Assessment of vancomycin utilization among Lebanese hospitals

Diana N. Malaeb, PharmD, MPH, Iqbal M. Fahs, PharmD, Pascale Salameh, MPH, PhD, Souheil Hallit, MPH, PhD, Manal Saad, PharmD, Jassem Bourji, PharmD, Rabih Hallit, MD.

ABSTRACT

الأهداف: تقييم مدى ملاءمة جرعات فانكوميسين ومراقبتها في المستشفيات اللبنانية.

الطريقة: كانت هذه دراسة استعادية متعددة المراكز أجريت في 3 مستشفيات لبنانية خلال الفترة ما بين يناير ومارس 2018م. وكان المرضى الذين تبلغ أعمارهم 18 سنة وكبار السن الذين عولجوا بالفانكوميسين من أجل عدوى جهازية أو وقائية مؤهلة للالتحاق بالدراسة. تم تقييم الاتساق مع المبادئ التوجيهية جمعية الأمراض المعدية الأمريكية لتحديد ما إذا كانت جرعة فانكومايسين مناسبة، وكذلك لوقت قياس الحوض، والتركيز المستهدف تم الحصول عليها.

النتائج: من إجمالي 120 مريضاً ممن استوفوا معايير الاشتمال، تم إعطاء 11 (12%) فقط جرعة الصيانة المناسبة من فانكوميسين فيما يتعلق بوزن الجسم الفعلي. تم رصد مستويات الحوض ل 67 (55.8%) من المرضى، مع 20 (29.9%) من هؤلاء المرضى تحقيق مستويات الحوض العلاجية المناسبة من 15-20 ملغ/لتر. تم تنفيذ قياس وقت تركيز القاع قبل الجرعة الرابعة فقط في 28 (41.8%) من 67 مريضًا.

الخاتمة: تكشف هذه الدراسة عن وجود فجوة بين الاستخدام المناسب للفانكوميسين فيما يتعلق بالمبادئ التوجيهية الدولية في المستشفيات اللبنانية المدروسة. ويسلط الضوء على الحاجة إلى جرعات ورصد البروتوكولات المناسبة لاستخدام فانكوميسين في هذه المستشفيات.

Objectives: To assess the appropriateness of vancomycin dosing and monitoring at Lebanese hospitals.

Methods: This was a multicenter retrospective study conducted at 3 Lebanese hospitals between January and March 2018. Patients 18 years of age and older treated with vancomycin for a systemic infection or prophylaxis were eligible for study enrollment. Consistency with the Infectious Diseases Society of America guidelines was evaluated to determine whether the dose of vancomycin was appropriate, as well as for the time of trough measurement, and the target concentration obtained.

Results: From a total of 120 patients who met the inclusion criteria, only 11 (12%) were given the appropriate maintenance dose of vancomycin with respect to actual body weight. The trough levels were monitored for 67 (55.8%) patients, with 20 (29.9%) of these patients achieving appropriate therapeutic trough levels of 15-20 mg/l. The trough concentration time measurement before the fourth dose was only carried out in 28 (41.8%) of the 67 patients.

Conclusion: This study reveals a gap between the appropriate utilization of vancomycin with respect to the international guidelines in the studied Lebanese hospitals. It highlights the need for dosing and monitoring protocols suitable for vancomycin utilization in these hospitals.

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From the Department of Clinical Practice (Malaeb, Fahs, Saad, Bourji), Lebanese International University, Mouseitbah, from the Department of Pharmacy (Salameh), Faculty of Medicine, Lebanese University, Beirut, from the Department of Medicine and Medical Sciences (Hallit S, Hallit R), Holy Spirit University of Kaslik, Jounieh, Lebanon, and from the Department of Life Sciences and Health (Malaeb), Paris-Est University, Paris, France.

