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Original Research

Optimizing Vancomycin dosing in a sample of critically ill patients comparing current practices to individualized dose regimen: A Randomized study

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Abstract

Background: In 2020, a revised consensus guideline of therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections was published, and reviewed by many regulatory authorities Stated that, in patients with suspected or definitive serious MRSA infections, an individualized dose targeting area under the curve over 24 hour (AUC24) to minimum inhibitory concentration (MIC) ratio of 400 to 600 mcg*hr/mL should be advocated to achieve clinical efficacy and improving patient safety, while many hospitals in Iraq utilize fixed manufacturer-recommended dose for vancomycin in patients with normal renal function which is 30 mg/kg/d given as two or four divided daily doses. **Objective:** Comparing vancomycin AUC24/MIC ratio of patients receiving conventional vancomycin doses to patients receiving individualized doses calculated by pharmacokinetic dosing methods. **Methods:** A prospective randomized study conducted in the Intensive Care Units (ICU) of two tertiary centers at Baghdad Medical Complex (Baghdad Teaching Hospital and Ghazi Al-Hariri Hospital for Surgical Specialties), Patients were assigned alternately, 30 patients who met inclusion criteria were assigned to the conventional group (group 1), receiving the conventional dose of 1 g of vancomycin every 12 hours or any other dose prescribed by ICU physicians, representing the current practice; and 30 patients were assigned to the interventional group (group 2), where vancomycin dose was calculated by pharmacokinetic dosing method. **Results:** The target AUC24/MIC Ratio of 400 – 600 mcg*hr/mL was achieved in 6 (20%) patients of group 1, and 16 (53.33%) patients of group 2, which was statistically significant with P-value 0.000.

Conclusions: Individualized vancomycin dosing improved achievement of the therapeutic AUC24/MIC target versus conventional dosing (53.3% vs 20.0%) but was associated with increased nephrotoxicity.

Keywords: Vancomycin, Drug Monitoring, Area Under Curve, Intensive Care Units

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INTRODUCTION

Vancomycin is an antibiotic isolated from certain bacterial strains of Amycolatopsis orientalis (Nocardia orientalis, Streptococcus orientalis) or obtained by any other means[1-3]. An essential antibiotic for treating severe Gram-positive infections due to its large molecular weight and lack of penetration through Gram-negative cell membranes[1]. It is a bactericidal tricyclic glycopeptide (The class originator for glycopeptides and Teicoplanin is similar but longer lasting) having a molecular weight of 1446 Da that was first used in medicine in 1956[2,4,5]. Its chemical structure is shown in (Figure 1)[6]. Early batches of vancomycin included serious contaminants, which caused it to have fluctuating toxicity and earned the moniker "Mississippi mud." Production of this antibiotic was subsequently altered to ensure that preparations are completely free of these contaminants[7]. Today Methicillin-resistant *Staphylococcus aureus (*MRSA) and other Gram-positive beta-lactam-resistant bacteria are often treated with vancomycin as a first-line medication[8]. This agent works by inhibiting the cell wall biosynthesis by the establishment of stable complex murein pentapeptides, in other words, leading to the inhibition of additional peptidoglycan foundation[9]. This action sets off a chain of events and activates enzymes that break down cell walls and cause additional cell damage. The optimal bactericidal activity of vancomycin and its comparatively low price makes it one of the most regularly prescribed antibiotic[10].

When treating patients with Vancomycin, therapeutic drug monitoring (TDM) is known as a vital element of the management strategy. Vancomycin use that is safe and effective must adhere to recommendations regarding loading dose, TDM, and dosage reduction in renal dysfunction and other pathophysiological circumstances. Vancomycin under-dosing directly contributes to the growth of vancomycin-resistant enterococci, and vancomycin-resistant Staphylococcus aureus, an issue that is of particular concern internationally[11]. It has an α-distribution phase of ?30 min to 1 h and a β-elimination half-life of 6–12 h (Figure 2)[12] and is predominantly excreted by the renal route, within 24 hours of administration of a single dose, more than 80%-90% of

