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# The Value of Therapeutic Drug Monitoring of Vancomycin in Treatment in a Tertiary Hospital, Cho Ray Hospital, Viet Nam

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors LNH and LHH designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author LTNQ managed the literature searches, gathered study data, entered data and supported in data analysis. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** To evaluate the value of therapeutic drug monitoring (TDM) of vancomycin in clinical practice.
**Methods:** To review retrospectively on 292 hospital cases (111 females, 181 males) treated with vancomycin, July to October 2014, at ChoRay Hospital. The main evaluating parameters were TDM criteria for vancomycin (dose, dosing interval, times of monitoring), trough level, dose adjustment, renal function follow-up, minimum inhibitory concentration of infectious agents, clinical response.
**Results:** Two hundred seventy-five patients (94.2%) received routine dose of 1 g vancomycin per IV infusion time. Dosing interval was given correctly to estimated glomerular filtration rate (eGFR) level 80.8% (235/291). The 1st monitoring after 9th dose was in 139 cases (47.6%). Trough level was lower than 10 mg/L in 86 patients (29.5%), higher than 20 mg/L in 96 (32.9%), and 110 in optimal range 10-20 mg/L (37.7%). Age and eGFR were 2 independent predictors for trough level.

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Dose adjustment were done in 6.9% (6/86) patients ≤ 10 mg/L, 20.8% (20/96) ones >20 mg/L, and 11.8% (13/110) ones 10-20 mg/L. Vancomycin concentrations in young patients were lower than those in elderly ones with OR = 5.9 [95%CI: 2.6 – 14.0], p = 0.0001. Response sensitivity was 69.3% (13/19) for dose reduction, and 83.3% (5/6) for dose increase. Dose adjustment did not make change in trough level compared to unadjusted ones. Nephrotoxicity rate was found as 8.4%. Treatment failure was 50% in patients with trough concentration/minimum inhibition concentration ratio ≤ 10 compared to 15% in ones with higher ratio > 10, p = 0.034. The failure rate was highest in patients received vancomycin ≤ 7 days (22/70: 31.4%), OR: 4 (2.0-7.7) p=0.002. The clinical AUC/MIC ratio cut-off, 190 mg/L/day, had 75.9% and 66.7%, respectively for sensitivity and specificity to predict the success result in treatment.

**Conclusion:** The criteria of TDM on vancomycin were not applied strictly, especially for dosing intervals, dosing adjustment and follow-up thereafter. The clinical pharmacodynamics of vancomycin is dependent on both concentration and duration of treatment.

*Keywords: Vancomcycin; therapeutic drug monitoring; clinical pharmacodynamics.*

## 1. INTRODUCTION

Vancomycin has been used as a first-line antibiotics for treatment of infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. The target concentration of vancomycin efficiently has become more important due to facing to the rapid increase of MRSA infections. In addition the therapeutic window of trough vancomycin level is narrow, as 10-15 mg/L to avoid development of resistant [2] or 15-20 mg/L for more resistant strains [3], but < 20 mg/L to minimize risk of nephrotoxicity [4]. Thus the therapeutic drug monitoring (TDM) is strongly recommended when using vancomycin. There are many guidelines for vancomycin TDM suggested by several organizations. A systematical review on 635 records related to vancomycin TDM selected out 12 clinical practice guidelines achieving high quality recommendations [5].

The aims of this study were to evaluate the practical value of vancomycin TDM when applying in routine treatment. The specific objectives were the compliance to criteria in vancomycin TDM (dosing intervals, dose adjustment, monitoring frequency on kidney function and vancomycin concentrations), nephrotoxicity of vancomycin, and clinical response (pharmacodynamics of vancomycin) of vancomycin treatment.

## 2. PATIENTS AND STUDY METHODS

Cho Ray Hospital is tertiary general hospital, located in Ho Chi Minh City, Viet Nam, having around 49 departments (including 11 in Surgery, 6 in Neurology, 11 in Medicine, Emergency, Intensive Care Unit, 4 in Laboratory, 4 in Radiology-Function Tests, and other departments). The volume of in-patients is around 2500 cases per day. Vancomycin is one of the important, expensive antibiotics used in routine treatment of infections with Gram-positive organism, especially for MRSA, VISA. The guidance for Vancomycin TDM has been approved and applied in all clinical wards since 2006.

The general content of vancomycin TDM guidance in Cho Ray Hospital can be briefly described as the initial/maintenance doses as 1000 mg/60 kg body weight/per IV infusion time; dosing intervals based on estimated glomerular filtration rate (eGRF): Q 8-12h for eGFR ≥ 50 ml/min/1.73 $m^2$, Q 24h for eGFR 35 – 49.9 eGFR ≥ 50 ml/min/1.73 $m^2$, Q 48h for eGFR 25 – 34.9 eGFR ≥ 50 ml/min/1.73 $m^2$, and Q72h or defining based on daily level of serum vancomycin for eGFR < 25 eGFR ≥ 50 ml/min/1.73 $m^2$; frequency of routine monitoring on a weekly basis at minimum requirement for patients with stable renal function, for cases with unstable renal function, hemodynamically compromised or at risk for nephrotoxicity, monitoring should be repeated at least 1-3 times weekly. The target trough concentrations were 10-15 mg/L for soft and skin tissue infections, abscess, cellulitis with MIC < 1 mg/L, 15-20 mg/L for soft and skin tissue infections, abscess, cellulitis with MIC ≥ 1 mg/L or complicated infections (endocarditis, osteomyelitis, bacteremia, prosthetic joint infection, or pneumonia), and 20-25 mg/L for infections involving central nervous system (bacterial meningitis).

This retrospective study reviewed 292 medical case reports of patients treated with vancomycin

and having at least one monitoring measurement of vancomycin concentration during treatment time. All medical case reports were from all clinical wards of hospital from June to September 2014. The main parameters investigated were patient anthropometrics (age, gender, clinical wards, date of admission, date of discharge), final disease diagnosis on discharge, all details relating to vancomycin TDM as treatment dose per IV perfusion time, rate of IV perfusion, dosing interval, blood creatinine and eGFR related to the initial dose given, time of the first monitoring vancomycin concentration (counting by treatment days and by times of drug given from the first dose of vancomycin), repeat frequency on kidney function evaluation (number of times for blood creatinine and eGFR investigation), dose adjustment for vancomycin after the first trough concentration results, repeat frequency on monitoring of trough concentrations in the whole treatment course; MIC results if available; and the patient status on hospital discharge.

The patient status on hospital discharge was classified into 2 groups: success (better or well improved) and failure (unimproved, worsened, or died).

