Pharmaceutical Sciences, 2021, 27(2), 201-208
doi:10.34172/PS.2020.70
https://ps.tbzmed.ac.ir/

Research Article

Evaluation of the Association between Trough and Area Under the Curve to Minimum Inhibitory Concentration Ratio (AUC24/MIC) of Vancomycin in Infected Patients with Methicillin Resistant *Staphylococcus aureus* (MRSA)

Ayda Esmaeili[1], Mohammadreza Salehi[2], Nava Makhdomi[3], Yalda H. Ardakani[4], Mehdi Rajabi[3,5], Soha Namazi[6*]

[1]*Clinical Pharmacy Department, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran.*
[2]*Department of Infectious Diseases and Tropical Medicines, Imam Khomeini Complex Hospital, Tehran University of Medical Sciences, Tehran, Iran.*
[3]*Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.*
[4]*Biopharmaceutics and Pharmacokinetic Division, Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*
[5]*Department of Clinical Pharmacy, University Hospitals of North Midlands NHS Trust, United Kingdom.*
[6]*Clinical Pharmacy Department, Faculty of Pharmacy, Tehran University of Medical Sciences,Tehran, Iran.*

Article Info

Article History:
Received: 13 April 2020
Accepted: 28 August 2020
ePublished: 2 January 2021

Keywords:
-Vancomycin
-AUC24/MIC
-Trough serum level
-Methicillin-resistant *Staphylococcus aureus* (MRSA)
-Therapeutic drug monitoring (TDM)

Abstract

Background: The recent studies emphasized on the correlation of vancomycin antibacterial effect with pharmacokinetics properties such as the area under the curve/minimum inhibitory concentration (AUC_{24}/MIC) ≥400 and serum trough level 15-20 mg /L in the patients with severe infection with methicillin-resistant Staphylococcus aureus (MRSA). The purpose is to assay the vancomycin pharmacokinetic properties in our population and evaluates the correlation between AUC_{24}/MIC and trough serum level of vancomycin in given patients.

Methods: The patients with a positive MRSA culture, treated with vancomycin, were enrolled in this cross-sectional study. Three plasma samples were obtained during the study including 30 min before fourth and the fifth dose as trough levels and 1 hour after the fourth dose as peak level to determine AUC_{24}. E-TEST determined the MIC of vancomycin.

Results: Thirty-eight patients with an average age of 48.33±16.44 were enrolled in this study. The mean ± SD of MIC was 0.99±0.30 mg/L. Thirty-four patients reached the adequate therapeutic range of AUC_{24}/MIC ≥ 400 due to the standard vancomycin dosing method. In comparison, only 7 and 10 patients had the first and second trough levels in target intervals of 15-20 mg/L, respectively. Due to the receiver operating characteristic curve test (ROC test), the trough level after the fourth dose had a strong correlation with target AUC_{24}/MIC with a sensitivity of 94.1% and specificity of 75.0%.

Conclusion: This study concluded using only a trough level is not appropriate for therapeutic drug monitoring (TDM) of vancomycin. In our population, target AUC_{24}/MIC (≥ 400) had a reasonably strong correlation with the trough level before the fifth dose which achieved with trough level ≥10.81 mg/L and MIC< 1 mg/L.

Introduction

Vancomycin as glycopeptide is an antibacterial which performs by inhibiting the cell wall biosynthesis was used since mid- 1950s to treat the multiple drug-resistant gram-positive bacteria such as *Enterococcus sp, Streptococcus sp, Staphylococcus sp.*[1,2] Vancomycin as a first-line for treating methicillin-resistant *staphylococcus aureus* (MRSA) with minimum inhibitory concentration (MIC) less than 1.5 mg/L, widely ordered in the hospitals ,especially in critical care settings.[1] Due to the vancomycin pharmacodynamics and pharmacokinetic properties, it is known as a time and concentration-dependent antibiotic. Due to the recent studies, the area under curve (AUC) ratio to MIC equal or more than 400 has a correlation with anti-bacterial effect against MRSA,[3,4] Due to the Son *et al.*[5] study, AUC_{24}/MIC less than 397.2 (by E-test) resulted in treatment failure. The meta-analysis by Prybylski *et al.*[6] indicated that the vancomycin trough serum levels of more than 15 mg/L did not lead to decrease in treatment failure ratio. Due to the studies, trough serum levels greater than 10 mg/L is necessary to reach AUC_{24}/MIC ≥ 400, but more than 50%

*Corresponding Author: Soha Namazi, E-mail: namazisoha@yahoo.com

of patients obtained the goal of AUC_{24}/MIC ≥ 400, while their trough levels are less than 15 mg/L.[7,8] In contrast to the trough levels of vancomycin ≥ 15 mg/L, while the AUC_{24}/MIC value between 400 and 600 did not have a close association with vancomycin induced nephrotoxicity.[8,9]