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Address correspondence and reprint request to: Dr. Souheil Hallit, Department of Medicine and Medical Sciences, Holy Spirit University of Kaslik, Jounieh, Lebanon. E-mail: souheilhallit@hotmail.com
ORCID ID: orcid.org/0000-0001-6918-5689

Vancomycin, a complex tricyclic glycopeptide, is a bactericidal antibiotic that inhibits peptidoglycan biosynthesis.[1-3] It is mainly effective against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Streptococcus viridans*, and species of *Bacillus*, *Actinomyces*, *Clostridium*, and *Corynebacterium*.[1] However, vancomycin use has become more relevant with the advent of *Methicillin-resistant Staphylococcus aureus* (*MRSA*) and Penicillin-

resistant pneumococcal infections.[4] Generally prescribed to combat severe infections caused by Gram-positive bacteria, vancomycin is used for the treatment of sepsis, pneumonia, endocarditis, meningitis, pre- and post-operative procedures prophylaxis, osteomyelitis, and soft tissue infections.[1,5,6] Knowledge of vancomycin dosing parameters and target trough levels is critical for effective treatment.[7] Inadequate dosing and monitoring of vancomycin may lead to sub-therapeutic bactericidal activity, treatment failure, toxicity, and the emergence of resistance.[8] Hence, a consensus statement from the American society of health-system pharmacists (ASHP), the Infectious diseases society of America (IDSA), and the Society of infectious diseases pharmacists (SIDP) was published, in 2009, based on a critical evaluation of the available scientific evidence.[9] This consensus recommends an initial vancomycin loading dose of 25-30 mg/kg followed by a maintenance dose of 15-20 mg/kg based on actual body weight and adjusted according to the patient's estimated creatinine clearance (CrCl).[9] Monitoring of vancomycin trough serum concentrations just before the fourth dose, when steady-state levels are achieved, is also recommended.[9] Minimum trough concentrations of vancomycin should be maintained above 10 mg/l to avoid the development of resistance.[9] To improve antibiotic penetration and optimize pharmacokinetic and pharmacodynamic targets, trough levels of 15-20 mg/l are required for complicated infections such as endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.[9] Despite this consensus, there remains disparity between the clinical utilization of vancomycin and guideline recommendations. Several studies have revealed various malpractices regarding vancomycin dosing, trough measurement timing, and trough concentration levels achievement.[10-19] For instance, Morrison et al,[10] reported that the timing of vancomycin trough level measurements was not adherent with the recommendations, as 41.3% were drawn too early before achievement of the steady state condition. This may lead to an overestimation of patients' true trough levels or possible under dosing of vancomycin.[10] In another study conducted by Bakke et al,[14] trough serum concentrations that were within therapeutic range (15-20 mg/l) were only 21.0% at 24 hours, 16.3% at 48 hours, and 32.9% at 72 hours. These studies underline the significant challenges in the utilization of vancomycin as it is a narrow therapeutic index drug that can be easily over or under dosed in most patients, and especially critical patients.

This study was conducted to assess the appropriateness of vancomycin dosing and monitoring at 3 Lebanese hospitals.

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Methods. A multicenter, retrospective, observational study was conducted at 3 Lebanese teaching hospitals from January-March 2018. Data was obtained from hospitalized admitted patients who received vancomycin during the study period. The study was approved by the Ethical committee at the Lebanese International University and the institutional review boards of the hospitals. The study was conducted according to ethical principles and standards that did not require informed consent as it was a retrospective study that did not pose any risk to the patient health and privacy. Written informed consent was not obtained from the patients as it was a retrospective study. Any personal identifying information was stripped from the data to protect patients' privacy. Patient data was collected and stripped from patient identification information for respecting patient privacy.

From a total of 226 medical records viewed for possible enrollment in the study, 120 patients met the inclusion criteria as their medical files included the vancomycin dosage and monitoring parameters that were needed for analysis. Patients treated with vancomycin for a systemic infection or prescribed for procedural prophylaxis were eligible for study enrollment. Patients treated with vancomycin for a local *Clostridium difficile* infection or those with acute renal failure, end-stage renal disease, and those on dialysis were excluded.

Study procedure. The proposal was submitted to all involved sites for approval before conducting the study. After obtaining the hospitals' consent, computer-based data from the 3 hospitals was elicited at the Infectious Department, Internal Medicine Department, Cardiac Care Unit and the Intensive Care Unit to gather the information of patients treated with vancomycin.

A data collection sheet was created to study the variables that were important to assess the appropriate use of vancomycin based on the recommendations of the ASHP, IDSA, and SIDP, in 2009.[9] The data collection sheet retrieved information regarding the demographic characteristics of the patients and the diagnosis (sepsis, pneumonia, soft tissue infection, endocarditis, meningitis, and pre-operative prophylaxis). Furthermore, quantitative information

including the trough concentration levels, the timing of the first drawn trough concentration, and vancomycin dose given in mg/kg were retrieved.