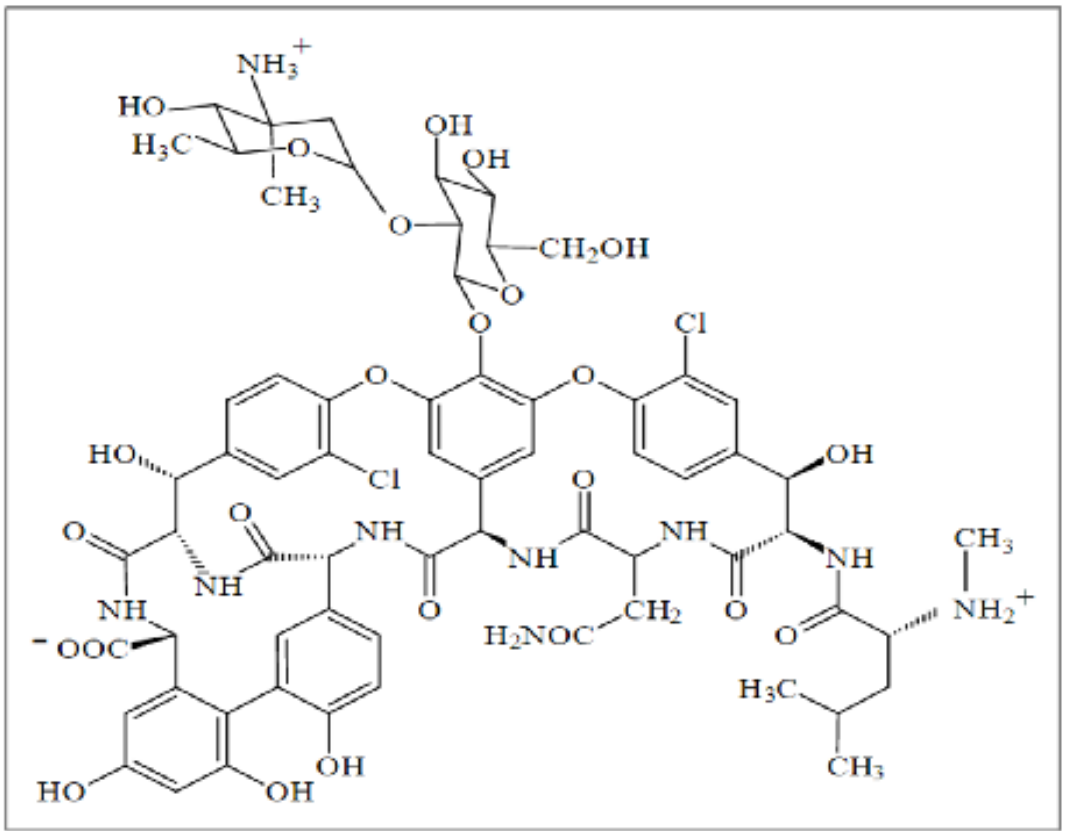

Figure 1. Structure of vancomycin Hydrochloride[6]

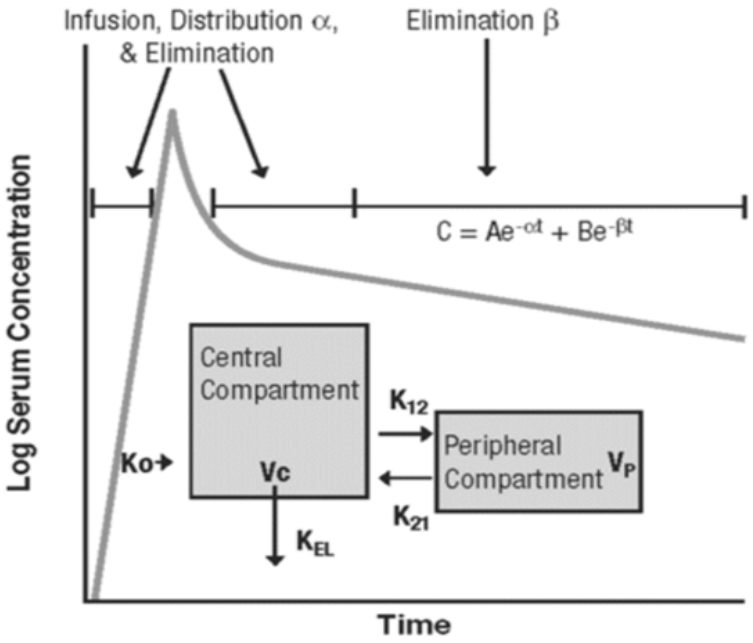

Figure 2: Schematic representation of a 2-compartment pharmacokinetic model, wherein C is the concentration, α and β are the respective elimination constants, e is the base of the natural logarithm, t is time, A and B are the respective zero time intercepts for α and β, Ko is the infusion rate constant, Vc is the volume of the central compartment, Vp is the volume of the peripheral compartment, K12 and K21 are intracompartmental rate constants, and KEL is the elimination rate constant from the central compartment[14].