The other complication shows the vancomycin resistance or less susceptible *staphylococcus aureus* (*Vancomycin-resistant Staphylococcus aureus* and *vancomycin-intermediate Staphylococcus aureus*) with MIC > 2 mg/L as a result of irrational vancomycin dosing and use.[10] On the other hand, MIC ≥ 1.5 mg/L is a predictor of treatment failure with vancomycin, and due to the guidelines, it's recommended to use other antibiotics such as linezolid as the first line of therapy instead of vancomycin;[1,11] therefore, it is the best practice to identify the MIC pattern of *staphylococcus aureus* in any given hospitals. On the other hand, there wasn't any published study that assesses pharmacokinetic properties of vancomycin in the non-critical ill general population in Iran.

The purposes of present study were to evaluate the pharmacokinetic properties of vancomycin in our general ill population, assess the correlation of AUC_{24}/MIC and steady-state trough levels of vancomycin and show the resistance pattern of MRSA in our hospital.

Materials and Methods

Method

This cross-sectional study was conducted at Imam Khomeini Hospital Complex affiliated to Tehran University of Medical Sciences (TUMS) in Tehran, Iran; patients (above 18 years old) with at least one positive blood, sputum, synovial fluid and cerebrospinal fluid (CSF) or other sources culture for MRSA were recruited in this study from October 2017 to the late December 2018. All patients signed informed consent letter before enrolling in this study. The Ethics Committee of TUMS approved this study, reference number; 1396/99. The exclusion criteria were as follows: dead in 3 days, changed in vancomycin dose within 72 hours, any intolerance or history of hypersensitivity reaction to vancomycin, acute kidney injury (AKI) due to RIFEL criteria[12] or chronic kidney disease with estimated glomerular filtration rate (eGFR) <15 ml/min or dialysis[13], lack of indication to receive the vancomycin on based our guidelines. Demographic, clinical, and laboratory data of patients were collected from their files and recorded in the gathering datasheet.

The intermittent base vancomycin dosing, prescribed with a loading dose of 20 mg/kg (maximum 2 gr) and then, 30 mg/kg/day (maximum total daily dose 3 gr/day), twice or three times daily, or dose adjusting due to eGFR which calculated with Cockcroft–Gault formula[14], as a maintenance dose until the clinical/laboratory indications of infection eradication. We didn't have any intervention in the vancomycin dosing regimen. Three blood samples were collected during the treatment to calculate the AUC_{24} of vancomycin as follows: the first sample was collected 30 minutes before the fourth dose of vancomycin as a first trough level, one hour after receiving the fourth dose as a peak serum level and the last sample 30 minutes before the fifth dose as second trough level, respectively.

All blood samples were centrifuged at 2500-3000 rpm for 10 minutes for plasma separation. A quantitative luminescent analysis method used to assay the vancomycin concentration with an Abbott analyzer instrument (USA). Inter and Intra assay variations of the instrument were 3-7.1% and 1.8-2.4%, respectively.

The vancomycin levels were used to calculate AUC_{24}, k elimination (K_e), the volume of distribution (V_d), half-life, and the clearance of vancomycin for each patient.[15,16] Due to each patient's MIC, AUC_{24}/MIC were calculated, and our goals were AUC_{24}/MIC≥400 and/or vancomycin trough level ≥ 15 mg/L and <20 mg/L.

The MIC of vancomycin was determined in MRSA detected samples with E test method, the kits were bought from Liofilchem S.r.I Company, Italy. All mentioned tasks were carried out at the microbiological laboratory of Imam Khomeini Hospital Complex.

Pharmacokinetic analysis

The standard one-compartment open model was conducted in this study using three serum samples obtained during the four and fifth dose intervals at a steady-state for individualized targeting of therapeutic drug levels.[17] Using two post-dose serum concentrations (the peak serum and second trough levels), the elimination rate constant (K_e) of each patient was directly calculated [K_e= (ln Css_{max}-ln Css_{min})/T-t', where Css_{max} and Css_{min} are the steady-state peak and trough serum concentrations and T and t' are the infusion time and dosage interval, respectively]. The half-life of compound was estimated with the elimination rate constant [$t_{1/2}$=0.693/K_e]. The volume of distribution is calculated utilizing [V_d=D/ (Css_{max}- Css_{min})], where D is the vancomycin dose. Each individual calculated that Ke and Vd parameters were used in one open compartment model to compute other required pharmacokinetics, including the patient's total body clearance (CLT) and AUC (0-∞). These two future parameters were calculated as [CL_T=K_e × V_d] and [$AUC_{(0-\infty)}$=D/ CL_T], respectively.[18]

