Evaluation of the association between trough and area under the curve to minimum inhibitory concentration ratio (AUC\textsubscript{24}/MIC) of vancomycin in infected patients with MRSA

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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.

Method:

The inpatients 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. Result:

38 patients with average age of 48.33 (SD 16.44) were enrolled in this study. The mean ± SD of MIC was reported as 0.99±0.30 mg/L. 34 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 94.10% and specificity of 75.00%.

Conclusion:

This study concluded using only a trough level is not appropriate for therapeutic drug monitoring (TDM) of the 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.

Key words:

Vancomycin, AUC$_{24}$/MIC, trough serum level, severe infection, methicillin-resistant *Staphylococcus aureus*, therapeutic drug monitoring (TDM)
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.\textsuperscript{1,2} Vancomycin as a first-line for treating methicillin-resistant \textit{staphylococcus aureus} (MRSA) with minimum inhibitory concentration (MIC) less than 1.5 mg/L, widely ordered in the hospitals, especially in critical care settings.\textsuperscript{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.\textsuperscript{3,4} Due to the Song, K.H et al.’s study, AUC\textsubscript{24}/MIC less than 397.2 (by E-test) resulted in treatment failure.\textsuperscript{5} The meta-analysis by Prybylski et al. indicated that the vancomycin trough serum levels of more than 15 mg/L did not lead to decrease in treatment failure ratio.\textsuperscript{6} Due to the studies, trough serum levels greater than 10 mg/L is necessary to reach AUC\textsubscript{24}/MIC $\geq$ 400, but more than 50\% of patients obtained the goal of AUC\textsubscript{24}/MIC $\geq$ 400, while their trough levels are less than 15 mg/L.\textsuperscript{7,8} In contrast to the trough levels of vancomycin $\geq$ 15 mg/L, while the AUC\textsubscript{24}/MIC value between 400 and 600 did not have a close association with vancomycin induced nephrotoxicity.\textsuperscript{8,9} The other complication shows the vancomycin resistance or less susceptible \textit{staphylococcus aureus} (Vancomycin-resistant \textit{Staphylococcus aureus} and vancomycin-intermediate \textit{Staphylococcus aureus}) with MIC $>2$ mg/L as a result of irrational vancomycin dosing and use.\textsuperscript{10} On the other hand, MIC $\geq$ 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;\textsuperscript{1,11} therefore, it is the best practice to identify the MIC pattern of \textit{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\textsubscript{24}/MIC and steady-state trough levels of vancomycin and show the resistance pattern of MRSA in our hospital.

\textbf{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\textsuperscript{12} or chronic kidney disease with estimated glomerular filtration rate (eGFR) $<15$ ml/min or dialysis\textsuperscript{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\textsuperscript{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\textsubscript{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. The quantitative luminescent analysis method used to assay the vancomycin concentration with an abbot analyzer instrument made in the 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\textsubscript{24}, k elimination (K\textsubscript{e}), the volume of distribution (V\textsubscript{d}), half-life, and the clearance of vancomycin for each patient.\textsuperscript{15,16} Due to each patient’s MIC, AUC\textsubscript{24}/MIC were calculated, and our goals were AUC\textsubscript{24}/MIC$\geq$400 and/or vancomycin trough level $\geq$ 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.\textsuperscript{17} Using two post-dose serum concentrations (the peak serum and second trough levels), the elimination rate constant (K\textsubscript{e}) of each patient was directly calculated $[K\textsubscript{e}=(\ln C\textsubscript{ss,max}-\ln C\textsubscript{ss,min})/T'$, where C\textsubscript{ss,max} and C\textsubscript{ss,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 $[t_{1/2}=0.693/K\textsubscript{e}]$. The volume of distribution is calculated utilizing $[V\textsubscript{d}=D/(C\textsubscript{ss,max}-C\textsubscript{ss,min})]$, 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—$\infty$). These two future parameters were calculated as $[CL\textsubscript{1}=K\textsubscript{e} \times V\textsubscript{d}]$ and $[AUC(0—\infty)=D/CL\textsubscript{T}]$, respectively.\textsuperscript{18}

Statistical analysis

For data analysis, the patients were categorized into two groups as follows: patients with eGFR$<$60ml/min, patients with eGFR $\geq$ 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 $\pm$ 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 $AUC_{24}/MIC \geq 400$, 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 $AUC_{24}/MIC \geq 400$ with strong specificity and sensitivity. AUC more than 0.8 is an indication for good accuracy. The p-value of less than 0.05 were showed a significant difference.

Results

The patients’ baseline characteristics:
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), 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. 3 (75.00%) and 2 (50.00%) patients with $AUC_{24}/MIC < 400$ 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 $AUC/MIC \geq 400$, 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. The $AUC_{24}$ measurement depend on method of infusion (continues and intermittent), 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, Tehran, 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 outcomes with other general populations. 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. $^{24-26}$

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.