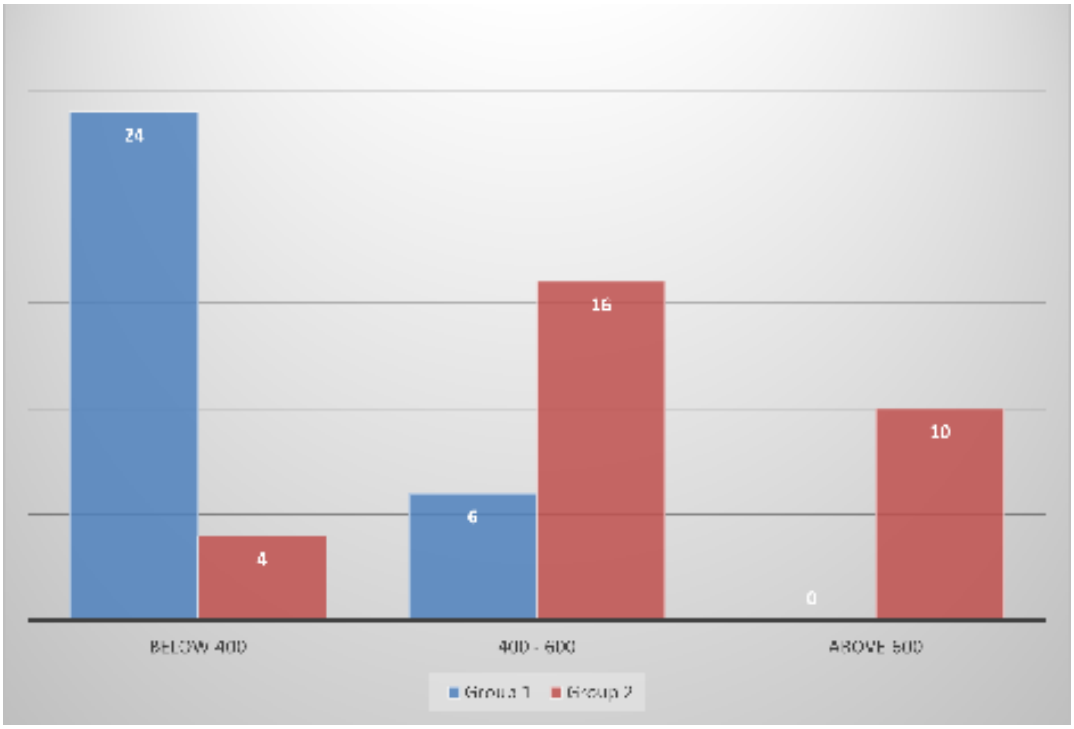

Figure 3: Subgroup analysis of vancomycin AUC24/MIC Ratio

it is recovered unchanged in the urine[13], Elimination t 1/2 is about 6 h in normal renal function[2].

The first consensus guideline for therapeutic monitoring of vancomycin in adult patients was published in 2009. The primary recommendations consisted of eliminating routine monitoring of serum peak concentrations, emphasizing a ratio of area under the curve over 24 hours to minimum inhibitory concentration (AUC/MIC) of ≥400 as the primary PK/PD predictor of vancomycin activity, and promoting serum trough concentrations of 15 to 20 mg/L as a surrogate marker for the optimal vancomycin AUC/MIC if the MIC was ≤1 mg/L in patients with normal renal function[4].

The recommended manufacturer dose for vancomycin in case of normal renal function is 30 mg/kg/d given in two or four divided doses per day. In normal-weight, the dose is usually 2 gram per day given as 1000 mg every 12 hours. However, these doses will not usually achieve recommended trough concentrations to treat serious infections[14]. These doses are still in the undergraduate lectures and textbooks and still widely used in daily practice.

In 2020 this guideline was revised by evaluating the current updated data associated with vancomycin dosing and serum concentration monitoring for serious MRSA infections[15]. Targeting individualized AUC/MIC_{BMD} ratio (with the MIC determined by broth microdilution [BMD]) of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) (A-II), using the doses of 15 to 20 mg/kg (based on actual body weight) to be administered 8-12 hours as an intermittent infusion in normal kidney function (A-II)[15]. Unencouraging Trough-only monitoring and its targets in patients with serious MRSA infections.

Previously, AUC monitoring necessitated the collection of different concentrations within the same dosage interval. A clinician would use this data to calculate the AUC using the linear-trapezoid rule. This method needed accurate vancomycin concentration measurements, rendering it unfeasible outside of a research setting. This, however, is no longer the case. With minimal PK sampling, it is now possible to predict the AUC reliably[15]. Bayesian pharmacokinetic computer programs utilized to estimates pharmacokinetic properties, using one or more drug concentrations, and the concentrations do not need to be at a steady state[14]. The most common concerns with Vancomycin are the occurrence of acute kidney injury, with a varies from 5% to 43% according to the 2020 revised consensus guideline[15].

The objective of this study is to Compare vancomycin initial trough levels and AUC_{24}/MIC ratio of patients receiving conventional vancomycin doses to patients receiving individualized vancomycin doses calculated by pharmacokinetic dosing methods.

METHODS

Study Design and Setting

This Study is a prospective randomized study conducted in the

Intensive Care Units (ICU) of two tertiary centers at Baghdad Medical Complex (Baghdad Teaching Hospital and Ghazi Al-Hariri Hospital for Surgical Specialties), from April 2022 through December 2022, Patients were assigned alternately, 30 patients who met inclusion criteria were assigned to the conventional group (group 1), receiving the conventional dose of 1 g of vancomycin every 12 hours or any other dose prescribed by ICU physicians, representing the current practice; and 30 patients were assigned to the interventional group (group 2), where vancomycin dose was calculated by pharmacokinetic dosing method. Initial vancomycin trough level and AUC_{24}/MIC ratio was assessed for both groups.

Study population

All patients admitted to the Intensive Care Units (ICU) of Baghdad Teaching Hospital and Ghazi Al-Hariri Hospital for surgical specialties who prescribed Vancomycin were reviewed for inclusion in this study.

Inclusion criteria

1) Patients of 18 years old to 65 years. 2) Patient who received at least three to four doses of vancomycin and a steady state level reached. 3)Vancomycin trough level was collected properly at steady state.

Exclusion criteria

1) Patient status was not appropriate to get a blood sample [hemodynamically unstable or severe anemia requiring frequent blood transfusion]. 2) Patient's refusal [if conscious]. 3) The serum sample was not drawn appropriately [sample Hemolysis or Clotted]. 4) Loss follow-up because of Patient's death, discharge, or vancomycin trough level could not be collected. 5) Patients on hemodialysis or continuous renal replacement therapy [CRRT]. 6) Concomitant nephrotoxic medications [Loop Diuretics, Aminoglycoside, Amphotericin, Piperacillin/Salbuctam]

Sampling for vancomycin trough level

Blood samples were collected from all eligible patients treated with vancomycin hydrochloride. Vancomycin levels were quantified with ARCHITECT iVancomycin Reagent Kit (REF:1P30-29/G81999R01/B1PD00) (Abbott Laboratories Abbott Park, IL 60064 USA) (lot: 01019K000) using a chemiluminescent microparticle immunoassay (CMIA) on an Abbott Architect System platform, The ARCHITECT i2000SR immunoassay analyzer (Abbott Laboratories, Abbott Park, IL, USA), the reagent kit contains 100 test and 12 tests were used for calibration. The tests were performed at Baghdad Therapeutic Drug Monitoring Center / Baghdad Teaching Hospital.