Statistical analysis

For data analysis, the patients were categorized into two groups as follows: patients with eGFR<60ml/min, patients with eGFR ≥ 60 ml/min. SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA) was used to conduct the statistical analysis. Continuous and categorical data were reported as mean ± SD and median (interquartile range), respectively. The Kolmogorov–Smirnov test performed the normality distribution of numerical variables. Parametric and non-parametric variables were compared with an independent t-test and Mann-Whitney U test, respectively. Pearson chi-square and Fisher's exact test were used to evaluating the correlation of AUC_{24}/ MIC ≥ 400, with first and second trough levels of vancomycin. The receiver operating characteristic (ROC) curve was used to determine the

threshold in trough level to have AUC_{24}/MIC ≥ 400 with strong specificity and sensitivity. AUC more than 0.8 is an indication for good accuracy.[19] The p-value of less than 0.05 were showed a significant difference.

Results

The total 45 patients considered, it was eligible to enroll in this study; however, 7 patients were excluded due to: death within 72 hours (2 patients), early switch to oral antibiotics due to early hospital discharge (2 patients), AKI induced with the vancomycin (2 patients)[20], discontinuing vancomycin earlier than the duration of the study (1 patient). Finally, complete data of 38 patients, including 9 females and 29 males were analyzed. The demographic and diagnostic data were shown in Table 1.

The mean ±SD of the MIC of MRSA in collected samples was 0.99±0.30, and 73.68% of these selected samples had MIC≤ 1 mg/L, and just MIC of 6 patients was 1.5 mg/L.

The serum levels of vancomycin and pharmacokinetic analyses were summarized in Table 2.

The comparison of pharmacokinetics in patients with GFR< 60 ml/min and ≥ 60 ml/min was shown in Table 3.

Figure 1 illustrated the first and second trough level data of patients with AUC_{24}/MIC < 400 and others. The MIC of 3 patients with AUC_{24}/MIC < 400, were 1.5 mg/L. Three (75.00%) and two (50.00%) patients with AUC_{24}MIC< 400

Table 1. Patient characteristics and diagnostic data at baseline (N= 38).

Variables	Mean ± SD
Age, year	48.33±16.44
Weight (Kg)	67.78±13.98
Height (cm)	168.08±11.65
BMI (Kg/M2)	23.71±2.86
Urea (mg/dL)	38.89±12.77
Creatinine (mg/dL)	1.01±0.26
Etiology	**Patients number (percentage %)**
Neutropenic fever	8 (21.05%)
Sepsis	6 (15.70%)
Surgery (general)	5 (13.15%)
Osteomyelitis	4 (10.52%)
Acute Myeloid Leukemia	3 (7.89%)
Squamous Cell Carcinoma in the buccal	3 (7.89%)
Infection after fracture	2 (5.26%)
Liver transplant	2 (5.26%)
Meningitis	2 (5.26%)
Cerebrovascular Accident	1 (1.63%)
Infected Liposarcoma	1 (1.63%)
Antibiotic IV therapy regimens + vancomycin	**Patients number (percentage %)**
Meropenem	16 (42.10%)
Clindamycin + Ciprofloxacin	5 (13.15%)
Imipenem	4 (10.52%)
Meropenem + Cotrimoxazol	3 (7.89%)
Ceftriaxon	3 (7.89%)
Cefazolin	2 (5.26%)
Meropenem + Ciprofloxacin	2 (5.26%)
Piperacillin- tazobactam	2 (5.26%)
Ciprofloxacin	1 (2.63%)

Table 2. Serum levels of vancomycin and pharmacokinetics analyses (N=38).

Parameters	Mean ± SD
Trough 1[a] (mg/L)	14.50 ± 6.33
Trough 2[b] (mg/L)	17.36± 6.74
Peak level (mg/L)	36.60 ± 13.32
AUC[c] (mg*hr/ L)	660.14 ± 289.66
AUC/ MIC[d]	730.61 ± 398.85
Ke[e] (1/hr)	0.03 ± 0.01
$T_{1/2}$[f] (hr)	22.82 ± 10.14
Volume of distribution (L)	54.28 ± 25.44
Volume of distribution/ weigh (L/kg)	0.82 ± 0.43
Clearance vancomycin (mL/minute/kg)	0.44 ± 0.23
eGFR[g] (ml/min)	93.55 ± 45.42

[a]Sample was collected 30 minutes before fourth dose of vancomycin at steady state, [b]Sample was collected 30 minutes before fifth dose of vancomycin at steady state, [c]area under the curve, [d]minimum inhibitory concentration, [e]elimination rate constant, [f]half- life, [g]estimated glomerular filtration rate.