Study outcomes. This study aimed to evaluate the utilization of vancomycin at Lebanese hospitals for systemic infections. Hence the main primary outcome assesses the appropriateness of vancomycin dosing and monitoring at the 3 Lebanese hospitals studied based on the ASHP, IDSA, and SIDP 2009 recommendations.

Statistical analysis. Data was analyzed using the Statistical Package of Social Sciences (SPSS), version 21.0 software (IBM Corp., Armonk, NY, USA). Dichotomous and categorical variables were presented as percentages, and the continuous variables were displayed as mean±standard deviation (SD). Frequency tables were generated for the patients receiving vancomycin doses with respect to each indication.

Results. A total of 226 patient records were screened, 120 met the requirements for study enrollment. Of these, 78 (34.5%) were excluded because samples for determination of trough levels were not drawn, 10 (4.4%) were excluded because of renal dysfunction at the start of vancomycin therapy, and 18 (7.9%) were excluded as while patients were started on vancomycin, the therapy was stopped before the trough level determination. **Table 1** provides a summary of the patients' demographic statistics, including gender, age, weight, and the CrCl level. The normal CrCl is 75-125 ml/min.

Vancomycin administration based on confirmed or suspected infections. Vancomycin in this study was administered to 120 patients, with 59 patients on vancomycin therapy for systemic infections and the rest for procedural prophylaxis. Of the 59 patients, around 80% were given vancomycin based on isolated bacterial culture results. Vancomycin administration was started empirically in only 20% of the cases depending on suspected infections. The most common isolated bacteria is *MRSA*, followed by *Methicillin-sensitive Staphylococcus aureus* (*MSSA*), and the least prevalent was the *Staphylococcus epidermis*.

Vancomycin dosing versus body weight. Medical records for all enrolled patients were checked for the dose administered. Vancomycin dosage given to all patients was 1 g every 12 hours and none of the patients received a loading dose before the administration of the maintenance dose. Assessment of vancomycin dose was checked in relation with the patient's body weight. Most of the screened patients fell within the range of 61-90 kg in the body weight index. **Table 2** displays average vancomycin doses based on body weight range of the patients. Of those weighing between 30-60 kg, only 12% of the patients (11 of 120) were receiving the appropriate vancomycin dosage in accordance with their average body weight, based on the ASHP, IDSA, and SIDP recommendations (15-20 mg/kg dose), with a mean vancomycin dosage of 19.24±2.81 mg/kg. **Table 2** shows the dose given of vancomycin in mg/kg in relation to weight categories.

Vancomycin dosage versus clinical localization of infection or prophylactically. **Table 3** provides the frequencies and the average vancomycin dosage given to patients based on the categorical distribution of infections, including sepsis, pneumonia, soft tissue infection, endocarditis, meningitis, in addition to preoperative prophylaxis and post-operative prophylaxis.

None of the categorical groups classified as complicated infections based on ASHP guideline satisfied the appropriate dosage of vancomycin

Table 1 - Demographics based on data elicited from 3 hospitals in Lebanon.

Variable	n (%)
Gender	
Male	52 (43.3)
Female	68 (56.7)
Age (years)	
18-30	10 (8.3)
31-59	24 (20.0)
≥60	86 (71.7)
Actual body weight (kg)	
30-60	19 (15.8)
61-90	67 (55.8)
91-120	34 (28.4)
CrCl (ml/min)	89 (74.2)
≥90	33 (37.1)
60-89	25 (28.1)
30-59	13 (14.6)
15-29	18 (20.2)
Serum creatinine (mg/dl) (Mean±SD)	1.97 ± 2.01
Average CrCl (ml/min) (Mean±SD)	64.41 ± 56.87

CrCl - creatinine clearance, SCr- serum creatinine
Creatinine clearance was estimated by Cockcroft-Gault Equation. CrCl={(l 40-age) x weight)/(72xSCr)} x 0.85 (if female).

Table 2 - Average vancomycin dosages and relevant standard deviations based on the body weight range of patients.

Body weight range (kg)	Mean vancomycin dosage (mg/kg)±SD
30-60	19.24±2.81
61-90	13.28±1.73
91-120	10.01±0.63

SD - standard deviation.