## 2.1 Vancomycin Assay

Vancomycin drug concentrations were analyzed by an in vitro chemiluminescent microparticle immunoassay (CMIA) in human serum (*ARCHITECT i1000SR* Immunoassay Analyze, Abbott Diagnostics, Chicago, IL, USA), at the Biochemistry department, Cho Ray Hospital. All drug samples were performed within the same day of collection day. The inter-assay coefficients of variation for vancomycin in *ARCHITECT i1000SR* were 5.0% at 6.1 mg/L, 4.9% at 18.6 mg/L, and 5.1% at 33.1 mg/L. The limit of detection of vancomycin was $\leq$ 2 mg/L.

## 2.2 Study Approval

The study was approved by the Ethical Committee of Cho Ray Hospital on 20-November 2015. All hospital case records were reviewed at the Hospital Files Room belonged to the General Planning Room of Cho Ray Hospital.

## 2.3 Statistical Analysis

Investigating data from hospital case records were transferred to study record form per each study case. All data was analyzed with the SPSS software (PASW Statistics 18). The descriptive data were presented in frequency, percentage, mean, standard of deviation, and range from minimum to maximum value. Chi-square analysis with or without odd ratio estimation were applied for testing significant difference in qualitative data. The t-test was used for comparison quantitative data between two independent variables. Multivariable binary logistic regression analysis was used to define the independent predictor for vancomycin concentration or risk factor for treatment failure from the monovariable risk factors/predictors. All statistical tests were considered as significantly different if p value < 0.05.

For evaluation of the predictors of trough concentrations of vancomycin, the concentrations were investigated in 3 sub-classes as: $\leq$ 10 mg/L versus > 10 mg/L; $\leq$ 20 mg/L versus > 20 mg/L, and optimal range [10 – 20 mg/L] versus “out of range” [< 10 mg/L or > 20 mg/L].

Nephrotoxicity was defined based on criteria as an increase of > 0.5 mg/dL or ≥ 50% increase of the later creatinine compared to the previous one [6-10].

The trough concentration/MIC ratio of vancomycin was used to study on the concentration-dependent pharmacodynamics of vancomycin.

It was because of the lack of the total area under the concentration curve of vancomycin, AUC/MIC ratio of vancomycin could not be evaluated and investigated against the treatment results in this retrospective study. We suggested an alternative parameter, called as “clinical AUC/MIC ratio” of vancomycin. The clinical AUC/MIC ratio of vancomycin was defined as the multiple of trough concentration/MIC ratio by duration of vancomycin treatment (days). This parameter was investigated as the both concentration-dependent and time-dependent pharmacodynamics of vancomycin against treatment result.

Receiver Operating Characteristic (ROC) Curve Analysis was applied for determination of cut-off value for clinical AUC/MIC ratio for prediction of treatment result (success versus failure).

# 3. RESULTS

## 3.1 Evaluation of Clinical Performance of TDM for Vancomycin

Two hundred and ninety-two patient cases were included in retrospective review, in which 111

females (38%). No different significance was found in gender on parameters as age groups, vancomycin dose per IV infusion time, dosing intervals, blood creatinine, vancomycin treatment time, patient status on hospital discharge. The difference was found only on eGFR level, females were lower than males (48.6±18.9 versus 54.0±14.0 ml/min/1.73 $m^2$; p = 0.006). Two hundred and seventy-five patients received 1g vancomycin per IV perfusion time (275/292: 94.2%). There were 99 cases with blood sample collection for the first monitoring of vancomycin from $4^{th}$ to $8^{th}$ treatment doses. Two hundred and twenty two patients had duration of vancomycin treatment > 7 days (222/292: 76.03%), only 56 cases received the second monitoring of vancomycin concentration (56/222: 25.2%) (Table 1).

**Table 1. Patient characteristics and parameters for evaluation of clinical performance of TDM for vancomycin**

| Characteristics | | Female | Male | Total | p |
|---|---|---|---|---|---|
| **Number** | | **111** | **181** | **292** | |
| Age (yr.) (mean ± SD) | | 56.7±17.1 | 54.5±16.9 | 55.4±17.0 | 0.28 |
| Age groups (yr.) | ≤ 20 | 2 | 5 | 7 | 0.07 |
| | 21 - 40 | 19 | 32 | 51 | |
| | 41 - 60 | 33 | 78 | 111 | |
| | > 60 | 57 | 66 | 123 | |
| Vancomycin dose/time (g) | 0.5 | 7 | 9 | 16 | 0.66 |
| | 1.0 | 104 | 171 | 275 | |
| | 2.0 | 0 | 1 | 1 | |
| Vancomycin dosing interval (hr.) | 8 | 4 | 8 | 12 | 0.096 |
| | 12 | 80 | 144 | 224 | |
| | 24 | 12 | 16 | 28 | |
| | 36 | 1 | 1 | 2 | |
| | 48 | 3 | 8 | 11 | |
| | 72 | 9 | 2 | 11 | |
| | 96 | 2 | 2 | 4 | |
| Blood creatinine (mg/dL) | | 1.61±1.85 | 1.50±1.98 | 1.54±1.90 | 0.63 |
| eGFR (ml/min/1.73 $m^2$) | | 48.6±18.9 | 54.0±14.0 | 51.9±16.2 | 0.006* |
| eGFR: < 60/ ≥ 60 | | 37/74 | 38/142 | 75/216 | 0.02* |
| eGFR (ml/min/1.73 $m^2$) | ≥ 50 | 79 | 149 | 228 | 0.026* |
| | 35 – 49.9 | 7 | 11 | 18 | |
| | 25 – 34.9 | 4 | 7 | 11 | |
| | < 25 | 21 | 13 | 34 | |
| Time of $1^{st}$ monitoring (dosing times) | ≤ $3^{rd}$ | 22 | 32 | 54 | 0.09 |
| | $4^{th}$ - $8^{th}$ | 45 | 54 | 99 | |
| | ≥ $9^{th}$ | 44 | 95 | 139 | |
| Vancomycin treatment time (day) mean ± SD | | 12.9±8.5 | 13.0±8.2 | 13.0±8.3 | 0.92 |
| Vancomycin treatment time (day) | 1 - 7 | 29 | 41 | 70 | 0.88 |
| | 8 - 14 | 47 | 84 | 131 | |
| | 15 - 21 | 20 | 36 | 56 | |
| | 22 - 28 | 8 | 10 | 18 | |
| | 29 - 35 | 3 | 7 | 10 | |
| | > 35 | 4 | 4 | 8 | |
| TDM vancomycin $2^{nd}$ (n, %) | | 19 17.1% | 37 20.4% | 56 19.2% | 0.5 |
| Vancomycin dosing change (n, %) | | 13 11.7% | 26 14.4% | 39 13.4% | 0.8 |