Ethylenediaminetetraacetic known as potassium EDTA tube (tubes with lavender-purple stopper) was used to collect patient blood samples to obtain convenient blood plasma, as it is one of the verified specimen types and collecting tubes to be used with this assay as mentioned in the manual by ARCHITECT iVancomycin Reagent Kit.

Blood plasma was drawn and collected to determine initial Trough vancomycin concentration (30 minutes to one hour before the next dose) after steady-state concentration was reached, which occurs after the third to the fourth dose of vancomycin hydrochloride[14]. Blood plasma drawn at night shifts and holidays were stored according to the indicated conditions by ARCHITECT iVancomycin Reagent Kit manual; ≤ 3 days at room temperature, ≤ 8 days at 2-8□, ≤ 3 months at 20□ or colder. The blood samples were obtained by venous puncture or central lines, transferred to EDTA tubes, and separated by centrifugation for 8 to 10 min to obtain plasma as soon as possible after sample collection, plasma is visually inspected for proper separation and lack of hemolysis; and subsequently stored if needed for the required time within the appropriate condition.

DATA COLLECTION

The data collected from patient's medical files in a designed questionnaire which includes the following: hospital name, date of admission, patient's name, date of blood sample acquired, Demographic characteristics (age, gender, weight, and height), cause of admission, past medical history, ICU hospitalization days, ICU hospitalization during vancomycin therapy, baseline serum creatinine, and bacterial culture and sensitivity (C/S) results. The prescribed Vancomycin dose was registered and the first blood sample collection is scheduled on a separate note, and initial Vancomycin trough level was recorded. Nephrotoxicity side effect was evaluated, and recorded. All data were transferred to a master excel sheet for further study analysis.

Vancomycin initial dose calculations

Vancomycin hydrochloride (Voxin®) a product of Vianex S.A, with the lot number 011254A, is used for all patients included in this study. Vancomycin's initial dose was calculated using the pharmacokinetic dosing method which it is the most flexible allowing individualized target serum concentrations to be chosen for a patient[12]. The aim of initial vancomycin dosing is to calculate the optimal dose for the patient based on their disease state, factors that affect the pharmacokinetics of vancomycin, and the location and severity of the infection[14]. Vancomycin concentrations at steady-state peaks at the pharmacokinetics method are chosen to ensure optimal antibiotic penetration to the infection site and to prevent adverse drug responses. This value often falls within the range of 30–50 mg/L[14].

Ethical approval

The study was approved by the Iraqi board for medical

Specializations and ethical committee at Baghdad teaching hospital. Before patient participation in the Study, consent was obtained from the patients or from their relatives if not applicable, after thorough explanation of the study.

Sample size and power

An a priori calculation was performed for a chi-square test of independence in an r×c contingency table (df = 2), assuming a Cohen's w = 0.4 (medium-to-large effect), two-sided α = 0.05, and power = 0.80. Under these assumptions, the minimum total sample size is ≈61. (G*Power 3.1).

Statistical analysis

All patient data were transferred from an Excel master sheet and analyzed using the Statistical Package for the Social Sciences (SPSS, version 23). Descriptive statistics expressed as (mean ± standard deviation "SD") for continuous variables, and frequencies with percentages for categorical variables. Several contingency tables were created, and proper statistical tests were conducted. Categorical variables were compared using the chi square test, while means were compared using the independent sample T-test. Two-sided P < 0.05 was considered statistically significant. Where applicable, effect sizes (e.g., Cohen's w for chi-square; mean difference with 95% CI for t-tests) are reported, with results presented in tables and/or figures.

RESULTS

A total of 100 patients were reviewed for inclusion at ICU wards of Baghdad Teaching Hospital and Ghazi Al-Hariri Hospital for Surgical Specialties during the study period. 23 patients excluded from the study, 39 patients were fit to the inclusion criteria and assigned to the conventional group (group 1), where 9 patients are dropped because vancomycin trough level couldn't be collected. 38 patients were assigned to the interventional group (group 2), where loss of follow up occurred with 8 patients during the study period. As a result, 60 patients were included in this study, 30 patients in each group.