Table 3. Serum levels of vancomycin and pharmacokinetics analyses according to eGFR[a] less than 60 ml/min or higher (n=38).

Parameters	eGFR[a]<60ml/min (N=7)	eGFR1≥60ml/min (N=31)	P- value[b]
Trough 1[c] (15-20 mg/L) (N%)	1(14.32%)	6 (19.45%)	0.76
Trough 2[d] (15-20 mg/L) (N%)	3 (42.93%)	7 (22.68%)	0.27
Ke[e] (1/hr)[e,f]	0.028 (0.019-0.032)	0.036 (0.027-0.041)	0.02
T1/2 (hr)[e,g]	24.43 (21.82-36.35)	19.47 (16.91-25.43)	0.02
Volume of distribution (L)[e]	51.91 (38.35-60.12)	49.32 (36.86- 68.31)	0.94
Clearance of vancomycin (L/hr)[e]	1.2 (0.9-1.6)	1.7 (1.4-2.1)	0.04

[a]Estimated glomerular filtration rate, [b]P-value <0.05 was considered as significant. [c]Sample was collected 30 minutes before fourth dose of vancomycin at steady state, [d]Sample was collected 30 minutes before fifth dose of vancomycin at steady state, [e]The value reported as median (interquartile range), [f]elimination rate constant, [g]half- life

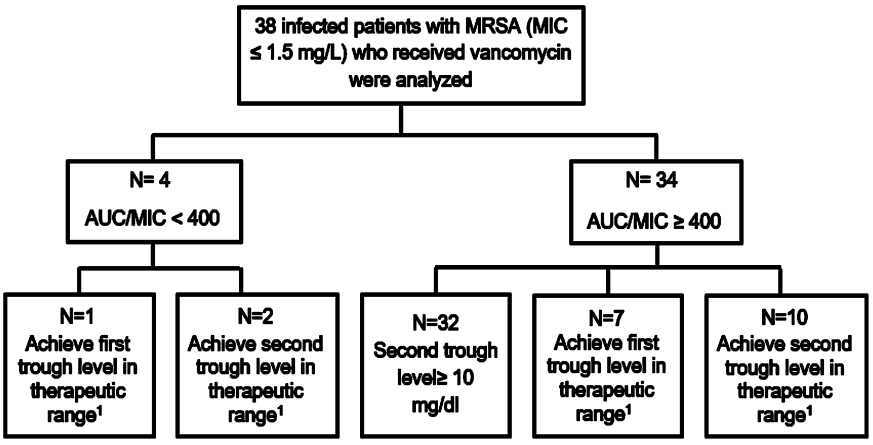

Figure 1. AUC/MIC and therapeutic trough level of vancomycin in patients with infected by MRSA. The first trough level: sample was collected 30 minutes before fourth dose of vancomycin at steady state The second trough level: sample was collected 30 minutes before fifth dose of vancomycin at steady state. Therapeutic range: serum level of vancomycin is equivalent to 15-20 mg/dl.

had vancomycin, first and second trough level less than 10 mg/L, respectively.

The clearance of vancomycin had a strong correlation (r: 0.84; p-value < 0.05) and liner pattern (slope: 0.01) with eGFR which tested with Pearson.

AUC_{24}/ MIC was moderately correlated with second trough (Figure 2), first trough level, and peak level of vancomycin with r: 0.59, 0.51, and 0.52, respectively (p-value < 0.05).

Due to ROC test which showed the cutoff point in the second trough level of vancomycin to have AUC/MIC ≥ 400, was 10.81 mg/L with sensitivity and specificity of 94.10% and 75.00%, respectively; the area under the curve was 0.84 with p-value<0.05 (CI 95%= 0.62-1.06). For peak and first trough level no cut off was defined due to p-value > 0.05.

Discussion

Due to the recent studies, AUC_{24}/MIC ratio equal and greater than 400 has played the main influence on patients' clinical response to therapy with vancomycin, and also decrease in risk of treatment failures was observed by higher AUC_{24}/MIC ratio.[5,21,22] The AUC_{24} measurement depend on method of infusion (continues and intermittent)[23], intermittent base dosing method was used in this study.

The present study was performed to evaluate the correlation of AUC_{24}/MIC and trough level of vancomycin based on the standard dosing protocol, measure pharmacokinetic factors, and show the pattern of MIC in MRSA positive culture in our population at Imam Khomeini hospital complex, Teharan, Iran, simultaneously.