Table 3 - Frequency of patients and average vancomycin dosage (mg/kg) based on clinical localization of infection or prophylaxis recorded.

Indication	n (%)	Mean of vancomycin dosage
Sepsis	17 (14.2)	13.70
Pneumonia	15 (12.5)	13.66
Soft tissue infection	18 (15.0)	13.14
Endocarditis	5 (4.2)	12.03
Meningitis	4 (3.3)	12.97
Pre-operative prophylaxis	29 (24.1)	12.80
Post-operative prophylaxis	32 (26.7)	12.70

Table 4 - Frequency of patients and average vancomycin dosage based on creatinine clearance level.

CrCl (ml/min)	n (%)	Mean of vancomycin dosage (mg/kg)
≥90	33 (37.1)	14.01
60-89	25 (28.1)	13.76
30-59	13 (14.6)	12.82
15-29	18 (20.2)	10.17

CrCl - creatinine clearance.

(15-20 mg/kg). However, certain indications such as pneumonia and sepsis had higher mg/kg dosing.

Vancomycin dosing versus creatinine clearance level. Creatinine clearance values were available for 89 patients (74.2%), though vancomycin dosage should be calculated and adjusted based on this parameter. **Table 4** reveals the average vancomycin dosage based on patients' CrCl levels. The table shows that the vancomycin dosages decrease as CrCl levels decrease, with none being in the appropriate range of 15-20 mg/kg.

Trough concentration monitored. Monitoring of the trough concentrations is considered the most suitable method for checking the efficacy of vancomycin dosage. The therapeutic drug monitoring was not carried out for 53 cases (44.2%), and monitored for 67 patients (55.8%) only with 20 of these patients (29.9%) had appropriate trough concentration levels (15-20 mg/l). **Table 5** provides the frequencies and percentages of the patients monitored for trough concentrations.

Trough concentration time measurement. The time for trough concentration measurement represents another monitoring factor that must be assessed. Only 28 of the 67 patients (41.8%) had their trough levels measured in accordance to the international recommendations, namely, before the fourth dose. The rest of the patients had their first trough concentration measured before the second and the third dose. **Table 6** displays the distribution of the patients with respect to the time of trough concentration measured.

Table 5 - Frequencies and percentages of patients monitored for trough concentrations based on mg/l categories for 67 patients.

Trough concentration (mg/l)	n (%)
<15	28 (41.8)
15-20	20 (29.9)
>20	19 (28.3)

Table 6 - Frequencies and percentages of patients based on trough timing for 67 patients.

Trough timing	n (%)
Before 2nd dose	20 (29.9)
Before 3rd dose	17 (25.4)
Before 4th dose	28 (41.8)
Before 5th dose	2 (2.9)

Discussion. Vancomycin has been the leading antimicrobial in the treatment of *MRSA* infections. However, outcomes have worsened and failure rates have increased due to inappropriate utilization and monitoring.[20] The goal of this study was to assess the appropriateness of vancomycin dosing and monitoring in 3 Lebanese hospitals.

Vancomycin was administered to 59 infectious cases that were confirmed with biological data. These results are much better than those reported by other studies, where empiric treatment based on suspected infection was started in 66.3% of cases.[14] This reflects a good clinical practice in Lebanese hospitals through mainly basing vancomycin administration on culture results.

However, in this study, only 12% of the patients (11 of 120) were receiving an appropriate vancomycin dose in accordance with their body weight, with a mean vancomycin dose of 19.24±2.81 mg/kg. This proportion was lower than that reported by a retrospective cohort study conducted in United States of America in 2013 on the prescribing habits of vancomycin in the Emergency Department, where 19.6% of patients (47 of 240) received an appropriate dose based on the recommended 15-20 mg/kg vancomycin dose.[21] However, the average vancomycin dose was lower (14.6±5.7 mg/kg).[21] Such low percentages of adequate vancomycin dosing according to actual body weight may be due to the lack of awareness of these consensus guidelines or the minimal clinical evidence supporting improved outcomes.