In this study, the patients' demographic characteristics and serum creatinine for the two groups, having each group with 30 patients, included (age, gender, weight, height) expressed as mean ± standard deviation and/or percentage. The results showed that the mean ± standard deviation (SD) of age for group 1 was 42.8 ± 19.07 years, and for group 2 was 43.8±18.49 years, which was non-significant (P-value = 0.837). The male participants were 20 (66.67%) of group 1, and 16 (53.33%) of group 2, where female participants were 10 (33.33%) for group 1, and 14 (46.67%) for group 2, statistical difference between the two groups was non-significant (P-value = 0.292). The mean ± SD of weight was 79.1 ± 12.85 kg for group 1, and 85.67 ± 23.92, which was

Table 1. Demographic characteristics and serum creatinine

Variables		Group 1(n=30)	Group 2(n=30)	*P*-value
Age (years)		42.8 ± 19.07	43.8 ± 18.49	0.837*1
Gender	**Male**	20 (66.67%)	16 (53.33%)	0.292*2
	Female	10 (33.33%)	14 (46.67%)	
	Total	30	30	
Weight (Kg)		79.1 ± 12.85	85.67 ± 23.92	0.19*1
Height (Cm)		172.27 ± 7.98	172.67 ± 11.73	0.878*1
Serum creatinine		0.848 ± 0.439	0.788 ± 0.478	0.616*1

* 1 Independent T-test, level of significance at P-value < 0.05

*2 Chi-square test, level of significance at *P*-value < 0.05

Table 2. Vancomycin-related variables

Variables	Group 1 (n=30)	Group 2 (n=30)	*P*-value
Vancomycin Clearance (ml/min/kg)	1.32 ± 0.64	1.45 ± 0.85	0.529*
Patients' Volume of Distribution (L)	55.43 ± 9.46	50.7 ± 10.83	0.077*
vancomycin elimination rate constant (K_e) (h^-)	0.114 ± 0.052	0.144 ± 0.076	0.084*
vancomycin half-life (h)	6.93 ± 3.77	6.5 ± 3.9	0.665*
dosage interval (h)	12.4 ± 2.2	9.33 ± 1.9	0.000*
Total daily dose (mg)	2000 ± 262.61	3766.67 ± 1472.35	0.000*
Vancomycin duration of therapy (days)	12.7 ± 2.83	12.27 ± 3.9	0.624*
Total Grams administered	27 ± 7.65	43.6 ± 21.7	0.000*

* Independent T-test, level of significance at *P*-value < 0.05

non-significant (P-value = 0.19). The mean ± SD of height was 172.27 ± 7.98 cm for group 1, and 172.67 ± 11.73 for group 2, which was non-significant (P-value = 0.878). The mean ± SD of serum creatinine was 0.848 ± 0.439 for group 1, and 0.788 ± 0.478, which was non-significant (P-value = 0.616), as shown in Table 1.

The results of Vancomycin-related variables (vancomycin clearance, patients' volume of distribution, vancomycin elimination rate constant (k_e), and vancomycin half-life, total daily doses, dosage interval of vancomycin, and total grams of vancomycin administered to each patient over hospitalization period) indicated that the mean ± SD of vancomycin clearance was 1.32 ± 0.64 ml/min/kg for group 1, and 1.45 ± 0.85 ml/min/kg for group 2 with P-value = 0.529 which is non-significant. The mean ± SD of patients' volume of distribution (Vd) was 55.43 ± 9.46 L for group 1, and 50.7 ± 10.83 L for group 2, with P = 0.077 which is statistically non-significant. The mean ± SD of the vancomycin elimination rate constant was 0.114 ± 0.052 h^- for group 1, and 0.144 ± 0.076 h^- for group 2, statistical analysis was non-significant between the two groups with P-value = 0.084. The mean ± SD of vancomycin half-life for group 1 was 6.93 ± 3.77 h, and for group 2 was 6.5 ± 3.9 h, with P-value = 0.665 statistically non-significant. For vancomycin doses information, It was shown that The mean ± SD of dosage interval in the group 1 was 12.4 ± 2.2 h, and was 9.33 ± 1.9 h for group 2, and the mean ± SD of total daily doses administered in group 1 were 2000 ± 262.61 mg, and in group 2 were 3766.67 ± 1472.35 mg, both of which were statistically significant with P-value = 0.000 for both dosage intervals and total daily doses of vancomycin. The mean ± SD of vancomycin grams administered to each patient over hospitalization period of the group 1 were 27 ± 7.65 g, and 43.6 ± 21.71 g for group 2, statistical analysis was significant with P-value = 0.000. Vancomycin duration of therapy for the two groups was statistically non-significant, P-Value = 0.624, where the mean ± SD of group 1 was 12.7 ± 2.83 days, and for group 2 was 12.27 ± 3.9 days, as shown in Table 2.

Vancomycin serum trough levels (in mcg/dl units) acquired from the two groups is analyzed, and the result of the statistical analysis was significant, with P-value = 0.000 where the mean ± SD of group 1 was 6.35 ± 3.85 mcg/dl, and 19.89 ± 11 mcg/dl for group 2. The measured AUC_{24}/MIC Ratio using vancomycin concentrations and the Bayesian pharmacokinetic computer program are analyzed. At which the mean ± SD of group 1 was 283.1 ± 89.28 mcg*hr/mL, and of group 2 was 682.67 ± 329.248 mcg*hr/mL, P-value = 0.000 which is statistically significant. The results as shown in Table 3.

The percentage of patients achieving the target AUC_{24}/MIC Ratio (between 400 – 600 mcg*hr/mL) is calculated. In order to do so, the AUC_{24}/MIC Ratio was divided into 3 ranges, below 400 mcg*hr/mL, 400 – 600 mcg*hr/mL, and above 600 mcg*hr/mL. the target AUC_{24}/MIC Ratio of 400 – 600 mcg*hr/mL was achieved in 6 (20%) patients of group 1, and 16 (53.33%) patients of group 2, which was statistically significant with P-value of 0.000. The results as shown in Table 4 and Figure 3.