As there was no published study to evaluate vancomycin pharmacokinetics in Iranian healthy population to compare our results, so we compared our pharmacokinetic out-comes with other general papulations. It's known that V_d was influenced with the different patient's related parameters as follows: age, renal function, muscle mass, mechanical ventilation, nutrient status (such as hypo-proteinemia which altered protein binding ration of the drug), changes in the integrity of vessel in sepsis, unstable hemodynamic, which none of participates in the present study had these situations.[24-26]

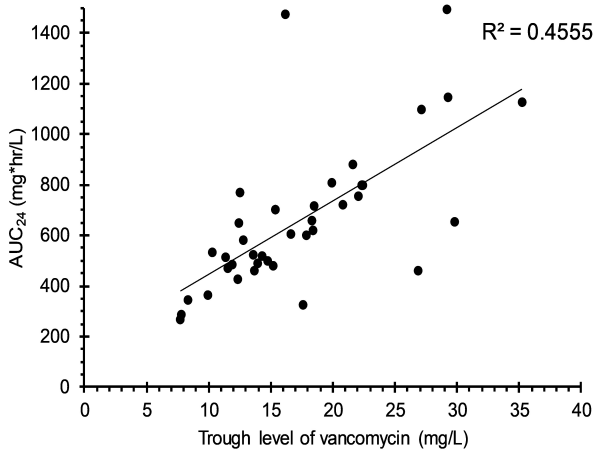

Figure 2. The AUC_{24} versus vancomycin trough concentration before fifth dose.

According to the literature, in adult with normal renal function (GFR>60 ml/min), an average vancomycin half-life is 8 hr (rang=7-9)[27], range of V_d is 0.4-1 L/kg,[28] and clearance range is 0.71 to 1.31 mL/minute/kg.[29]

In our subjects with normal renal function, mean±Sd of V_d was 0.82 ± 0.46 L/kg. It's known that V_d was influenced with the different patient's related parameters as follows: age, renal function, muscle mass, mechanical ventilation, nutrient status (such as hypo-proteinemia which altered protein binding ration of the drug), changes in the integrity of vessel in sepsis, unstable hemodynamic, which none of participates in the present study had these situations,[24-26] therefore our V_d was in rang of healthy population.

clearance of vancomycin and the average half-life of our patients were 0.46 ± 0.25 mL/minute/kg and 19.47 hr (16.91-25.43) respectively; as a consequence, K_e and clearance of vancomycin in our patients were lower, and half-life was longer in comparison to other general populations; so we need to set up further studies to determine the kinetic properties of vancomycin in our population.

The MIC of MRSA isolated from 38 patients' various clinical specimens were equal or lower than 1.5 mg/dl (mean ± SD: 0.99±0.30), which means all incubated *S.aureus* were vancomycin sensitive; However Shekarabi *et al.* reported that the prevalence of vancomycin-intermediate *S.aureus* was increasing with the time in hospitals of Iran.[30] Recently, Razegi *et al.* reported that 35 out of 78 MRSA collected positive culture, had MIC_{BMD} > 2 mg/dl, simultaneous 5 cases of them had MIC_{BMD} 8 mg/dl that means vancomycin-intermediate *S.aureus* (VISA).[31]

Due to our results, 34 patients (89.50%) had AUC_{24}/MIC greater than 400, while just 4 and 7 patients had the first and second trough levels in therapeutic range (15-20 mg/L). There was a moderate correlation between AUC_{24}/MIC and first and second trough levels (r: 0.51, r: 0.59, p-value < 0.05).

So, it was concluded that it is not necessary to reach therapeutic trough range (15-20 mg/L) until we have AUC_{24}/MIC_{Etest} equal or greater than 400 in patients with MIC_{Etest} <1 mg/dl which asserted with Patel *et al.*[32] before us. Regarding a recent emphasis on AUC_{24}/MIC greater than 400, our study showed there is no need to increase the vancomycin doses to reach a level of 15-20 mg/L up to have goal AUC_{24}/MIC.

The broth micro dilution [BMD] method is a standard gold method for measuring MIC.[33] There are differences in MIC of micro-organism determined by the BMD method or E-Test. Still, as the E-test result prepares faster than BMD, our hospital uses an E-test to identify MIC of micro-organism in there.[34] Due to some studies[35,36] which presented MIC measured with E-test is 1.5-2 fold higher than MIC of BMD; therefore, it seems that we used BMD to measure MIC, AUC_{24}/MIC would be over 400 again.

Shahrami *et al.*[37] study was conducted to compare the standard and individualized vancomycin dosing on 20 critically ill patients to achieved AUC_{24}> 400 and steady-state trough level> 15 mg/L. They reported that

individualization based dosing vancomycin is superior to standard dosing vancomycin to achieve therapeutic trough level of 15-20 mg/l and higher steady state AUC_{24}; Considering this study, 65.5% of patients (n=10) with standard dosing failed to achieve therapeutic trough level, but just 14.3% had AUC_{24} less than 400. Although the design of Shahrami study[37] was different to compare with ours, such as 1) subjects were critical ill, 2) had an intervention and 3) they did not measure MIC and just reported AUC_{24}; we both concluded that AUC_{24} was a better parameter to optimize vancomycin dosing.

