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Evaluation of the local protocol of vancomycin-therapy based on targeted trough level and extrapolated area under the curve in Tengku Ampuan Rahimah General Hospital

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Abstract

This study aimed to evaluate the suitability and target concentration achievement of the current local protocol of vancomycin-therapy that is based on targeted trough level and extrapolated area under the curve in TAR hospital, Selangor, Malaysia. A retrospective case series was carried out among the inpatient cases of vancomycin therapy who aged 18 years and above using TDM reports and a validated Bayesian software; PrecisePK®. The collected data were analyzed using the SPSS tool to study the association between trough levels, AUC_{24}/MIC and other investigating factors. This study showed that 87.3% of study participants have AUC_{24}/MIC ≥ 800 mg.h/L which is beyond the recommended AUC_{24}/MIC. Only 2.7% of the trough readings have achieved the targeted AUC_{24}/MIC 400-600 mg.h/L. The findings indicated that AUC_{24}/MIC was significantly correlated with trough concentration and inversely with the MIC. The observed high AUC_{24}/MIC could be primarily attributed to the low MIC values in HTAR. The variation of MRSA MIC due to the different test methods and other technical concerns causes AUC_{24}/MIC interpretation to be arguable. Current study emphasizes the limitations of trough-guided dosage, as well as the complexity of the interpretation of the obtained high values of AUC_{24}/MIC. The abnormally low locally reported MRSA MICs ended up with very high AUC_{24}/MICs which needs the MIC tests to be relooked, technically. On the other hand, the vancomycin dose adjustment guidelines need to consider this between and within variations of MIC with its great impact on AUC_{24}/MIC.

Keywords: Vancomycin; Area under curve; Minimum inhibitory concentration; Bayesian analysis

Introduction

Vancomycin is a tricyclic glycopeptide antibiotic, commonly used treat serious inpatient infections caused by Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) infection(1). Vancomycin follows a time-dependent mechanism; hence the key to dosing vancomycin is to retain its plasma concentration above a particular threshold to ensure the therapy's effectiveness while avoiding resistance. Therapeutic drug monitoring (TDM) is required on many occasions of vancomycin therapy due to its narrow therapeutic index(2). Conventionally, the therapeutic range for vancomycin peak and trough levels is 20-40 µg/mLand 10-20 µg/mL, respectively(3). Practically, there is no consistency in existing vancomycin dose

recommendations or actual practice from hospital to hospital, each hospital follows a certain vancomycin therapy protocol, which is usually combined with customized therapy based on TDM results(3-4). The common practice is to assess and monitor the vancomycin trough level (targeting 15-20 µg/mL) after 4 doses when steady state is achieved. The recent Infectious Diseases Society of America (IDSA) vancomycin guideline indicates that AUC_{24}/MIC 400-600 mg.h/L determines vancomycin activity and by shifting the trough-based monitoring to AUC-based method, targeting AUC/MIC 400-600 mg.h/L, better results are expected(4). The aims of this study were to evaluate the current local protocol of vancomycin-therapy that is based on targeted trough level (summarized in Table 1) and extrapolated area under the curve in Tengku Ampuan Rahimah (TAR) general hospital, which is located in Klang, Malaysia(5)and to evaluate the achievement of the targeted trough level of vancomycin. To estimate vancomycin AUC from the individual serum concentration versus time profile, PrecisePK® (a validated Bayesian software)(6)was used. Then efficacy target AUC_{24}/MIC wasdetermined and compared to the local protocol in HTAR.

Methods

Study Design

This was a retrospective case series of inpatient cases of vancomycin therapy at Tengku Ampuan Rahimah General Hospital.

Study Settings

The internal therapeutic drug monitoring (TDM) forms of the hospital database at Tengku Ampuan Rahimah (TAR) general hospital, Shah Alam, Selangor, Malaysia were the source of data in this study. The recruitment of the study subjects followed a sequential manner and included the cases between December 2019 and January 2021 until the targeted sample size was achieved.

Study Participants

All adult cases (18 years old and above) who received intravenous vancomycin for minimum two full days with at least one measured concentration were included in the current study. Patients under vancomycin therapy with an expected survival of fewer than 72 hours and hemodialysis cases were excluded.

Sample Size

The required sample size was 143 vancomycin readings according to G-power® 3.1.9.7, considering the significance level (one-tailed) of 0.05, power 0.8 and effect size of 0.3.

Study Instrument

The required data were extracted from the hospital TDM forms. Since the reported plasma concentrations of vancomycin were not consistently trough levels (as per definition for trough level) a validated software, PrecisePK® v2.0.0.2.0.0 under lease from Healthware Inc., the U.S. was used to extrapolate the plasma concentrations of vancomycin and to estimate the AUC by individual serum concentrations.