The number of patients with concomitant nephrotoxicity incidence is acquired, with only group 2 having nephrotoxicity incidence, 6 (20%) of patients, With zero incidence for group 1. The statistical analysis was significant with P-value = 0.009. The results as shown in Table 5.

The percentage of vancomycin doses prescribed according to culture and sensitivity (C/S) or as an empirical therapy at admission is acquired. For group 1, 23 (76.67%) patient was prescribed vancomycin according to culture and sensitivity, and 7(23.33%) patients as empirical therapy. While for group 2, 21 (71%) patient was prescribed vancomycin according to C/S, and 9 (30%) patients as an empirical therapy, P-value = 0.559. The results as shown in Table 6.

DISCUSSION

According to the latest updates regarding vancomycin therapeutic monitoring on 2020, individualized AUC/MIC_{BMD} ratio targeting 400 to 600 mcg*hr/mL enhance patient safety and vancomycin efficacy, utilizing doses of 15 to 20 mg/kg (based on actual body weight) given every 8 - 12 hr as an intermittent infusion, A question here arise, does current hospital practice in Iraq achieve the target $AUC_{(24)}$/MIC ratio in ICU patients? many hospitals in Iraq lack specialized TDM centers where Vancomycin doses can be assessed and monitored properly, making optimal dose therapy and adjustment more difficult, in addition to the risk of therapy failure and the increased emergence of bacterial-resistant strains.

This study showed no statistically significant differences between the two groups regarding the patients' demographic characteristics, serum creatinine levels, table 1, and vancomycin-related variables, Table 2. The similarity between the groups enhances the robustness of the later statistical analyses by decreasing possible confounding variables.

In general, Vancomycin is prescribed to ICU patients as either an empirical therapy or according to culture and sensitivity (C/S), as in Table 6, Most of the patients in this study were prescribed vancomycin according to culture and sensitivity, with group 1, 23 (76.67%) patients were prescribed according to C/S, and 7 (23.33%) patients prescribed empirical therapy, while for group 2, vancomycin doses were 21 (71%), 9 (30%), respectively. P-value = 0.559.

Vancomycin-related variables

In table 2, most of the group 1 regimen received a dosing

Table 3. Vancomycin serum trough levels and AUC_{24}/MIC Ratios

Variables	Group 1(n=30)	Group 2(n=30)	*P*-value
Trough level (mcg/dl)	6.35 ± 3.85	19.89 ± 11	0.000*
AUC_{24}/MIC (mcg*hr/mL)	283.1 ± 89.28	682.67 ± 329.248	0.000*

***** Independent T-test, level of significance at *P*-value < 0.05

Table 4. Subgroup analysis of vancomycin AUC_{24}/MIC Ratio

Vancomycin AUC_{24}/ MIC ration (mcg*hr/ mL)	Group 1 (n=30)	Group 2 (n=30)	*P*-value
Below 400	24 (80%)	4 (13.33%)	0.000*
400 - 600	6 (20%)	16 (53.33%)	
Above 600	0 (0%)	10 (33.33%)	
Total	30 (100%)	30 (100%)	

***** Chi-square test, level of significance at *P*-value < 0.05

interval of 12.4 ± 2.2 hr, while the group 2 dose interval was 9.33 ± 1.9 hr with a P-value of 0.000, this was the first statistically significant difference between the two groups showing that fixed interval doses can't be applied to most patients and should be individualized. Regarding the vancomycin total daily dose, the statistical significance was also apparent with a great difference in the administered doses, at which, the group 1 dose mean ± SD, was 2000 ± 262.61 mg/day, while for the group 2 was 3766.67 ± 1472.35 mg/day, a much higher dose, with a P-value of 0.000, which suggests under-dosing as an apparent difference. The total number of vancomycin grams administered in the two groups was evaluated, with 27 ± 7.65 g for group 1, and 43.6 ± 21.71 g for group 2, P-value = 0.000, this significant difference showed that the estimated number of vancomycin grams prescribed in the individualized regimen (group 2) are much greater than the grams in the conventional group 1 during the course of therapy, This result strengthened our conclusion about the under-dosing problem.

Vancomycin trough level and AUC_{24}/MIC ratio

Recent guidelines are not recommending trough levels as a monitoring parameter, because latest researches has shown that trough levels might not be the best surrogate for AUC values, as Patel et al., 2011[16], reported a wide variety of AUC values from numerous various dosing schedules producing comparable trough values. Because trough level is an important variable in identifying AUC_{24}/MIC ratio, statistical analysis was implemented, Table 3, and the mean ± SD of vancomycin trough levels at steady state for group 1 was 6.35 ± 3.85 mcg/dl, for group 2 was 19.89 ± 11 mcg/dl, with significant P-value = 0.000. highlighting no achievement of target trough levels 15 – 20 mcg/dl, as predicted due to the great difference between the total daily vancomycin doses administered between the two groups and the under-dosing issue in group 1, at which there is a direct proportional relationship between vancomycin dose and vancomycin trough level, which were higher at group 2 compared to group 1. But according to the latest updates, AUC_{24}/MIC ratio will represent a better monitoring parameter in comparison to vancomycin trough level, by using Bayesian software programs[18,17].