Due to ROC test, if the second trough level sample were greater than 10.81mg/L, AUC_{24}/MIC would be more than 400 with good accuracy, specificity 75% and sensitivity 94% (p-value< 0.05, CI 95% (0.62-1.06)); our cut off point was in line with Rybak *et al.* results which showed that almost always AUC_{24}/MIC ratio was not achieved 400 or more with serum level of vancomycin less than 10 mg/L.[28] Additionally, it was noted in our population that the steady-state of the trough level of vancomycin was reached at least after the four doses. This observation is argued to be rational, due to the half-life of vancomycin in our population with GFR<60 ml/min and ≥ 60 ml/min which was 24.43 and 19.47 hr, while in healthy population, the range of vancomycin elimination half-life is suggested to be 6-12 hr.[38]

Khoie *et al.*39 accomplished a study in 22 patients with chronic kidney disease (15≤GFR≤60 mL/min) treated with vancomycin due to traditional dosing to determine AUC_{24}/MIC and trough level of forth dose. They expressed that the traditional method for dosing vancomycin was not proper to achieve the therapeutic level of vancomycin,[40] which was similarly confirmed by our investigation; However, the population of the two studies was different.

Our results showed the strong correlation between creatinine and vancomycin clearance with r: 0.84 and p-value < 0.05, similar to other studies.[24,41] Several pharmacokinetic studies have suggested many equations that showed the relation between the clearance of vancomycin and eGFR[42,43]; however, our study was subjected to limited sample size; Therefore, these equations were not considered to be a practical option.

Other recent studies noted that vancomycin MIC ≥ 1.5 mg/L for *Staphylococcus aureus* has the main role to predict the treatment failure and choosing a proper first-line antibiotics.[11,44] The average vancomycin MIC of MRSA in our study was 0.98 ± 0.28 mg/L, and vancomycin was prescribed as the first-line to treat the MRSA with usual dose 15-20 mg/kg twice daily (usually 2 gr per day), in our setting which was reasonable in patients with eGFR≥60 ml/min.

Like any other investigational studies, our study was subjected to limitations. The effect of vancomycin trough level versus AUC_{24}/MIC on clinical outcomes could not be compared in our patients. There are two reasons for these limitations: 1) patients received other antibiotics alongside vancomycin, 2) culture form site of infection was not conducted 72 hours after vancomycin starting to determine MRSA eradication. Therefore, further studies are necessary to confirm the association between clinical outcome and AUC_{24}/MIC.

The another limitation of the study is MIC detemination with E-test in this study which do not obey the European Committee on Antimicrobial Susceptibility Testing (EUCAST) reports.[45]

Conclusion

Our results showed that steady-state trough level base vancomycin dosing is not an appropriate method for therapeutic drug monitoring (TDM). In our patients, AUC_{24}/MIC ≥ 400 was achieved with trough level ≥10.81 mg/L of the fourth dose and MIC< 1 mg/L. The target $AUC_{24}/MIC_{E\text{-}test}$ (≥ 400) had reached in almost all patients (89.49%), meanwhile, just 7 and 10 of them achieved therapeutic steady-state trough level after receiving four and five doses, respectively.

Ethical Issues

All patients signed informed consent letter before enrolling in this study. The Ethics Committee of TUMS approved this study, reference number; 1396/99.

Author Contributions

AE: Conception and design of the study, assembly, analysis and/or interpretation of data the experiments and procedures, statistical analysis, Drafting and revision of the manuscript, MS: The experiments and procedures, confirmed the final manuscript. NM: Generation, collection, experiments and procedures, confirmed the final manuscript. MR: Design of the study, confirmed the final manuscript. YHA: Assembly, analysis and/or interpretation of data the experiments and procedures, statistical analysis, confirmed the final manuscript. SN: Conception and design of the study, the experiments and procedures, statistical analysis, corrected and confirmed the final manuscript.

Conflict of Interest

The authors claim that there is no conflict of interest.