**significantly different*

**Table 1. Patient characteristics and parameters for evaluation of clinical performance of TDM for vancomycin (cont.)**

| Characteristics | | Female | Male | Total | p |
|---|---|---|---|---|---|
| **Number** | | **111** | **181** | **292** | |
| Vancomycin concentrations (mg/L) | ≤ 10 | 28 | 58 | 86 | 0.024* |
| | 10.1 – 15.0 | 19 | 36 | 55 | |
| | 15.1 – 20.0 | 18 | 37 | 55 | |
| | 20.1 – 30.0 | 20 | 33 | 53 | |
| | > 30 | 26 | 17 | 43 | |
| Patient status on hospital discharge | good | 95 | 153 | 248 | 0.71 |
| | unimproved | 4 | 9 | 13 | |
| | worsened | 10 | 17 | 27 | |
| | died | 2 | 2 | 4 | |

**significantly different*

Almost patients had eGFR ≥ 60 ml/min/1.73m$^2$ (n=216, 216/291: 74.2%). Dosing interval 8-12 h was indicated for patients with eGFR ≥ 50 ml/min/1.73 m$^2$ (217/291: 74.6%). The dosing interval of 8-12 h was applied in 18 patients with eGFR ≤ 49.9 ml/min/1.73 m$^2$, including 6 cases with low eGFR ≤ 34.9 ml/min/1.73 m$^2$. The dosing interval of 24 h was found in 10 with eGFR ≥ 50 and in 14 cases with low eGFR ≤ 34.9. Eleven cases with eGFR < 25 ml/min/1.73 m$^2$ received dosing interval of 36-48 hr. Total number of cases received dosing interval correctly to TDM guidance for vancomycin was 235 (235/291: 80.8%) (Table 2).

## 3.2 Evaluation of the Trough Concentration of Vancomycin in the First Monitoring

### 3.2.1 Patients with trough concentrations of vancomycin ≤ 10 mg/L

There were 86 patient cases with vancomycin ≤ 10 mg/L in the first monitoring, accounted 29.5%. Table 3 presented 4 significant risk factors in monovariable analysis affecting to the difference between two patient groups, ≤ 10 mg/L versus > 10 mg/L, as follows: age >40 yrs. (OR = 2.2 [95%CI: 1.2 – 4.1], p=0.01), clinical wards of Internal (internal wards + ICU) (OR = 2.0 [95% CI: 1.1 – 3.7], p=0.02), dosing intervals ≥ 24 hrs. (OR= 5.3 [95%CI: 2.0 – 13.9], p=0.001), and eGFR < 60 ml/min/1.73 m$^2$ (OR= 4.6 [95%CI: 2.1 – 10.2], p=0.001).

Table 4 showed only 2 independent risk factors for low concentration of vancomycin ≤ 10 mg/L: eGFR affecting in the negative way to have lesser cases with vancomycin ≤ 10 mg/L (eGFR < 60, OR < 1); and age groups affecting in the positive way to have more cases with vancomycin ≤ 10 mg/L (age higher, OR >1), p < 0.05 for both.

### 3.2.2 Patients with trough concentration of vancomycin > 20 mg/L

Ninety-six patients had vancomycin concentrations > 20 mg/L in the first monitoring, accounted 32.9%. The factors affecting to vancomycin concentrations > 20 mg/L were evaluated in Table 5.

Table 5 presented 3 risk factors in monovariable analysis affecting to the difference between two groups of patients based on the cut-point value of 20 mg/L as follows: gender (female) (OR = 1.9 [95%CI: 1.1 – 3.1], p=0.015), age > 60 yrs. (OR = 1.8 [95%CI: 1.1 – 3.0], p = 0.017), and eGFR < 60 ml/min/1.73 m$^2$ (OR = 3.3 [95%CI: 1.9 – 5.6], p=0.0001).

Table 6 showed only 2 independent risk factors for low concentration of vancomycin ≤ 20 mg/L: eGFR affecting in the positive way to have more cases with vancomycin ≤ 20 mg/L (eGFR > 60, OR > 1); and age groups affecting in the negative way to have lesser cases with vancomycin ≤ 20 mg/L (age higher, OR < 1), p < 0.05 for both (binary logistic regression analysis).

### 3.2.3 Patients with trough vancomycin concentrations in optimal range [> 10 and ≤ 20 mg/L]

Ten hundred and ten patients had vancomycin in optimal range, > 10 and ≤ 20 mg/L, in first monitoring time, accounted percentage of 37.7%. The factors affecting to vancomycin concentration, [>10-≤20 mg/L], was evaluated in Table 7.

**Table 2. Correlation between eGFRs and vancomycin dosing interval**

| Dosing interval | eGFR (ml/min/1.73 $m^2$) | | | | Total |
|---|---|---|---|---|---|
| | ≥ 50 | 35 – 49.9 | 25 – 34.9 | < 25 | |
| 8 h | 10 | 1 | 0 | 0 | 11 |
| 12 h | 207 | 11 | 4 | 2 | 224 |
| 24 h | 10 | 4 | 7 | 7 | 28 |
| 36 h | 0 | 0 | 0 | 2 | 2 |
| 48 h | 0 | 2 | 0 | 9 | 11 |
| 72 h | 1 | 0 | 0 | 10 | 11 |
| 96 h | 0 | 0 | 0 | 4 | 4 |
| Total | 216 | 23 | 24 | 28 | 291 |

**Table 3. Comparison of factors affecting to concentration of vancomycin between 2 patient groups: low concentration ≤ 10 mg/L versus high concentration > 10 mg/L**

| Characteristics | | Vancomycin Trough concentration ≤ 10 mg/L | | Vancomycin Trough concentration > 10 mg/L | | p |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| **N = 292** | | **86** | **29.5** | **206** | **70.5** | |
| Gender: Male/female | | 58/28 | | 123/83 | | 0.21 |
| Age (yr.) (mean ± SD) | | 46.3±16.4 | | 59.1±15.8 | | 0.0001* |
| Age group (yr.) | ≤ 20 | 4 | 57.1 | 3 | 42.9 | <0.001* |
| | >20 - ≤40 | 28 | 54.9 | 23 | 45.1 | |
| | >40 - ≤60 | 36 | 32.4 | 75 | 67.6 | |
| | > 60 | 18 | 14.6 | 105 | 85.4 | |
| Clinical wards | Surgery | 24 | 42.1 | 33 | 57.9 | 0.014* |
| | Internal | 49 | 24.3 | 153 | 75.7 | |
| | ICUs | 13 | 39.4 | 20 | 60.6 | |
| Vancomycin dose/time (g) | 0.5 | 4 | 25 | 12 | 75 | 0.74 |
| | 1.0 | 82 | 29.8 | 193 | 70.2 | |
| | 2.0 | 0 | | 1 | | |
| Vancomycin dosing interval (hr.) | ≤ 12 | 81 | 34.3 | 155 | 65.7 | <0.001* |
| | ≥ 24 | 5 | 8.9 | 51 | 91.1 | |
| eGFR (ml/min/172$m^2$) | < 60 | 8 | 10.7 | 67 | 89.3 | <0.001* |
| | ≥ 60 | 77 | 35.6 | 139 | 64.4 | |
| Time of 1st monitoring (dosing times) | ≤ 3 | 12 | 22.2 | 42 | 77.8 | 0.11 |
| | 4 - 8 | 25 | 25.3 | 74 | 74.7 | |
| | ≥ 9 | 49 | 35.3 | 90 | 64.7 | |