The MIC of MRSA isolated from 38 patients’ various clinical specimens were equal or lower than 1.5 mg/dl ($\text{mean ± SD: } 0.99±0.30$), 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$_{\text{BMD}}$ > 2 mg/dl, simultaneous 5 cases of them had MIC$_{\text{BMD}}$ 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$_{\text{Etest}}$ equal or greater than 400 in patients with MIC$_{\text{Etest}}$ <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 microorganism in there.\textsuperscript{34} Due to some studies\textsuperscript{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, $\text{AUC}_{24}/\text{MIC}$ would be over 400 again.

Shahrami et al.’s study was conducted to compare the standard and individualized vancomycin dosing on 20 critically ill patients to achieved $\text{AUC}_{24} > 400$ and steady-state trough level $> 15\text{ mg/L}$. They reported that individualization based dosing vancomycin is superior to standard dosing vancomycin to achieve therapeutic trough level of $15\text{-}20\text{ mg/L}$ and higher steady state $\text{AUC}_{24}$.

Considering this study, $65.5\%$ of patients (n=10) with standard dosing failed to achieve therapeutic trough level, but just $14.3\%$ had $\text{AUC}_{24}$ less than 400.\textsuperscript{37} Although the design of Shahrami study 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 $\text{AUC}_{24}$; we both concluded that $\text{AUC}_{24}$ was a better parameter to optimize vancomycin dosing.

Due to ROC test, if the second trough level sample were greater than $10.81\text{ mg/L}$, $\text{AUC}_{24}/\text{MIC}$ 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 $\text{AUC}_{24}/\text{MIC}$ ratio was not achieved 400 or more with serum level of vancomycin less than $10\text{ mg/L}$.\textsuperscript{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 $< 60\text{ ml/min}$ and $\geq 60 \text{ ml/min}$ 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.\textsuperscript{38}

Khoie et al. accomplished a study in 22 patients with chronic kidney disease\textsuperscript{39} ($15 \leq \text{GFR} \leq 60\text{ mL/min}$) treated with vancomycin due to traditional dosing to determine $\text{AUC}_{24}/\text{MIC}$ 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,\textsuperscript{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.\textsuperscript{24,41} Several pharmacokinetic studies have suggested many equations that showed the relation between the clearance of vancomycin and eGFR \textsuperscript{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 $\geq 1.5\text{ mg/L}$ for \textit{Staphylococcus aureus} has the main role to predict the treatment failure and choosing a proper first-line antibiotics.\textsuperscript{11,44} The average vancomycin MIC of MRSA in our study was $0.98 \pm 0.28\text{ mg/L}$, and vancomycin was prescribed as the first-line to treat the MRSA with usual dose $15\text{-}20\text{ mg/kg}$ twice daily (usually 2 gr per day), in our setting which was reasonable in patients with eGFR $\geq 60\text{ ml/min}$.

Like any other investigational studies, our study was subjected to limitations. The effect of vancomycin trough level versus $\text{AUC}_{24}/\text{MIC}$ 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 AUC24/MIC.
The other limitation of the study was that in our hospital, MIC was still measured with E-test, and
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, AUC24/MIC ≥ 400 was achieved
with trough level ≥10.81 mg/L of the fourth dose and MIC< 1 mg/L. The target AUC24/MICE-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.
10. McGuinness WA, Malachowa N, DeLeo FR. Vancomycin resistance in


31. Razeghi M, Saffarian P, Goudarzi M. Incidence of inducible clindamycin resistance and antibacterial resistance genes variability in clinical staphylococcus


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


45. EUCAST T. European committee on antimicrobial susceptibility testing, breakpoint tables for interpretation of mics and zone diameters. European Society of Clinical Microbiology and Infectious Diseases Basel …; 2015.
Table 1: Patient characteristics and diagnostic data at baseline (N= 38)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>48.33±16.44</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>67.78±13.98</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.08±11.65</td>
</tr>
<tr>
<td>BMI (Kg/M^2)</td>
<td>23.71±2.86</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>38.89±12.77</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.01±0.26</td>
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</table>