References

1. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55. doi:10.1093/cid/ciq146
2. Stevens DL. The role of vancomycin in the treatment paradigm. Clin Infect Dis. 2006;42(Suppl 1):S51-7. doi:10.1086/491714
3. 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(13):925-42. doi:10.2165/00003088-200443130-00005

4. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the infectious diseases society of america, the american society of health-system pharmacists, and the society of infectious diseases pharmacists. Clin Infect Dis. 2009;49(3):325-7. doi:10.1086/600877
5. Song KH, Kim HB, Kim HS, Lee MJ, Jung Y, Kim G, et al. Impact of area under the concentration-time curve to minimum inhibitory concentration ratio on vancomycin treatment outcomes in methicillin-resistant *Staphylococcus aureus* bacteraemia. Int J Antimicrob Agents. 2015;46(6):689-95. doi:10.1016/j.ijantimicag.2015.09.010
6. Prybylski JP. Vancomycin trough concentration as a predictor of clinical outcomes in patients with *Staphylococcus aureus* bacteremia: A meta-analysis of observational studies. Pharmacotherapy. 2015;35(10):889-98. doi:10.1002/phar.1638
7. Iwamoto T, Kagawa Y, Kojima M. Clinical efficacy of therapeutic drug monitoring in patients receiving vancomycin. Biol Pharm Bull. 2003;26(6):876-9. doi:10.1248/bpb.26.876
8. Álvarez R, López Cortés LE, Molina J, Cisneros JM, Pachón J. Optimizing the clinical use of vancomycin. Antimicrob Agents Chemother. 2016;60(5):2601-9. doi:10.1128/aac.03147-14
9. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother. 2013;57(2):734-44. doi:10.1128/aac.01568-12
10. McGuinness WA, Malachowa N, DeLeo FR. Vancomycin resistance in *Staphylococcus aureus*. Yale J Biol Med. 2017;90(2):269-81.
11. Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Relationship between vancomycin mic and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob Agents Chemother. 2008;52(9):3315-20. doi:10.1128/aac.00113-08
12. Ricci Z, Romagnoli S. Acute kidney injury: Diagnosis and classification in adults and children. Contrib Nephrol. 2018;193:1-12. doi:10.1159/000484956
13. Kdigo 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (ckd-mbd). Kidney Int Suppl. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. doi:10.1159/000180580
15. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986;11(4):257-82. doi:10.2165/00003088-198611040-00001
16. Shargel L, Andrew B, Wu-Pong S. Applied biopharmaceutics and pharmacokinetics. Stamford: Appleton & Lange; 1999.
17. Ye ZK, Li C, Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: A systematic review. PLoS One. 2014;9(6):e99044. doi:10.1371/journal.pone.0099044
18. Jumah MTB, Vasoo S, Menon SR, De PP, Neely M, Teng CB. Pharmacokinetic/pharmacodynamic determinants of vancomycin efficacy in enterococcal bacteremia. Antimicrob Agents Chemother. 2018;62(3):e01602-17. doi:10.1128/aac.01602-17
19. Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression. NewYork: John Wiley & Sons; 2013. doi:10.1002/9781118548387
20. Pereira M, Rodrigues N, Godinho I, Gameiro J, Neves M, Gouveia J, et al. Acute kidney injury in patients with severe sepsis or septic shock: A comparison between the 'risk, injury, failure, loss of kidney function, end-stage kidney disease' (rifle), acute kidney injury network (akin) and kidney disease: Improving global outcomes (kdigo) classifications. Clin Kidney J. 2017;10(3):332-40. doi:10.1093/ckj/sfw107
21. Men P, Li HB, Zhai SD, Zhao RS. Association between the auc0-24/mic ratio of vancomycin and its clinical effectiveness: A systematic review and meta-analysis. PLoS One. 2016;11(1):e0146224. doi:10.1371/journal.pone.0146224
22. DiMondi VP, Rafferty K. Review of continuous-infusion vancomycin. Ann Pharmacother. 2013;47(2):219-27. doi:10.1345/aph.1R420
23. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the american society of health-system pharmacists, the infectious diseases society of america, the pediatric infectious diseases society, and the society of infectious diseases pharmacists. Am J Health Syst Pharm. 2020;77(11):835-64. doi:10.1093/ajhp/zxaa036
24. Medellín-Garibay SE, Romano-Moreno S, Tejedor-Prado P, Rubio-Álvaro N, Rueda-Naharro A, Blasco-Navalpotro MA, et al. Influence of mechanical ventilation on the pharmacokinetics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother. 2017;61(12):e01249-17 doi:10.1128/aac.01249-17
25. Usman M, Fobker M, Hempel G. Investigation of the age dependency of vancomycin clearance by population pharmacokinetic modeling. Int J Clin Pharmacol Ther. 2018;56(2):56-63. doi:10.5414/cp203033
26. Oyaert M, Spriet I, Allegaert K, Smits A, Vanstraelen K, Peersman N, et al. Factors impacting unbound vancomycin concentrations in different patient populations. Antimicrob Agents Chemother. 2015;59(11):7073-9. doi:10.1128/aac.01185-15
27. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO, Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother. 1982;21(4):575-80. doi:10.1128/aac.21.4.575
28. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Jr., Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the american society of health-system pharmacists, the infectious diseases society of america, and the society