**significantly different*

**Table 4. Multivariable binary logistic regression analysis on 4 monovariable risk factors related to vancomycin concentration ≤ 10 mg/L**

| Factors | B | p | Odd ratio | 95%CI for odd ratio | |
|---|---|---|---|---|---|
| | | | | Lower 95% CI | Upper 95% CI |
| Vancomycin dosing interval | 0.726 | 0.267 | 2.07 | 0.57 | 7.45 |
| eGFR | -1.28 | 0.019* | 0.28 | 0.09 | 0.81 |
| Age groups | 1.0 | 0.000* | 2.72 | 1.87 | 3.95 |
| Clinical ward (surgery) | -0.077 | 0.76 | 0.93 | 0.56 | 1.53 |

**significantly different*

**Table 5. Comparison of factors affecting to concentration of vancomycin between 2 patient groups: concentration ≤ 20 mg/L versus high concentration > 20 mg/L**

| Characteristics | | Vancomycin Trough concentration ≤ 20 mg/L | | Vancomycin Trough concentration > 20 mg/L | | p |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| **N = 292** | | **196** | **67.1** | **96** | **32.9** | |
| Gender: Male/female | | 131/65 | | 50/46 | | 0.015* |
| Age (yr.) (mean ± SD) | | 53.6 ± 17.2 | | 59.0 ± 16.1 | | 0.011* |
| Age group (yr.) | ≤ 20 | 7 | / | 0 | / | 0.036* |
| | >20 - ≤40 | 38 | 74.5 | 13 | 25.5 | |
| | >40 - ≤60 | 78 | 70.3 | 33 | 29.7 | |
| | > 60 | 73 | 59.3 | 50 | 40.7 | |
| Clinical wards | Surgery | 41 | 45.1 | 16 | 54.9 | 0.46 |
| | Internal | 131 | 64.9 | 71 | 35.1 | |
| | ICUs | 24 | 72.7 | 9 | 27.3 | |
| Vancomycin dose/time (g) | 0.5 | 12 | 75 | 4 | 25 | 0.60 |
| | 1.0 | 183 | 66.5 | 92 | 33.5 | |
| | 2.0 | 1 | / | 0 | / | |
| Vancomycin dosing interval (hr.) | ≤ 12 | 164 | 69.5 | 72 | 30.5 | 0.07 |
| | ≥ 24 | 32 | 57.1 | 24 | 42.9 | |
| eGFR (ml/min/172m$^2$) | < 60 | 35 | 46.7 | 40 | 53.3 | <0.001* |
| | ≥ 60 | 160 | 74.1 | 56 | 25.9 | |
| Time of monitoring (dose times) | ≤ 3 | 38 | 70.4 | 16 | 29.6 | 0.36 |
| | 4 - 8 | 61 | 61.6 | 38 | 38.4 | |
| | ≥ 9 | 97 | 69.8 | 42 | 30.2 | |

**significantly different*

**Table 6. Multivariable binary logistic regression analysis on 4 monovariable risk factors related to vancomycin concentration ≤ 20 mg/L**

| Factors | B | P | Odd ratio | 95%CI for Odd Ratio | |
|---|---|---|---|---|---|
| | | | | Lower 95% CI | Upper 95% CI |
| Gender | -0.437 | 0.10 | 0.65 | 0.38 | 0.09 |
| eGFR | 0.441 | 0.01* | 1.55 | 1.11 | 2.17 |
| Age groups | 0.000 | 0.000* | 0.32 | 0.18 | 0.56 |

**significantly different*

Table 7 showed only 1 factor in monovariable analysis affecting to the difference between 2 patient groups, vancomycin concentration "out of range" [≤ 10 or > 20 mg/L] versus [>10-≤20 mg/L] as age ≤ 40 (OR = 3.1 [95% CI1.6 – 6.0], p=0.0008). Patients in age group ≤ 40 yr. had high "out of range" percentage of 77.6% (45/58 cases), including 13 cases with > 20 mg/L (13/58: 22.4%) and 32 with ≤ 10 mg/L (32/58: 55.2%). Inversely, the elderly group, > 60 y, had 68 cases with "out of range" vancomycin concentrations (68/123, 55.2%), including 50 with > 20 mg/L (50/68: 73.5%) and 18 with ≤ 10 mg/L (18/68: 26.5%).

### 3.3 Evaluation of Efficacy of Dose Adjustment on Trough Concentration of Vancomycin

There were 182 patients with vancomycin concentration of out of optimal range, included 86 cases with low concentrations ≤ 10 ng/ml and 96 ones with high concentrations > 20 mg/L. The study found only 39 cases (39/292: 13.4%) having vancomycin dose adjustment after the first concentration monitoring, including 6 cases with low concentrations ≤ 10 mg/L (6/86: 6.9%); 20 patients with high concentrations > 20 mg/L (20/96: 20.8%), and 13 cases with vancomycin in optimal range, 10-20 mg/L (13/110: 11.8%). Among 39 cases with dose adjustment, 29 had dose reduction (dose reduced: 6; prolongation of

dosing interval: 22; combination of both: 1) and 10 with dose increase (dose increased: 1, shortening the dosing interval: 12-48 hr: 9). Dosing interval was used as the main key in dose adjustment in 32 cases (32/39: 82.1%).

The remaining cases included 158 with continuation on the first treatment doses – no dose adjustment (including 49, 52 and 57 cases with low, high and in optimal vancomycin concentrations, respectively), and 95 with the stop of vancomycin after the first concentration monitoring.

There were 151 cases with vancomycin > 15 mg/L, but only 27 had the 2nd monitoring (17.9%). Nineteen among 39 patients with dose adjustment had the second vancomycin monitoring. Comparing to first concentrations, 9 among 13 cases with dose reduction had concentration decreased (sensitivity 9/13: 69.3%), and 5 among 6 cases with dose increase had concentration increased (sensitivity 5/6: 83.3%), p = 0.03.

Thirty-seven patients, without dose adjustment, had 2nd vancomycin concentration monitoring, results as 11 cases having concentrations in optimal range, 10-20 mg/L, (11/37: 29.7%) and 26 others with "out of range" concentrations (70.3%).