As the patient's weight increased the likelihood of Vancomycin dose given was lower than recommended. Also, higher doses than recommended were being

prescribed for the treatment of certain conditions such as sepsis and pneumonia. This could be due to the implementation of a predetermined hospital protocol. In fact, a higher weight based-dose is most probably due to a higher predetermined fixed dose. In addition, obesity can alter different pharmacokinetic parameters of vancomycin. Due to the hydrophilicity of vancomycin and the increase in both adipose tissue and muscle mass associated with obesity, the volume of distribution of vancomycin in obese patients is higher compared to non-obese patients.[22] Moreover, obesity is associated with an increase in certain circulating proteins that alter free serum vancomycin concentration.[22] Vancomycin clearance is also higher among obese patients owing to increased blood flow secondary to increased cardiac output and blood volume.[22] Hence, obesity is an important fator that should be taken into consideration in vancomycin dosing. This study concludes that most of the physicians are not adminsitering a loading dose before the maintenance dose, which clearly explains why most patients will not achieve the required trough appropriate for the management of their diseases.

The study revealed a proportional relationship between CrCl level and vancomycin dosage, with none of the dosages being in the appropriate level of 15-20 mg/kg.[9] As the clearance level decreases, the average vancomycin dosage decreases as well. This practice is not reflective of the consensus guideline recommendations of applying similar vancomycin dosages of 15-20 mg/kg at prolonged intervals and adjusted based on monitored trough levels.[9]

More than half of the patients (55.8%) in this study were monitored for trough level with 29.9% of these having had appropriate trough concentrations between 15-20 mg/l. Comparable to our study, the proportions of trough serum concentrations within therapeutic range (15-20 mg/l) out of a total 237 concentrations reported by Bakke et al,[14] were 21.0% at 24 hours, 16.3% at 48 hours, and 32.9% at 72 hours. In a Malaysian study carried out in 2014, serum vancomycin trough levels were monitored in only 79 patients and for just 18 of them (22.8%) trough levels were found to be within the therapeutic range.[19] Blot et al,[15] presented higher therapeutic trough concentrations in their multicenter point-prevalence study where 45% of the patients did not achieve the minimum threshold value of ≥15 mg/l. These variations in results among the studies may be explained by the different protocols, educational and training programs, and locations where the studies were conducted. Most of the patients, 28 of the 67 patients (41.8%) whose vancomycin trough levels were monitored, had their trough concentrations measured before the fourth dosage. In a study conducted by Traugott et al,[12] the majority of inappropriate vancomycin trough levels were due to improper timing of sample collections (55%). Also, the initial vancomycin blood concentration was drawn appropriately based on time in 43.4% of the cases in Phillips et al.[18] These results reflect an awareness, which may be improved, of the proper timing of vancomycin trough concentration measurement. The inappropriate monitoring of vancomycin can be attributed to inadequate or absence of input from clinical pharmacists while prescribing, and the lack of multidisciplinary approaches in these hospitals.

Study limitations. This study has several limitations. Firstly, the small sample size that may reduce the significance of the results. Another limitation is data sampling from 3 hospitals only, which limits the generalizability of the results and was expected to increase the percentage of error among the results obtained. In addition, the retrospective design was also a limitation as it limited prospective interference with the patients and increased the percentage of the missing data. For instance, the paper does not provide any association between vancomycin level and outcomes (efficacy or safety). This data was not available for the study team as this was a retrospective study and not all required information was recorded. Moreover, despite the importance of medical records, data was provided by hospital personnel; recording errors cannot be underestimated. Another important limitation is that the most precise target for vancomycin therapy is the attainment of an area under the curve/minimum inhibitory concentration (AUC)/MIC ≥400. However, trough serum concentrations were used as a surrogate marker for AUC/MIC. This study investigates the degree of appropriate use of vancomycin within the guidelines. Therefore, this study serves as a baseline assessment of the current clinical practice and a starting point for a better guideline adherence.

In conclusion, vancomycin requires time to reach therapeutic concentrations and doses should be based on body weight to avoid sub-therapeutic levels that can augment resistance. The present study reveals significant challenges in the utilization of vancomycin, which represents an immediate threat of therapeutic failure and reduced antibiotic susceptibility. This study adds to the literature that physicians are not following the IDSA guidelines concerning the use of vancomycin, its dosage and monitoring. Hence, educating clinicians regarding appropriate vancomycin dosing with an emphasis on achieving therapeutic troughs (15-20 mg/l) is recommended to achieve compliance with the latest

consensus guidelines. In addition, the implementation of a dosing and monitoring protocol at each hospital would be of extreme importance.

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