of infectious diseases pharmacists. Am J Health Syst Pharm. 2009;66(1):82-98. doi:10.2146/ajhp080434
29. de Hoog M, Mouton JW, van den Anker JN. Vancomycin: Pharmacokinetics and administration regimens in neonates. Clin Pharmacokinet. 2004;43(7):417-40. doi:10.2165/00003088-200443070-00001
30. Shekarabi M, Hajikhani B, Salimi Chirani A, Fazeli M, Goudarzi M. Molecular characterization of vancomycin-resistant *Staphylococcus aureus* strains isolated from clinical samples: A three year study in Tehran, Iran. PLoS One. 2017;12(8):e0183607. doi:10.1371/journal.pone.0183607
31. Razeghi M, Saffarian P, Goudarzi M. Incidence of inducible clindamycin resistance and antibacterial resistance genes variability in clinical *Staphylococcus aureus* strains: A two-year multicenter study in Tehran, Iran. Gene Rep. 2019;16:100411. doi:10.1016/j.genrep.2019.100411
32. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. Vancomycin: We can't get there from here. Clin Infect Dis. 2011;52(8):969-74. doi:10.1093/cid/cir078
33. Dhand A, Sakoulas G. Reduced vancomycin susceptibility among clinical *Staphylococcus aureus* isolates ('the mic creep'): Implications for therapy. F1000 Med Rep. 2012;4:4. doi:10.3410/m4-4
34. Kuo CF, Lio CF, Chen HT, Wang YT, Ma KS, Chou YT, et al. Discordance of vancomycin minimum inhibitory concentration for methicillin-resistant *Staphylococcus aureus* at 2 μg/ml between vitek II, E-test, and broth microdilution. Peer J. 2020;8:e8963. doi:10.7717/peerj.8963
35. Jung Y, Song KH, Cho J, Kim HS, Kim NH, Kim TS, et al. Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant *Staphylococcus aureus* bacteraemia. Int J Antimicrob Agents. 2014;43(2):179-83. doi:10.1016/j.ijantimicag.2013.10.017
36. Brown J, Brown K, Forrest A. Vancomycin auc24/mic ratio in patients with complicated bacteremia and infective endocarditis due to methicillin-resistant *Staphylococcus aureus* and its association with attributable mortality during hospitalization. Antimicrob Agents Chemother. 2012;56(2):634-8. doi:10.1128/aac.05609-11
37. Shahrami B, Najmeddin F, Mousavi S, Ahmadi A, Rouini MR, Sadeghi K, et al. Achievement of vancomycin therapeutic goals in critically ill patients: Early individualization may be beneficial. Crit Care Res Pract. 2016;2016:1245815. doi:10.1155/2016/1245815
38. Zamoner W, Prado IRS, Balbi AL, Ponce D. Vancomycin dosing, monitoring and toxicity: Critical review of the clinical practice. Clin Exp Pharmacol Physiol. 2019;46(4):292-301. doi:10.1111/1440-1681.13066
39. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Kidney Int Suppl (2011). 2017;7:1-59. Erratum in: Kidney Int Suppl (2011). 2017 Dec;7(3):e1. doi:10.1016/j.kisu.2017.10.001
40. Khoei A, Soltani R, Emami J, Badri S, Taheri S. Therapeutic drug monitoring of vancomycin by auc(τ)-mic ratio in patients with chronic kidney disease. Res Pharm Sci. 2019;14(1):84-92. doi: 10.4103/1735-5362.251856
41. Ji XW, Ji SM, He XR, Zhu X, Chen R, Lu W. Influences of renal function descriptors on population pharmacokinetic modeling of vancomycin in chinese adult patients. Acta Pharmacol Sin. 2018;39(2):286-93. doi:10.1038/aps.2017.57
42. Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrob Agents Chemother. 1984;25(4):433-7. doi:10.1128/aac.25.4.433
43. Haeseker M, Croes S, Neef C, Bruggeman C, Stolk L, Verbon A. Evaluation of vancomycin prediction methods based on estimated creatinine clearance or trough levels. Ther Drug Monit. 2016;38(1):120-6. doi:10.1097/ftd.0000000000000250
44. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: A systematic review and meta-analysis. Clin Infect Dis. 2012;54(6):755-71. doi:10.1093/cid/cir935
45. European committee on antimicrobial susceptibility testing, breakpoint tables for interpretation of mics and zone diameters. European Society of Clinical Microbiology and Infectious Diseases. EUCAST, Basel, Switzerland. 2015.