Among 19 cases with dose treatment adjusted, 6 patients reached concentrations in range of 10-20 mg/L (6/19: 31.6%) and 13 still be out of target (68.4%)-including 4 cases with low concentrations ≤ 10 mg/L and 9 with high ones > 20 mg/L. Thus, the dose adjustment did not give any difference effect compared to group without dose intervention in above (p = 0.95).

### 3.4 Vancomycin and Nephrotoxicity

There were 190 cases having measurement of creatinine in 2nd time after receiving vancomycin treatment duration, from 0 day to 40 day counting from the first day of vancomycin given (mean ± SD 7.4±7.1 days, range: 0 -40 days), in which 16 cases was found as nephrotoxicity (based on criteria as an increase of > 0.5 mg/dL or ≥ 50% increase) [6-10], accounting as 8.4%. Among of these 190 patients, 56 cases had 2nd monitoring vancomycin in which 4 out of 5 nephrotoxic cases had concentrations > 30 mg/L (4/5: 80%) compared to 6/51 in non-nephrotoxic group (6/51: 11.7%), OR = 30 (95% CI: 2.9 – 315), p = 0.004.

**Table 7. Comparison of factors affecting to concentration of vancomycin between 2 patient groups: Concentration [> 01 -≤ 20 mg/L] versus high concentration [≤ 10 or > 20 mg/L]**

| Characteristics | | Vancomycin trough concentration [>10-≤20 mg/L] | | Vancomycin trough concentration [≤ 10 or > 20 mg/L] | | p |
|---|---|---|---|---|---|---|
| | | N | % | n | % | |
| **N = 292** | | **110** | **37.7** | **182** | **62.3** | |
| Gender: Male/female | | 73/37 | | 108/74 | | 0.23 |
| Age (yr.) (mean ± SD) | | 59.3±15.6 | | 53.0±17.4 | | 0.002* |
| Age group (yr.) | ≤ 20 | 3 | 42.9 | 4 | 57.1 | 0.021* |
| | >20 - ≤40 | 10 | 19.6 | 41 | 80.4 | |
| | >40 - ≤60 | 42 | 37.8 | 69 | 62.2 | |
| | > 60 | 55 | 44.7 | 68 | 55.3 | |
| Clinical wards | Surgery | 17 | 29.8 | 40 | 70.2 | 0.28 |
| | Internal | 82 | 40.6 | 120 | 59.4 | |
| | ICUs | 11 | 33.3 | 22 | 66.7 | |
| Vancomycin dose/time (g) | 0.5 | 8 | 50.0 | 8 | 50.0 | 0.25 |
| | 1.0 | 101 | 36.7 | 174 | 63.3 | |
| | 2.0 | 1 | / | 0 | / | |
| Vancomycin dosing interval (hr.) | ≤ 12 | 83 | 35.2 | 153 | 64.8 | 0.07 |
| | ≥ 24 | 27 | 48.2 | 29 | 51.8 | |
| eGFR (ml/min/172 $m^2$) | < 60 | 27 | 36 | 48 | 64 | 0.7 |
| | ≥ 60 | 83 | 38.4 | 133 | 61.6 | |
| Time of monitoring (dose times) | ≤ 3 | 26 | 48.1 | 28 | 51.9 | 0.2 |
| | 4 - 8 | 36 | 36.4 | 63 | 63.6 | |
| | ≥ 9 | 48 | 34.5 | 91 | 65.5 | |

**significantly different*

**Table 8. Comparison of factors affecting to clinical efficacy of vancomycin between 2 patient groups: Success and failure**

| Characteristics | | Treatment results | | p |
|---|---|---|---|---|
| | | Success | Failure | |
| **Number** | | **248** | **44** | |
| Gender: female/male | | 95/153 | 16/28 | 0.8 |
| Age (yr.) (mean ± SD) | | 55.0±17.2 | 57.5±15.9 | 0.28 |
| Age groups (yr.) | ≤ 20 | 6 | 1 | 0.68 |
| | 21 - 40 | 46 | 5 | |
| | 41 - 60 | 94 | 17 | |
| | > 60 | 102 | 21 | |
| Vancomycin dose/time (g) | 0.5 | 12 | 4 | 0.48 |
| | 1.0 | 235 | 40 | |
| | 2.0 | 1 | 0 | |
| Vancomycin dosing interval (hr.) | 8 | 9 | 3 | 0.45 |
| | 12 | 191 | 33 | |
| | 24 | 23 | 5 | |
| | 36 | 1 | 1 | |
| | 48 | 11 | 0 | |
| | 72 | 9 | 2 | |
| | 96 | 4 | 0 | |
| Blood creatinine (mg/dL) (mean ± SD) | | 1.53±2.0 | 1.6±1.4 | 0.8 |
| eGFR (ml/min/1.73 $m^2$) (mean ± SD) | | 52.5±15.8 | 48.9±18.3 | 0.18 |
| eGFR: < 60/ ≥ 60 | | 60/188 | 16/28 | 0.14 |
| eGFR (ml/min/1.73 $m^2$) | ≥ 60 | 188 | 28 | 0.38 |
| | 40.0 – 59.9 | 19 | 4 | |
| | 20 – 39.9 | 20 | 5 | |
| | < 20 | 21 | 7 | |

**significantly different*

### 3.5 Clinical Efficacy of Vancomycin (Pharmacodynamics of Vancomycin)

Clinical efficacy was classified as success if patients discharged in good or better condition, and as failure for the unimproved, worsened or died cases. There were 248 successful cases and 44 failure cases (15.07%) classified as unimproved 13, worsened 27 and died 4. The factors affecting to clinical efficacy of vancomycin between 2 patient groups, success and failure, showed in Table 8. The failure rate was highest in patients received vancomycin ≤ 7 days (22/70: 31.4%), OR: 4 (2.0 -7.7) p=0.002.

The trough vancomycin concentration/MIC ratio showed as suggested important criteria relating to the success of treatment. Failure rate was 50% (3/6) in patients with ratio ≤ 10 times compared to 15% (9/60) in patients with higher ratio > 10 times, with p = 0.034. There were 4 predictors for treatment success of vancomycin in monovariable analysis as trough conc./MIC ratio ≤ 10 (OR = 5.7 [95% CI: 0.98 – 32.6], p=0.06), type of infection as complicated infection (OR= 3.4 [95%CI: 1.6 – 7.1], p=0.0009), vancomycin treatment time ≤ 7 days (OR = 4 [95%CI: 2.1 – 7.7], p=0.0005 , and clinical ward group of ICU (OR=2.4 [95%CI: 1.03 – 5.6], p = 0.043) (Table 8).

The binary logistic regression analysis revealed only vancomycin treatment time ≤ 7 days as independent risk factor for low (poor) incidence rate of success treatment result with OR = 0.1 (95% CI: 0.02 – 0.5), p = 0.005 compared to the longer one (Table 9).