In this study only one vancomycin trough level is used to measure AUC_{24}/MIC ratio and the results was displayed within Table 3, as mean ± SD, for group 1 was 283.1 ± 89.28 mcg*hr/mL, and group 2 was 682.67 ± 329.248 mcg*hr/mL, a statistically significant analysis with P-value = 0.000. Compared to target levels (400 – 600 mcg*hr/mL), group 1 mean was severely sub-therapeutic, while group 2 mean level was above therapeutic levels with ± SD of 329.248 mcg*hr/mL.

To understand this result, AUC_{24}/MIC ratio was furtherly subdivided into subgroups to exhibit the difference on a more detailed range, Table 4. Target AUC_{24}/MIC ratio was Achieved at a higher percentage in group 2 compared to group 1 with severe subtherapeutic levels, where group 1 had 6 (20%) results compared to a much better results at group 2 of 16 (53.33%) patients, which is predicted due to more individualized dose regimen at group 2. For the supra-therapeutic range (400 – 600 mcg*hr/mL), a clear difference is apparent at group 2 with 10 (33.33%), compared to 0 results for group 1. This can be justified by certain reports accompanied these results, with 6 results occurred due to nephrotoxicity side effect, Table 5, 4 results were due to improper dosing administration, with 2 of them during the night shift, at which the dose was given with 2 hours deviation after the intended administration time. The other 2 results were due to about 2 hours deviation before the intended administration time, at which the blood sample was drawn and the vancomycin trough level was recorded to reflect upon this misadministration behavior. For all of these patients, vancomycin dose was readjusted and nurse education and follow-up support were re-introduced. This highlight the team work challenges regarding the implementation of proper TDM practice, other problem became apparent which is the staff frequent rotation in the health care system that is conducted between day and night shifts, and ICU-beds, making the follow up and handout is quite challenging and sometimes not optimal.

The results of group 1 were similar to Bevalagi et al., 2022[19],

Table 5. Concomitant nephrotoxicity			
Variables	**Group 1 (n=30)**	**Group 2 (n=30)**	**P-value**
Nephrotoxicity	0 (0%)	6 (20%)	0.009*

***** Chi-square test, level of significance at *P*-value < 0.05

Table 6. Vancomycin culture and sensitivity			
Variables	**Group 1 (n=30)**	**Group 2 (n=30)**	***P*-value**
According to C/S	23 (76.67%)	21 (71%)	0.559*
As an empirical therapy	7 (23.33%)	9 (30%)	

* Chi-square test, level of significance at P-value < 0.05

a prospective, single center study conducted at ICU setting of a tertiary care center in India with patients receiving 1g twice daily, a total of 83 vancomycin blood samples were analyzed, the mean AUC/MIC was 153 mcg*hr/mL.

Mali et al., 2019[20], found that of fifteen patients received 1g every 12 hour at critical illness center, India, had mean AUC_{24} of 295.89 µg*hr/mL (±153.82), Out of 45 trough levels, 32 (71.11%) concentrations were below recommended range, which is comparable to the results obtained from group 1.

Shahrami et al., 2016[21], a study conducted in Iran, with high similarity in terms of study design and results, at which group 1 received a fixed dose of (15mg/kg every 8 hours) and group 2 received individualized doses. AUC at steady state was also significantly higher in group 2 compared to group 1, 665.9 ± 136.5 mg·hr/L versus 490.7 ± 101.1 mg·hr/L) (P = 0.008), with supra-therapeutic results.

Although one vancomycin concentrations can be used to measure AUC_{24}/MIC ratio by Bayesian computer program, and this was supported by the most updated consensus guideline and literature, Al-Sulaiti et al.,[22] showed that assessing AUC using both peak and trough concentrations (rather than trough-only estimations) may improve vancomycin-associated therapeutic cure, and recommending that until further data are available, it is preferable to estimate the Bayesian AUC using two vancomycin concentrations (peak and trough).

Vancomycin-induced Nephrotoxicity

The prevalence of Vancomycin induced nephrotoxicity varies from 5% to 43%[15]. According to the literature, the risk of AKI increases with trough concentration, especially when it is retained above 15 to 20 mg/L[23] which my also be applied to AUC_{24}/MIC ratio.

In this study, Nephrotoxicity occurrence was highly associated with high AUC_{24}/MIC ratio as shown in table 6, with group 1 having 0 patients, and group 2 having 6 (20%) patients. This result was expected due to the low vancomycin trough levels and AUC_{24}/MIC ratio achieved by group 1 compared to that of group 2. According to Aljefri et al., 2019[24], a meta-analysis of eight observational studies found that nephrotoxicity risk decreases with AUC_{24} lower than approximately 650 mg·hr/L. Similarly, new evidence suggests that the risk of AKI increases over the vancomycin AUC spectrum, particularly when the daily AUC surpasses 650 to 1,300 mgh/L[15].

Suzuki et al., 2012[25], a study in japan assessed the mean AUC in relation to nephrotoxicity and found that most patients with nephrotoxicity had AUC value between 600 – 800 mg·hr/L, compared with 400 – 600 mg·hr/L in those without nephrotoxicity (P = 0.014).

Lodise et al., 2009[26], a study included 166 patients found that risk of nephrotoxicity increased by 2.5 fold with AUC values exceeding 1300 mg·hr/L compared with patients with lower levels (30.8% compared to 13.1%, P = 0.02).

