mg/L, was only afforded by total daily dose 4 g, either given as 1 g every 6 hours (34.78%) or 2 g every 12 hours (18.68%). Total risk of nephrotoxicity for each intermittent dosage regimen was presented in **Figure 5**. Standard dose of vancomycin afforded the lowest risk of nephrotoxicity (18.27%). The highest risk of nephrotoxicity was afforded from dosage regimen 1 g every 6 hours (32.96%).

DISCUSSION

The present simulation study was performed to assist clinicians optimizing vancomycin in the era of MIC creep. The lowest total daily dose simulated in our study was 1 g every 12 hours can afford desired PTA >80% for MRSA infection with MIC 0.5 mg/L and 1.0 mg/L. Our finding was supported by Kuti, et al and Patel, et al.[23,24] The similar results were obtained for both MIC 0.5 mg/L and 1.0 mg/L. These findings suggested

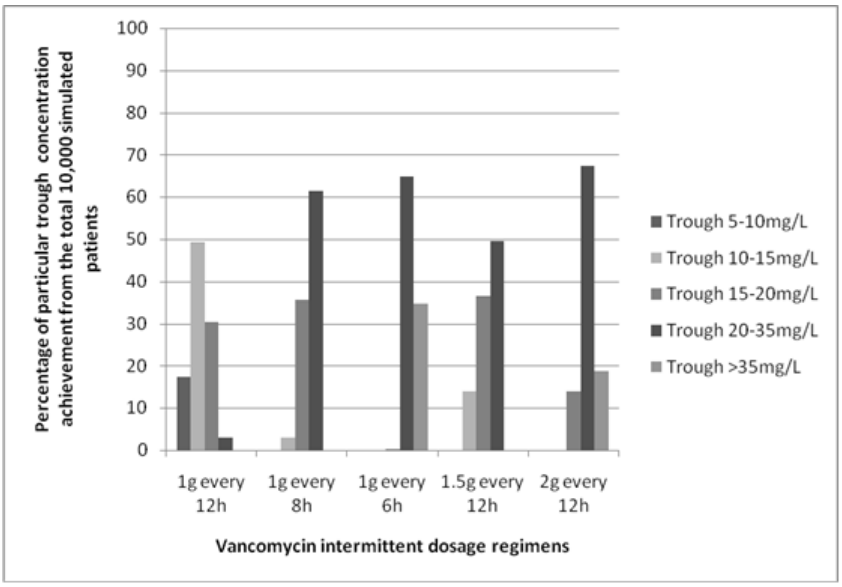

Figure 4. Percentage of particular trough concentration achievement of intermittent dosage regimens.

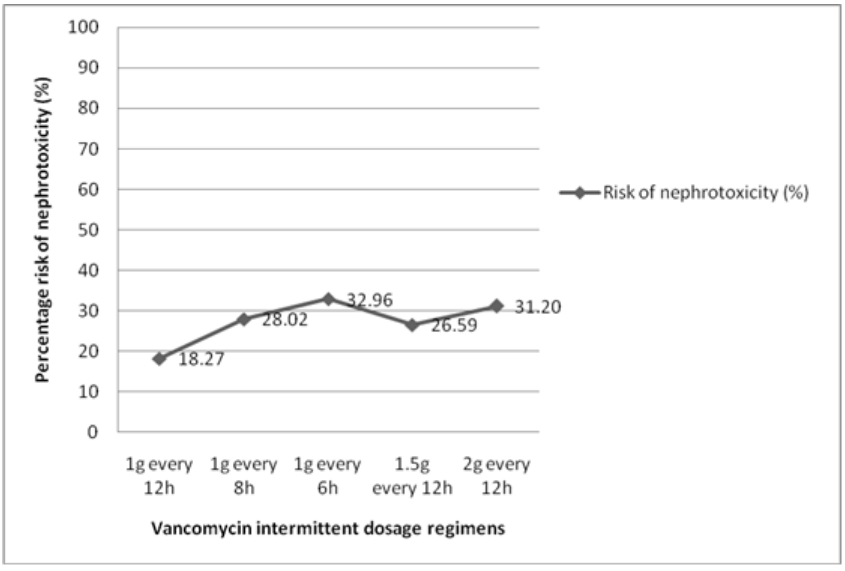

Figure 5. Risk of nephrotoxicity of several intermittent dosage regimens with concomitantly given other nephrotoxic agents.

the ramification that no further advantages could be granted by giving more intensive vancomycin dosage regimens, either increased the vancomycin dose or given more frequently particular dose of vancomycin to treat infection caused by MRSA with MIC ≤1 mg/L.

However, standard intermittent dosage regimen will not achieve the desired PTA when used to treat MRSA with MIC 1.5 mg/L. To our knowledge, this study was the only study that analyzed the achievement of PTA for treating MRSA with MIC 1.5 mg/L. Intermittent dosage regimens with total daily dose of 3 g would be best recommendation to achieve PTA >80% to treat MRSA with MIC 1.5 mg/L. While MRSA with MIC 2.0 mg/L, finding from present study was in accordance with the findings of study conducted by Kuti, et al[23] and Patel, et al[24] to support the use of vancomycin intermittent dosage regimens with total daily dose 4 g to achieve the desired PTA value.