There were 66 patients had done the MIC for *S. aureus* detected in pathological samples. The trough concentration of vancomycin was not different in 4 levels of MIC, but the ratio between concentration over MIC was different at cut-off point as value of 30, p = 0.015 (Table 10).

### 3.6 The Clinical AUC/MIC Ratio (Combination of Time –Dependent and Concentration-Dependent Pharmacodynamics [Killing Action] of Vancomycin)

The clinical AUC/MIC ratio was defined as multiple of trough concentration/MIC ratio with

duration of treatment of vancomycin (days). The ROC showed the area under the curve (AUC) of clinical AUC/MIC of 0.727 [0.54 – 0.92], p = 0.015. Cut-off value suggested as 190 mg/L/day (Fig. 1). The sensitivity and specificity of this clinical AUC/MIC cut-off value was 75.9% and 66.7%, respectively for the prediction of success result in treatment (Table 11).

**Table 8. Comparison of factors affecting to clinical efficacy of vancomycin between 2 patient groups: Success and failure (cont.)**

| Characteristics | | Treatment results | | | | p |
|---|---|---|---|---|---|---|
| | | Success | | Failure | | |
| **Number** | | **248** | | **44** | | |
| Vancomycin treatment time (day) (mean ± SD) | | 13.7±8.4 | | 9.0±6.5 | | 0.001* |
| Trough vancomycin concentration 1st monitoring (n [mean±SD]) (mg/L) | | n = 248<br>18.1±13.1 | | n = 44<br>20.0±13.3 | | 0.39 |
| Vancomycin treatment time (days) | 1 - 7 | 48 | | 22 | | 0.002* |
| | 8 - 14 | 116 | | 15 | | |
| | 15 - 21 | 50 | | 6 | | |
| | 22 - 28 | 17 | | 1 | | |
| | 29 - 35 | 9 | | 1 | | |
| | > 35 | 8 | | 0 | | |
| Vancomycin dosing change (n, %) | | 13 | 11.7% | 26 | 14.4% | 0.8 |
| TDM vancomycin 2nd (n, %) | | 19 | 17.1% | 37 | 20.4% | 0.5 |
| Trough vancomycin concentration 2nd monitoring (n [mean±SD]) (mg/L) | | n = 51<br>21.22±16.4 | | n = 5<br>33.1±22.5 | | 0.14 |
| Type of Infection | CNS infection | 23 | | 2 | | 0.004* |
| | Complicated infection | 126 | | 35 | | |
| | Soft and skin tissue infection | 99 | | 8 | | |
| MIC (mg/L) | <1 | 35 | | 5 | | 0.59 |
| | ≥ 1 | 2 | | 0 | | |
| Trough conc. 1st /MIC ratio (times) | ≤ 10 | 3 | | 3 | | 0.06 |
| | > 10 - 180 | 51 | | 9 | | |
| Vancomycin treatment time grouping (days) | ≤ 7 days | 48 | | 22 | | 0.0001* |
| | ≥ 8 days | 200 | | 23 | | |
| Clinical wards | Surgery-Internal | 224 | | 35 | | 0.037* |
| | ICU | 24 | | 9 | | |

**significantly different*

**Table 9. Multivariable binary logistic regression analysis on 4 monovariable risk factors related to the incidence rate of success for cases treated with vancomycin**

| Factors | B | P | OR | 95% CI of OR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Trough conc./MIC ratio ≤ 10 | -1.53 | 0.163 | 0.22 | 0.025 | 1.86 |
| SSTI vs CNS infection | 1.472 | 0.376 | 4.36 | 0.17 | 113.2 |
| SSTI vs Comp. Infection | 1.786 | 0.067 | 5.97 | 0.88 | 40.26 |
| Vancomycin time ≤ 7 days | -2.31 | 0.005* | 0.1 | 0.02 | 0.5 |
| Surgery-Internal vs ICU | -19.33 | 1.0 | 0 | / | / |

**significantly different*

**Table 10. Relationship between trough concentration of vancomycin and the minimum inhibitory concentration (MIC) of *S. aureus***

| | | Minimum inhibitory concentration (mg/L) of *S. aureus* | | | | p |
|---|---|---|---|---|---|---|
| | | 0.12 | 0.5 | 0.75 | 1.0 | |
| Trough concentration (mg/L) | ≤ 10 | 1 | 4 | 5 | 3 | 0.14 |
| | 10.1 - ≤ 15 | 0 | 4 | 5 | 2 | |
| | 15.1 - ≤ 20 | 0 | 3 | 2 | 5 | |
| | 20 - ≤ 30 | 0 | 3 | 5 | 9 | |
| | > 30 | 0 | 8 | 0 | 7 | |
| Conc./MIC ratio | ≤ 30 | 0 | 8 | 13 | 19 | 0.015* |
| | > 30 | 1 | 14 | 4 | 7 | |

**significantly different*

**Table 11. Relationship between trough concentration/MIC ratio x treatment time of vancomycin (clinical AUC/MIC) (mg/L/day) – cut-off value and treatment results of infection disease**

| Trough concentration/MIC ratio x treatment time vancomycin (mg/L/day) – Cut-off value | Treatment results of infection disease | | p |
|---|---|---|---|
| | Success | Failure | |
| > 190 | 41 | 4 | 0.004* |
| ≤ 190 | 13 | 8 | |
| | Sensitivity: 75.9% | Specificity: 66.7% | |

**significantly different*

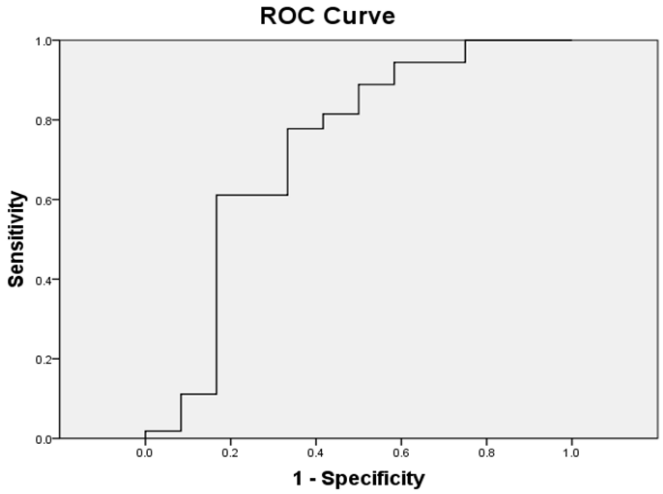


**Fig. 1. ROC of trough concentration/MIC ratio x treatment time of vancomycin versus "success" result of infection treatment of vancomycin. The area under the curve was 0.727 [0.54 – 0.92], p = 0.015. Cut-off value suggested as 190 mg/L/day**

## 4. DISCUSSION

### 4.1 Clinical Performance of Vancomycin Monitoring

The initial or maintenance dose of vancomycin is guided as 15-20 mg/kg [11], but clinical routine use as 0.5 - 1g per IV perfusion time. This study showed the dose of 1 g accounting 94.2% (275/292 cases). The vancomycin dosing interval based on renal clearance, briefly as 8-12 h for creatinine clearance ≥ 50 ml/min, 24 h for 35 – 49 ml/min, 48 h for 25-34 ml/min [11,10,2], and dose by daily level for < 25 ml/min, the correct dosing interval was found as 80.8% (235/291 cases) in this study. It had trend to shorten dosing interval compared to eGFR, i.e. dosing interval 12 h was given to cases with eGFR < 50 ml/min/1.73 $m^2$.