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Patients number (percentage %)</th>
</tr>
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<tbody>
<tr>
<td>Neutropenic fever</td>
<td>8 (21.05%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (15.70%)</td>
</tr>
<tr>
<td>Surgery (general)</td>
<td>5 (13.15%)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>4 (10.52%)</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>3 (7.89%)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma in the buccal</td>
<td>3 (7.89%)</td>
</tr>
<tr>
<td>Infection after fracture</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>1 (1.63%)</td>
</tr>
<tr>
<td>Infected Liposarcoma</td>
<td>1 (1.63%)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Antibiotic IV therapy regimens + vancomycin</th>
<th>Patients number (percentage %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>16 (42.10%)</td>
</tr>
<tr>
<td>Clindamycin + Ciprofloxacin</td>
<td>5 (13.15%)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>4 (10.52%)</td>
</tr>
<tr>
<td>Meropenem + Cotrimoxazol</td>
<td>3 (7.89%)</td>
</tr>
<tr>
<td>Ceftriaxan</td>
<td>3 (7.89%)</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Meropenem + Ciprofloxacin</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Piperacillin- tazobactam</td>
<td>2 (5.26%)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 (2.63%)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
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<tr>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Trough 1&lt;sup&gt;1&lt;/sup&gt; (mg/L)</td>
<td>14.50 ± 6.33</td>
</tr>
<tr>
<td>Trough 2&lt;sup&gt;2&lt;/sup&gt; (mg/L)</td>
<td>17.36 ± 6.74</td>
</tr>
<tr>
<td>Peak level (mg/L)</td>
<td>36.60 ± 13.32</td>
</tr>
<tr>
<td>AUC&lt;sup&gt;3&lt;/sup&gt; (mg*hr/ L)</td>
<td>660.14 ± 289.66</td>
</tr>
<tr>
<td>AUC/ MIC&lt;sup&gt;4&lt;/sup&gt;</td>
<td>730.61 ± 398.85</td>
</tr>
<tr>
<td>K&lt;sub&gt;e&lt;/sub&gt;&lt;sup&gt;5&lt;/sup&gt; (1/hr)</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;&lt;sup&gt;6&lt;/sup&gt; (hr)</td>
<td>22.82 ± 10.14</td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td>54.28 ± 25.44</td>
</tr>
<tr>
<td>Volume of distribution/ weigh (L/kg)</td>
<td>0.82 ± 0.34</td>
</tr>
<tr>
<td>Clearance vancomycin (mL/minute/kg)</td>
<td>0.44 ± 0.23</td>
</tr>
<tr>
<td>eGFR&lt;sup&gt;7&lt;/sup&gt; (ml/min)</td>
<td>93.55 ± 45.42</td>
</tr>
</tbody>
</table>

1- Sample was collected 30 minutes before fourth dose of vancomycin at steady state, 2- Sample was collected 30 minutes before fifth dose of vancomycin at steady state, 3- area under the curve, 4- minimum inhibitory concentration, 5- elimination rate constant, 6- half-life, 7- estimated glomerular filtration rate
Table 3: Serum levels of vancomycin and pharmacokinetics analyses according to eGFR<sup>1</sup> less than 60 ml/min or higher (n=38)

<table>
<thead>
<tr>
<th></th>
<th>eGFR&lt;sup&gt;1&lt;/sup&gt;&lt;60ml/min</th>
<th>eGFR&lt;sup&gt;1&lt;/sup&gt;≥60ml/min</th>
<th>P- value&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough 1&lt;sup&gt;2&lt;/sup&gt; (15-20 mg/L) (N%)</td>
<td>1 (14.32%)</td>
<td>6 (19.45%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Trough 2&lt;sup&gt;2&lt;/sup&gt; (15-20 mg/L) (N%)</td>
<td>3 (42.93%)</td>
<td>7 (22.68%)</td>
<td>0.27</td>
</tr>
<tr>
<td>P&lt;sub&gt;-value&lt;/sub&gt;</td>
<td>0.76</td>
<td>6 (19.45%)</td>
<td>1 (14.32%)</td>
</tr>
<tr>
<td>N=31</td>
<td>7 (22.68%)</td>
<td>3 (42.93%)</td>
<td></td>
</tr>
<tr>
<td>N=7</td>
<td>6 (19.45%)</td>
<td>1 (14.32%)</td>
<td></td>
</tr>
<tr>
<td>K&lt;sub&gt;e&lt;/sub&gt;&lt;sup&gt;5&lt;/sup&gt; (1/hr)&lt;sup&gt;4&lt;/sup&gt;,</td>
<td>0.028 (0.019-0.032)</td>
<td>0.036 (0.027-0.041)</td>
<td>0.02</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;&lt;sup&gt;6&lt;/sup&gt; (hr)&lt;sup&gt;4&lt;/sup&gt;,</td>
<td>24.43 (21.82-36.35)</td>
<td>19.47 (16.91-25.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume of distribution (L)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>51.91 (38.35-60.12)</td>
<td>49.32 (36.86-68.31)</td>
<td>0.94</td>
</tr>
<tr>
<td>Clearance of vancomycin</td>
<td>1.2 (0.9-1.6)</td>
<td>1.7 (1.4-2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>(L/hr)&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1- Estimated glomerular filtration rate, 2- Sample was collected 30 minutes before fourth dose of vancomycin at steady state, 3- Sample was collected 30 minutes before fifth dose of vancomycin at steady state, 4- The value reported as median (interquartile range), 5- elimination rate constant, 6- half- life, 7- P-value <0.05 was considered as significant.
Figure 2: the AUC24 versus vancomycin trough concentration before fifth dose was shown in figure 2. The R² was 0.4555.