Data Analysis

For normally distributed variables, the results were reported as mean ±SD, and for non-normally distributed variables, the results were reported as median (inter-quartile range). The Chi -Square test was used to compare categorical variables. Spearman's and Pearson's correlation analyses were used

Table 1: Vancomycin dosing protocol for the patients in HTAR

Dosing of Vancomycin	Monitoring Parameters
Loading Dose = 25mg/kg Maintenance Dose = 15-20mg/kg	Time for sampling = 0.5 -1 hr prior to next dose and 2-4 hrs after giving the dose Target Trough Concentration = 10-20mg/L Target Peak Concentration = 20-40mg/L If subsequent Trough Concentration levels exceed 20mg/L, withhold MD and repeat TDM according to half-life.

to look at the correlation between the variables. Regression test was run between AUC24/MIC vs investigating factors. A scatterplot of trough vancomycin concentration and AUC24/MIC were plotted to provide a visual inspection of the actual relationship and highlight the short-comings of trough-guided dosing.

Study Approvals

The study proposal was approved and granted by UCSI University Centre of Excellence for Research, Value Innovation and Entrepreneurship (CERVIE) with the code REIG-FPS-2020/053. Approval from Director of Hospital and Head of Department of Pharmacy was obtained for data collection. The ethics approval was also obtained from the Ministry of Health Ethics Committee (MREC).

Table 2: Demographic and clinical characteristics

Variables	Values (n1, n2)
Age (yrs.) (Mean ± SD)	45.59 ± 15.14
Weight (kg) (Median IQR)	65 (38-110)
Height (m) (Median IQR)	1.60 (1.30-1.89)
BMI (kg/m^2) (Median IQR)	24.03 (17.58- 37.18)
Vancomycin Clearance (L/hr) (Median IQR)	3.075 (0.47- 18.41)
Gender	
Female No. (%)	n1: 70 (46.7), n2: 18 (38)
Male No. (%)	n1: 80 (53.3), n2: 29 (61.7)
Ethnicity No. (%)	
Malay	n1: 105 (70.0), n2: 32 (68.08)
Indian	n1: 39 (26.0), n2: 12 (25.25)
Chinese	n1: 4 (2.7), n2: 2 (4.25)
Others	n1: 2 (1.3), n2: 1 (2.1)
Co-morbidities No. (%).	
Diabetes Mellitus	6 (30.7)
Hypertension	28 (18.7)
Dyslipidemia	5 (3.3)
Others	71 (47.3)
Indication for Vancomycin Use No. (%).	
MRSA and other bacteria	100 (65.4)
Sepsis	10 (6.7)
Diabetic Foot ulcer	3 (2)
Others	37 (25.9)

Results and Discussion

Demographic and clinical characteristics

A total of 150 vancomycin readings from 47 patients were deployed in this study.

Table 2 shows the demographic data of these patients and Table 3 summarizes the overall vancomycin exposure values among inpatient investigated cases.

Correlation Analyses

Figure1 shows the scatter plots of the relationship between AUC_{24}/MIC and trough concentration.

According to the chi square of independence, the group of AUC_{24}/MIC beyond 800 has the highest frequency, accounting for (87.3%) of the study population. In contrast, the AUC_{24}/MIC (400-600) group, which represents the efficacy marker for vancomycin, has the smallest number of readings, accounting for only (2.7%) of the cases analyzed. Around (34%) of the study population has trough values greater than 25 g/mL, and (20.7%) account for those with trough level within the range (15-25) g/mL. While (44.7%) of the study population have trough values less than 15 g/mL. MRSA isolates have the highest number accounting

Table 3: Total vancomycin exposure variables

Vancomycin Exposure	Values
Vancomycin dose (mg) (Median IQR).	750 (500 -2000)
Vancomycin dose (mg) (Mean ± SD).	843.833 ± 306.85
AUC_{24}/MIC (Median IQR).	1372.95 (61.30 – 8126.84)
AUC_{24}/MIC (Mean ± SD).	1629.94 ± 1033.68
MIC (Mean ± SD).	0.42 ± 0.151
Trough concentration (µg/mL) (Mean ± SD).	17.70 ± 10.16
Peak concentration (µg/mL) (Mean ± SD).	33.87 ± 13.50