The first time for vancomycin monitoring be performed was guided at 4th dose in person with normal renal function; and in earlier time if patients in critical ill, unstable renal function or receiving vancomycin dosing interval ≥ 24 hours [11,2]. This study investigated on currently practical application of vancomycin in a tertiary hospital revealed only 99 cases having the first monitoring of vancomycin at 4th to 8th dose (33.9%), and 139 cases on 9th dose or later (47.6%). Frequency of monitoring recommended as once-weekly time for hemodynamically stable patients, or more frequency, 2-3 times weekly, for patients with unstable renal function, hemodynamitically compromised. This study found only 56 cases received the second monitoring of vancomycin concentration among 222 cases having vancomycin treatment >7 days (56/222: 25.2%).

### 4.2 Pharmacokinetics of Trough Concentration of Vancomycin

The percentage 37.7% (110/292 cases) of patients reaching optimal range of trough concentration, 10-20 mg/L, in the first regimen of vancomycin in this study was equivalent to those revealed in previous prospective studies in Viet Nam [12,13]. Both retrospective study and prospective studies showed 30 - 60% of cases needed dose adjustment after the first regimens of vancomycin following to experience or guidance. The American Thoracic Society (ATS) suggested an initial empirical vancomycin dose of 15 mg/kg every 12 hours in adults with normal renal function (equivalent to 1 gram/12 hrs.) [144]. However, based on pharmacokinetics of vancomycin, that empirical dose of vancomycin could not produce trough concentration of 15-20 mg/L as proved by this study. The proportion of predicted optimal vancomycin trough concentration in range 10-20 mg/L during the first 4 days of therapy was 22%, and 77% in lower concentrations (< 10 mg/L) [15]. Pediatric pharmacokinetics of vancomycin in Canadian also reported the proportion of 60% trough concentrations fell within therapeutic range 5-10 mg/L up to the fifth day of vancomycin treatment [16].

A recent retrospective pharmacokinetic analysis of serum levels of vancomycin determined during routine monitoring of 46 patients in a medical ICU concluded that standard dosages of vancomycin led to a 33% risk of not achieving the recommended area under the concentration-time curve over 24 h/MIC breakpoint for *S. aureus* [17]. The dose of 15 mg/kg of vancomycin given every 8 hours in children gave around 60% of cases reaching concentration of 5-15 mg/L [18]. In conclusion, the first vancomycin treatment doses, based on experience or monogram-based guidance, did not get the trough concentrations in target range, thus the dose adjustment must be considered as important point for any cases treated with vancomycin.

Up to now, it seems no data indicating that achieving the optimal concentration is easy and safe by the dose adjustment. The increase or decrease of dose in adjustment caused the proportional response in drug concentration. This study showed that comparing to the first concentrations, sensitivity of vancomycin concentration decreased as 69.3% with dose reduction, and 83.3% with dose increase, p = 0.03. Although having the parallel response of concentrations to the dose adjustment, but it could not be enough to bring concentrations to the target of optimal range.

This study showed the failure of reaching to the optimal range of vancomycin concentrations, 10-20 mg/L, in 19 cases with dose treatment adjusted, 6 patients reached concentrations in range of 10-20 mg/L (31.6%) and 13 still be out of target (68.4%). Comparing to 37 cases without dose adjustment but receiving the 2nd concentration monitoring, 11 cases in optimal range, 10-20 mg/L, (29.7%) and 26 others out of range concentration (70.3%). Thus, the dose adjustment did not give any positive effect (p = 0.95). Thomson et al. [15], using population pharmacokinetic model suggested the new high dose guidance of vancomycin to get 55% chance having optimal concentrations, as 1250 and 1500 mg per 12 hours for renal clearance 90-110 ml/min and > 110 ml/min, respectively. It means the higher dose for higher renal clearance. This study revealed the odd ratio for having high concentration ≥ 20 mg/L in patients with eGFR < 60 was 3.3 (95% CI: 1.9 -5.6), p = 0.0001. The odd ratio (OR) for low vancomycin concentrations in young patients compared to elderly ones was 5.9 [95% CI: 2.6 – 14.0], p = 0.0001. In conclusion, the talent in management of dose adjustment is a challenge of good combination of all factors such as population pharmacokinetic model, eGFR level, age of patients.

In this study, the independent predictors affecting to vancomcycin had been evaluated in details by

classification of concentrations into 3 subclass analysis. The first subclass comparison between concentrations ≤ 10 mg/L versus > 10 mg/L 2 independent factors were found as eGFR < 60 ml/min/1.73 $m^2$ (p=0.001) and older age >40 yrs. (p=0.01) in prefer to have the high vancomycin concentrations > 10 mg/dL. The second one between concentrations ≤ 20 mg/L versus > 20 mg/L 2 independent factors were the same as eGFR <60 ml/min/1.73 $m^2$ (p=0.0001) and elderly age > 60 yr. (p = 0.017). And the third one between optimal concentrations, > 10 - ≤ 20 mg/L, versus"out of range" concentrations, ≤ 10 or >20 mg/L, only one factor was age affecting to vancomycin concentration. The odd ratio (OR) of capacity of "out of range" concentration (≤ 10 or > 20 mg/L) in young patients (≤ 40 yr.) compared to elderly ones (> 40 yr.) was 2.5 [95%CI: 1.3 – 4.8], p = 0.0009. In conclusion, the main factors affecting to trough concentration of vancomcyin were eGFR < 60 ml/min/1.73 m2, older age > 40 yr., elderly age > 60 yrs. These factors should be considered in both initial doses and adjusting doses of vancomycin. This finding was in agreement with the population pharmacokinetic model for initial higher doses (1250-1500 mg vancomycin) for patients with high renal clearance > 90 ml/min suggested by Thomson et al. [15]. Thus, in clinical treatment, using high initial doses of vancomycin is needed for young patients with normal kidney function.

### 4.3 Vancomycin and Nephrotoxicity

Role of vancomycin monitoring in preventing nephrotoxicity was guided in ASHP Therapeutic Position Statements 2008 [2]. The frequency of monitoring may be more to patients targeting to produce sustained trough concentrations of 15-20 mg/L or higher, or who are at risk of toxicity, such as receiving concurrent nephrotoxins. In this study, 151 cases having trough concentrations > 15 mg/L, but only 27 cases received 2nd monitoring.