All PTA in intermittent dosage regimens were at steady state condition as recommended by the Infectious Diseases Society of America (IDSA) guideline.[5] This study also presented analysis of PTA for each intermittent dosage regimen against percent cumulative MIC distribution of MRSA to present the MIC50 and MIC90 of MRSA strain (**Figure 2**). Based on cumulative MIC distribution, 50% of MRSA had MIC ≤1 mg/L. Standard dosage regimen would be able to achieve MIC50. It was not required more intensive vancomycin dosage regimens to achieve MIC50. However, to achieve MIC90, more intensive dosage regimen was needed. Ninety percent of MRSA strain in EUCAST database had an MIC between 1.5 mg/L to 2.0 mg/L. Only dosage regimens with a total daily dose 4 g, either given as dosage regimen 1 g every 6 hours or 2 g every 12 hours, could afford MIC90 based on this MIC distribution data.

Specific dosage regimen afforded more favourable PTA than others in certain MIC. In general, the value of PTA was very helpful to guide the health care professional in determining the dose of vancomycin for definite antibiotic treatment after MIC disclosed. However, as empiric antibiotic treatment, it is inconceivable to retrieve MIC value at the time of treatment initiation; thus PTA might not be advantageous. In contrast, the CFR would be more beneficial with regards to estimation of probability to be success when using vancomycin intermittent dosage regimen in random MIC value of susceptible MRSA strain.

The present study revealed that the most intensive intermittent dosage regimens, either given as 2 g every 12 hours or 1 g every 6 hours, were needed to achieve desired CFR value. Finding of present study was consistent with study from del Mar Fernandez de Gatta, et al.[25] conducted in patients with malignant haematological disease and study from Revilla, et al.[12] conducted in ICU patients. The MIC distribution of Staphylococcus aureus in their studies were similar to the EUCAST database which most MIC value was 1.0 mg/L. They found that vancomycin with total daily dose 2 g provided the lowest CFR achievement, while total daily dose 4 g achieved the desired CFR value. Unfortunately, the authors did not clearly state the method of vancomycin administration whether given as the intermittent infusion or continuous infusion.

Results from our sensitivity analysis for intermittent dosage regimens pointed out several important findings. Intermittent standard dosage regimen could afford CFR >80% when MRSA strain had MIC <1.0mg/L. In the setting where most of identified MRSA strain had MIC >1.0 mg/L, higher total daily dose of intermittent was ultimately needed. Total daily dose of 3 g is suggested to achieve CFR >80% when no MRSA with MIC 2.0 mg/L. Nonetheless, if there are 25% of MRSA with MIC 2.0 mg/L, the CFR achievement of intermittent dosage regimen of 4 g/day would be the best option to achieve optimal CFR. Lastly, if all identified MRSA strain (100%) had MIC 2.0 mg/L, the 84.33% PTA could be afforded by intermittent dosage regimens 4 g/day.

Our sensitivity analysis emphasizing the used of higher dose of vancomycin in settings where MRSA with MIC >1.0 mg/L. Canut, et al[26] conducted a study in 3 different European countries, including: Belgium, United Kingdom/ Ireland, and Spain, and each country had different profile of MIC distribution. There were less than 3% and almost 20% of MIC 2.0 mg/L in Spain

and United Kingdom/Ireland, respectively while all MRSA in Belgium had MIC <1.0 mg/L. Vancomycin at least 1 g every 8 hours or 2g every 12 hours were needed to achieve CFR >90% in Spain and United Kingdom/Ireland, respectively. Our sensitivity analysis also recommended vancomycin with total daily dose 4 g, either 1 g every 6 hours or 2 g every 12 hours, in Thai settings where approximately 25% of MRSA had MIC 2.0 mg/L.

With regards to risk of nephrotoxicity, intermittent dosage regimens presented in our study had similar nephrotoxicity conducted in Patel, et al where four dosage regimens simulated which were: 500mg every 12 hours, 1 g every 12 hours, 1.5 g every 12 hours, and 2 g every 12 hours.[24] The occurrences of the nephrotoxicity for each dosage regimen were 10%, 16%, 25%, and 34%, respectively. As a result, more aggressive dosing regimens are more likely to decline patient's renal function.

Beside several important findings were elucidated from the present study, the authors also acknowledged several limitations. First limitation was the PTA and risk of nephrotoxicity might be overestimated as a prediction for empirical treatment because the population PK equation models were measured after multiple doses of vancomycin administration. Moreover, superimposed method applied to calculate the vancomycin concentration at steady state condition might also contribute to the overestimated results. Second limitation was the assumption that the simulated patients had no renal insufficiency. Therefore, our recommendations could not be applied to all Thai critically ill patients. Further study is necessary to determine the best dosage regimen for critically ill population with advanced renal impairment. Final limitation was related with another MRSA virulence factors such as biofilm production. This might need different desired PK-PD indices when vancomycin is intended to overcome MRSA strain. Further investigations are in need whether desired AUC0-24/MIC ≥400 mg.hr/L could also effectively use as the surrogate marker of vancomycin efficacy for MRSA strain with biofilm production.

CONCLUSION

Standard dose of vancomycin could potentially not achieve the desired PK/PD indices if it was used to treat MRSA infection with "MIC Creep" phenomenon. Instead, vancomycin 3 g/day, either given as 1 g every 8 hours or 1.5 g every 12 hours, might be the best recommended empirical dose of vancomycin in the setting where MRSA has MIC 1.5 mg/L. The best dosage regimen for each setting should have a balance between high achievement of efficacy and acceptable risk of nephrotoxicity. However, it was difficult to make a threshold of the acceptable risk of nephrotoxicity for particular vancomycin dosage regimen. No consensus of the threshold of the acceptable risk of nephrotoxicity could be found. Further studies are needed to verify the conclusions drawn from these simulations.

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