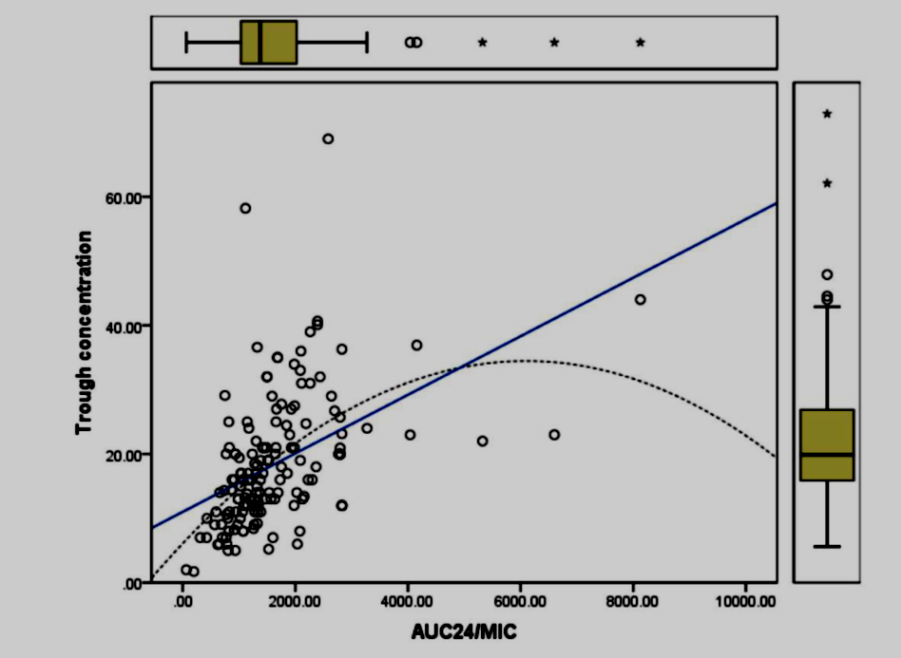

Figure 1: Scatterplot of relationship between trough concentration and AUC_{24}/MIC

for 106 (70.7%) of all cases. A very minimal culture growth under the vancomycin efficacy marker of AUC_{24}/MIC 400-600, which accounted for 2.7% for both MRSA and non-MRSA.

Discussion

The Pearson Chi-square value was 0.006 which supports the theory that trough concentrations do correlate with AUC_{24}/MIC. However, using trough guided dosing for the study population in HTAR still leads to large value of AUC_{24}/MIC above 800 exceeding the efficacy range which is between 400-600. According to the American Society of Health-System Pharmacists consensus guideline(7), the degree of variation between AUC_{24}/MIC can be accounted by the fact that lots of concentration time curves eventually lead to the same trough values. It was also intriguing to see that trough concentrations of less than 15 g/mL had AUC_{24}/MIC values of more than 800. Normally the patient will be given a loading dose (weight-based dose), followed by maintenance dose based on the patient kidney function and body weight, then trough concentration will be monitored as the pre-vancomycin sample will be drawn just before the third or fourth dose when steady states achieved. Only 20.7% of the study population was able to achieve the trough concentration of 15-25 µg/mL and none of them have achieved the targeted AUC_{24}/MIC. While 44.7% of the study population has trough level less than 15 µg/mL and still they can reach AUC_{24}/MIC above 800. The majority of the study population showed a very high value of AUC_{24}/MIC, more than 800, which indicates that they are at the highest risk of nephrotoxicity. However, there was no record of nephrotoxicity in these patients with AUC_{24}/MIC greater than 800. The majority of MRSA records have very high AUC_{24}/MIC values above 800, with the mean average above the range 1780. Moreover, according to the Malaysian Clinical Pharmacokinetics Pharmacy Handbook, to achieve the goal AUC_{24}/MIC of 400, the minimum trough concentration would have to be at least

15 mg/L for Vancomycin MIC values of 1 mg/L, and achieving target of AUC_{24}/MIC between 600-800, the minimum trough concentration would have to be between 15-20mg/L for Vancomycin MIC values of 2 mg/L(8).Hence assuming that trough level is not the surrogate marker, still it is not expecting to achieve that unexplained high value of AUC_{24}/MIC. Therefore, it is important to highlight that, since the majority of 'trough concentrations' do not meet the expectations' target, then they will produce inaccurate interpretations leading to treatment failure(9). A significant relationship (P=0.001), exists between AUC_{24}/MIC and the MIC. Not surprisingly we found that calculation of the vancomycin AUC_{24}/MIC is MIC method dependent. In this study, MIC values record very small numbers varying between 0.19 to 1.0 µg/ml (< 1 µg/ml), with average mean of 0.42, therefore the resulting value is high because MRSA infections are strongly influencing the MIC distribution in our study. The MIC determination method has a substantial impact on the determination of vancomycin AUC_{24}/MIC(10-11). Many factors must be considered in order to produce accurate MIC, such as determination methods of MIC (ex. broth microdilution method (BMD), agar dilution and E-test)(12). According to Casapao and colleagues, Etest method is more likely to produce a higher value of MIC_{Etest} (up to 2 folds higher) than MIC_{BMD}, hence MIC which determined using E-test, should target AUC/MIC_{Etest} between 200-400 (consider equivalent to 400-600)(7).