Practice Recommendation

Implementation of individualized vancomycin dosing with Bayesian software should be encouraged in Iraqi ICUs, with pharmacist-led monitoring and dose adjustment are essential to maintain target ratio within a safe therapeutic window and minimize nephrotoxicity.

CONCLUSION

In this research, individualized vancomycin dosing achieved the AUC_{24}/MIC target more frequently than conventional dosing (53.3% vs 20.0%), respectively. However, this individualized dosing reflected a higher rate of vancomycin-induced nephrotoxicity. Consistent with the international studies, we observed an exposure–toxicity relationship: Where higher AUC_{24}/MIC ratio were associated with greater nephrotoxicity risk.

AUTHOR'S CONTRIBUTION

Noor Sameer Al-Khayyat: Conceptualization, Methodology, Project Administration, Formal analysis, Writing – original draft.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

References

1. Katzung BG. Basic and Clinical Pharmacology 14th Edition: McGraw-Hill Education; 2018.
2. Laurence L. Brunton RH-D, Bjorn C. Knollmann. Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 13th Edition: McGraw-Hill Education; 2018.
3. Brayfield A. Martindale, The Complete Drug Reference 38th Edition: Pharmaceutical Press; 2014.
4. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Jr., Craig WA, Billeter M, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2009;29(11):1275-9.
5. James M. Ritter RF, Graeme Henderson, Yoon Kong Loke, David MacEwan, Humphrey P. Rang. Rang and Dale's Pharmacology 9th Edition: Elsevier Ltd.; 2020.
6. Schäfer M, Schneider TR, Sheldrick GM. Crystal structure of vancomycin. Structure. 1996;4(12):1509-15.
7. Levine DP. Vancomycin: a history. Clin Infect Dis. 2006;42 Suppl 1:S5-12.
8. Moellering RC, Jr. Vancomycin: a 50-year reassessment. Clin Infect Dis. 2006;42 Suppl 1:S3-4.
9. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. Clin J Am Soc Nephrol. 2009;4(8):1388-400.
10. Kan WC, Chen YC, Wu VC, Shiao CC. Vancomycin-Associated Acute Kidney Injury: A Narrative Review from Pathophysiology to Clinical Application. Int J Mol Sci. 2022;23(4).
11. Ye ZK, Li C, Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: a systematic review. PLoS One. 2014;9(6):e99044.
12. Rybak MJ. The Pharmacokinetic and Pharmacodynamic Properties of Vancomycin. Clinical Infectious Diseases. 2006;42(Supplement_1):S35-S9.
13. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986;11(4):257-82.
14. Bauer LA. Applied Clinical Pharmacokinetics 3rd Edition: Mc Graw Hill Education; 2014.
15. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835-64.
16. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. Vancomycin: we can't get there from here. Clin Infect Dis. 2011;52(8):969-74.
17. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. Adv Drug Deliv Rev. 2014;77:50-7.
18. Heil EL, Claeys KC, Mynatt RP, Hopkins TL, Brade K, Watt I, et al. Making the change to area under the curve-based vancomycin dosing. Am J Health Syst Pharm. 2018;75(24):1986-95.
19. Belavagi D, Bhandari RK, Shafiq N, Gota V, Patil A, Pandey AK, et al. A study to explore the appropriateness of dosing regimen of vancomycin in critically ill patients in a tertiary care unit of India. Germs. 2022;12(2):238-52.
20. Mali NB, Deshpande SP, Wandalkar PP, Gupta VA, Karnik ND, Gogtay NJ, et al. Single-dose and Steady-state Pharmacokinetics of Vancomycin in Critically Ill Patients Admitted to Medical Intensive Care Unit of India. Indian J Crit Care Med. 2019;23(11):513-7.
21. Shahrami B, Najmeddin F, Mousavi S, Ahmadi A, Rouini MR, Sadeghi K, et al. Achievement of Vancomycin Therapeutic Goals in Critically Ill Patients: Early Individualization May Be Beneficial. Crit Care Res Pract. 2016;2016:1245815.
22. Al-Sulaiti FK, Nader AM, Saad MO, Shaukat A, Parakadavathu R, Elzubair A, et al. Clinical and Pharmacokinetic Outcomes of Peak-Trough-Based Versus Trough-Based Vancomycin Therapeutic Drug Monitoring Approaches: A Pragmatic Randomized Controlled Trial. Eur J Drug Metab Pharmacokinet. 2019;44(5):639-52.
23. Roy AK, Mc Gorrian C, Treacy C, Kavanaugh E, Brennan A, Mahon NG, et al. A Comparison of Traditional and Novel Definitions (RIFLE, AKIN, and KDIGO) of Acute Kidney Injury for the Prediction of Outcomes in Acute Decompensated Heart Failure. Cardiorenal Med. 2013;3(1):26-37.
24. Aljefri DM, Avedissian SN, Rhodes NJ, Postelnick MJ, Nguyen K, Scheetz MH. Vancomycin Area Under the Curve and Acute Kidney Injury: A Meta-analysis. Clin Infect Dis. 2019;69(11):1881-7.
25. Suzuki Y, Kawasaki K, Sato Y, Tokimatsu I, Itoh H, Hiramatsu K, et al. Is peak concentration needed in therapeutic drug monitoring of vancomycin? A pharmacokinetic-pharmacodynamic analysis in patients with methicillin-resistant staphylococcus aureus pneumonia. Chemotherapy. 2012;58(4):308-12.
26. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis. 2009;49(4):507-14.