There were 190 cases measured 2nd blood creatinine after receiving vancomycin having 16 cases with suggested nephrotoxicity rate as 8.4%, based on published criteria [6-10]. This finding was in range of rate of nephrotoxicity from 0% to 17% for vancomycin monotherapy and 7 to 35% with concurrent administration of aminoglycosides in previous studies [7,19-23].

Fifty-six cases had 2nd monitoring vancomycin in which 4 out of 5 nephrotoxic cases had trough concentrations > 30 mg/L (80%) compared to 6/51 in non-nephrotoxic group (11.7%), p = 0.004. Explanation in other way, the rate of nephrotoxicity was 40% (4/10) in patients with high concentration ≥ 30 mg/L, compared to 2.17% (1/46) if low concentration < 30 mg/L. This result was equivalent to one revealed from prospective study of Hidayat et al. [8] as nephrotocicity rate of 0% versus 12% in patients with trough vancomycin < 15 versus whom with ≥ 15 mg/L, p=0.01; or in study of Nguyen *et al*. 2007 [24]. The risks of nephrotoxicity may be as co-administration of other nephrotoxic agents, prolonged therapy and concentrations above 10 mg/L [10,25],vancomycin doses above 4 g/day [9], trough concentrations above 15 mg/L [26,7,8].

### 4.4 Clinical Pharmacodynamics of Vancomycin

There were 4 predictors for treatment failure of vancomycin in monovariable analysis as trough conc./MIC ratio ≤ 10 (OR = 5.7 [95% CI: 0.98 – 32.6], p=0.06), type of infection as complicated infection (OR= 3.4 [95%CI: 1.6 – 7.1], p=0.0009), vancomycin treatment time ≤ 7 days (OR = 4 [95%CI: 2.1 – 7.7], p=0.0005, and clinical ward group of ICU (OR=2.4 [95%CI: 1.03 – 5.6], p = 0.043). The finding of 3-4 predictors for treatment result from this study was so different from previous studies [27].

There was no difference in trough concentration of vancomycin in both 1st and 2nd monitorings between success cases and failure cases in this study. Feffres MN et al. in a retrospective study on 102 patients with health-care-associated MRSA pneumonia also found no significant differences between survivors and non-survivors in terms of trough serum vancomycin concentrations and AUCs [26]. The ratio between trough concentration of vancomycin over MIC of 10 times seemed to be a trend for prediction of treatment result in this study with OR of 5.7, but unfortunately not reaching to significant difference (p = 0.06). No relationships were found between peak concentrations, trough concentrations, or pharmacodynamic parameters (e.g., peak/MIC, time above the MIC, or AUC/MIC) and organism eradication or overall patient outcome [25].

The concept of concentration-dependent killing is simplified with pharmacodynamics parameter as peak/MIC ratio ≥ 10 times for aminoglycosides and fluoroquinolones [28,29]. The parameter for optimal response for time-dependent killing

antibiotics (beta-lactams, clindamycin, linezolid) as the time of drug concentrations above MIC is ≥ 50% of the dosing interval [28,29]. This study showed that the trough concentration of vancomycin/MIC ratio ≥ 10 times was accounting 91% (60/66 cases) and 100% of trough vancomycin concentrations were higher than MIC over the whole treatment time. Both these parameters showed that vancomycin has combining action on both concentration-dependent killing and time-dependent killing antibiotics as suggested from previous papers [28,30-32]. The duration of bacteremia was 2 days in nafcillin group and 5 days in vancomycin group [33]. In patients received vancomycin for endocarditis, the duration of bacteremia was even more prolonged with mean of 7 days [34]. The apparently slower bacterial killing action of vancomycin than previous studies has been recognized [30]. Bacteremia due to heterogeneous vancomycin-intermediate *S. aureus* (hVISA) was reported so long as 39 days [35].

The multivariable binary logistic regression analysis revealed only the duration of treatment of vancomycin was the only independent predictor for treatment success (OR = 0.1 [95% CI: 0.02 – 0.5], p = 0.005). This OR of 0.1 showed that the chance for treatment success in patients treated ≤ 7 days was 10 times lesser than whom who had the longer treatment (≥ 8 days).

The theoretical value of AUC/MIC ratio was not easily applied in clinical treatment because of the lack of peak concentration of vancomycin. Thus, we proposed a similar parameter called as "clinical AUC/MIC ratio". The clinical AUC/MIC ratio was defined as multiple of trough concentration/MIC ratio with duration of treatment of vancomycin (days). The ROC showed the area under the curve (AUC) of clinical AUC/MIC ratio of 0.727 [0.54 – 0.92], p = 0.015. Cut-off value suggested as 190 mg/L/day (Fig. 1). The sensitivity and specificity of this clinical AUC/MIC ratio cut-off was 75.9% and 66.7%, respectively for the prediction of success result in treatment (Table 11).

The clinical AUC/MIC ratio was suggested in this study with aiming to find out some clinical parameter for prediction the outcome of treatment. This finding was in agreement with hypothesis that vancomycin acts by both parameters: concentration-dependent and time-dependent actions [30,28,31,32]. This result will encourage clinical doctors in trying to prolong more treatment days of vancomycin as good as possible, may be more than 10 days, before saying about the failure of this luxury drug. The properly use of vancomycin according to both pharmacokinetics and pharmacodynamics will be supported by result of this study. The widespread resistance of *S. aureus* against vancomcycin has continued by times. The Centers for Disease Control and Prevention (CDC) in May-2015 announced the criteria for classification of vancomycin-intermediate *S. aureus* (VISA) with minimum inhibitory concentration (MIC) for vancomycin of 4-8 µg/ml, and vancomycin-resistant *S. aureus* (VRSA) with vancomycin MIC ≥16 µg/ml [36].

## 5. CONCLUSION

The therapeutic drug monitoring of vancomycin has been applied in routine clinical treatment. However, the guidance criteria of this TDM are not followed strictly, especially for dosing intervals, dosing adjustment and follow-up after the first monitoring. The changes in dose adjustment affected directly to drug concentrations afterwards, but not yet helping to reach into the target of optimal range, 10 – 20 mg/L. This is still a big challenge requirement the deep understanding of physicians about the pharmacokinetics and pharmacodynamics of vancomycin. The predictors for vancomycin concentrations were eGRF, age. Nephrotoxicity rate was found as 8.4%, often associated with high trough vancomcycin concentration > 30 mg/L. The clinical AUC/MIC ratio of 190 mg/L/day was the cut-off value for the prediction of success result in treatment with sensitivity and specificity of 75.9% and 66.7%, respectively.

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## CONSENT

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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