Therefore, clinicians should be aware that the current efficacy marker of AUC_{24}/MIC between 400-600 was determined using the reference BMD method(4); hence, when using different MIC determination methods to calculate the AUC_{24}/MIC ratio, adjustments to this target should be considered(10,13). Nowadays in clinical practice, the majority of vancomycin analysis and TDM is done using commercial assays such as chemiluminescence, enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), and fluorescence polarization immunoassay (FPIA)(14). These immunoassays have inherent drawbacks and some limitations, such as inconsistency in accuracy and precision. Some immunoassays have been shown to be impacted by vancomycin degradation products. These chemicals could be present in the isolated material, interfering with vancomycin concentration measurements. The lack of inter-technique standardization may have an impact on the comparability of detection methods, which is critical for accurate vancomycin concentration interpretation and treatment(14). According to the Current National Vancomycin Susceptibility Surveillance data, in most situations, the vancomycin MIC_{BMD} for empiric dose should be 1 mg/L(3). In HTAR, they have been using Viva-ProE System with EMIT® technology, it is a flexible method specialized for vancomycin testing analysis(15). Moreover, it is important to highlight that MIC values in this study are very small compared to what the guidelines and other papers reveal. Vancomycin MIC values for susceptible MRSA strains typically vary from 0.5 to 2 mg/L(16). These variations in the reported MIC values in HTAR are questionable as what could be the potential cause or reason behind that and Why MRSA strain is most sensitive to vancomycin for which the MIC is the lowest(12)? These reported small MIC values are playing a very important role in achieving that high level of AUC_{24}/MIC. A previous study by Hiroki Konishi highlighted that the EMIT technique considerably underestimated vancomycin concentrations, which was attributed to interference by endogenous compounds(17). As a result, when utilizing EMIT to detect vancomycin serum concentrations, endogenous interference should be completely addressed, and EMIT measurement variation should be decreased(14).

Methodological challenges accompany the precise determination of Vancomycin MIC for MRSA. Whereas those determination methods are not reliable enough to justify reporting the actual MIC values(11). When using MICs to guide treatment decisions, Clinicians should consider using a

supplementary broth microdilution test for confirmation, especially if the results are close to the cut-off value, which may reduce the inappropriate use of antibiotics and the emergence of resistant strains(13). However, the ability of Microbiology laboratories in general to accurately assess the MIC value is being questioned(12). According to EUCAST and CLSI, determining MIC value in a microbiological laboratory is challenging as the is the most reliable determination method is the broth microdilution method, which is a manual, demanding, and time-consuming process(12). According to the smallest reported MIC values and the previous studies, it is important to shed light on the accuracy and the precision technique of the MIC determination methods in HTAR. Future study should be considered to revise the standard and the technique of MIC determination method in HTAR which could cause the evaluation to be affected and to clarify the reason behind those low values. However, if dose modifications are done based on therapeutic drug monitoring and MIC measurements, MIC variation must be taken into account to avoid patient underdosing(18). The widespread use of AUC_{24}/MIC as the primary vancomycin monitoring measure may be premature due to a lack of technique standardization(19). It is important to standardize vancomycin detection protocols. Moreover, achieving the current efficacy marker AUC_{24}/MIC requires precise measurement of both the AUC and the MIC for the MRSA isolates. Which makes it a difficult target to achieve due to the inability to obtain accurate values and the lack of technique standardization(20). Hence widespread use of vancomycin efficacy marker AUC_{24}/MIC to be warranted.

A limitation of the current study is that the findings came from single hospital-based research. Consequently, antibiograms, practices, and protocols at other facilities may differ. Many cases were removed because they did not indicate confirmed infections with reported MIC values required for the study. The lack of validation for the extrapolated AUC derived from the PrecisePK® software was also recognized as a limitation. There was some delay in the data collection period due to the movement control restrictions in Malaysia (COVID-19).

Conclusion

Although IDSA guideline recommended AUC_{24}/MIC as the best indicator for vancomycin dose adjustment, the variation of MRSA MIC due to the different test methods and other technical concerns causes the indicator interpretation to be arguable. Current study emphasizes the limitations of trough-guided dosage, as well as the complexity of the interpretation of the obtained high values of AUC_{24}/MIC. The abnormally low locally reported MRSA MICs ended up with very high AUC_{24}/MICs which needs the MIC tests to be relooked, technically. On the other hand, the vancomycin dose adjustment guidelines need to consider this between and within variations of MIC with its great impact on AUC_{24}/MIC.

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Conflict of Interest

The authors declare no conflict of interest.

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