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Original Article

Prospective evaluation of vancomycin therapeutic usage and trough levels monitoring

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Abstract

Introduction: Vancomycin is the cornerstone of parenteral therapy for serious methicillin resistant *Staphylococcus aureus* infections. Optimal dosing of vancomycin is patient specific due to its narrow therapeutic window. The objective of this study is to evaluate the appropriate use of vancomycin focusing on the indication, dose, and therapeutic level monitoring.

Methodology: A prospective observational study was conducted in a tertiary care hospital over a 3- month period. A data collection form was used to gather information on 93 patients receiving vancomycin. Study outcomes were assessment of the appropriateness of vancomycin indication, dose, and therapeutic trough level.

Results: The use of vancomycin both empirically and after culture results was appropriate in 78.5 % of the patients. More than half of the patients (51.6 %) were given an inappropriate dose of vancomycin per actual body weight, creatinine clearance, and indication. Regarding therapeutic vancomycin monitoring, 69.0 % had inappropriate trough level monitoring. Only 15.7 % of the 166 measured troughs were within the target therapeutic level for the corresponding indication.

Conclusion: This study demonstrates the high level of inappropriate use of vancomycin. This is mainly attributed to inappropriate dose and trough level monitoring. Interventions to improve vancomycin prescribing and monitoring practices are needed. The presence of an interdisciplinary team may improve the appropriate use of medications with a narrow therapeutic index such as vancomycin.

Key words: vancomycin; indication; dose; trough; therapeutic level.

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Introduction

Inappropriate use of antibiotics is one of the most serious, but most controllable, causes for the development of multidrug resistant organisms. Vancomycin is the cornerstone of parenteral therapy for serious methicillin resistant *Staphylococcus aureus* (MRSA) infections [1]. Vancomycin-resistant clinical isolates of *Enterococcus* species (VRE) were reported for the first time in Europe in 1988; and later they spread in hospitals in the United States [2,3]. Since then, MRSA and VRE infections have been on the rise in hospitals in most countries around the world [4]).

Vancomycin, a glycopeptide antibiotic, has activity against Gram positive and some anaerobic micro-organisms [1]. It is indicated for the treatment of infections caused by susceptible strains of MRSA, *Clostridium difficile* associated colitis, and for patients with a history of anaphylaxis to a β-lactam antibiotic where Gram positive infections are detected or suspected [1]. Its effectiveness has been documented in infections including endocarditis, meningitis, septicemia, bone infections, lower respiratory tract infections, and skin and soft-tissue infections. Vancomycin has also a role in prophylaxis for endocarditis in certain high risk individuals, and for postoperative infections where local incidence of MRSA is high.

In the absence of susceptibility data, therapy with vancomycin is empiric until evidence from culture results confirms sensitive microorganisms. De-escalation is consequently indicated to prevent the development of resistant micro-organisms [5].

Optimal dosing of vancomycin is patient-specific due to its narrow therapeutic window. When used for at least five days, trough levels should be monitored [5,6]. Unlike vancomycin peak concentrations, steady state trough levels are recommended for monitoring its efficacy and toxicity [6].

The Infectious Diseases Society of America (IDSA) guidelines recommend that vancomycin trough concentrations always remain above 10 mg/L to prevent the development of resistant strains [6]. For more

severe deep- seated infections, a higher trough concentration of 15-20 mg/L is recommended [6]. An alternative antibiotic should be used for MRSA strains with a minimum inhibitory concentration (MIC) above 2 mg/L to vancomycin. With such elevated MIC, a correlated trough level to ensure efficacy would be between 32-40 mg/L triggering higher toxicity risks [6]. The major adverse effects of vancomycin are nephrotoxicity and ototoxicity. Nephrotoxicity is defined as a minimum of 2 or 3 consecutive documented increases in serum creatinine concentrations (an increase of 0.5 mg/dL or more than 50% increase from baseline after several days of vancomycin therapy). With the newer improved formulations of vancomycin, nephrotoxicity has become rare unless combined with other nephrotoxic drugs such as aminoglycosides, amphotericin B or radiocontrast dyes. Similarly, ototoxicity has been linked to impurities found in older formulations and might be additive with other ototoxic drugs such as aminoglycosides or loop diuretics. It starts with high frequency tinnitus, pressure in the ears, and loss of balance which can all be irreversible.

The prevalence of MRSA in Lebanon in 2005 was 11% [7] and almost tripled in 2014 [8]. Currently, up to one third of *Staphylococcus aureus* strains are resistant to oxacillin [8]. Previous studies worldwide have documented inappropriate use of vancomycin with rates ranging from 28% to 70% [9,10]. Several guidelines have been developed to limit the emergence of resistant micro-organisms which are associated with higher rates of morbidity, mortality, and healthcare costs [9,11]. For example, Blot *et al.* reported a 22% increase in mortality with MRSA infections as compared to methicillin sensitive *Staphylococcus aureus* (MSSA) infections [12]. A met-analysis was performed by Cosgrove *et al.* that showed almost double the mortality rate of MRSA versus MSSA bacteremia when the results were pooled with a random-effects model [13]. Moreover, a report by Evans *et al.* showed an increase in case fatality rates and hospital costs in the vancomycin resistant *Enterococcus* (VRE) group compared with those of matched controls [14]. The IDSA developed guidelines on the treatment of MRSA infections in adults and children and recommendations on the therapeutic monitoring of vancomycin [1,6]. The Centers for Disease Control and prevention (CDC) has also published recommendations for the prevention of the spread of vancomycin resistant micro-organisms [5]. The adherence of health care professionals to these guidelines will result in safe and effective use of vancomycin for optimal patient care [6].

Limited data are available in the literature regarding vancomycin use in Lebanese tertiary care hospitals. The objective of this study is to evaluate the appropriate use of vancomycin focusing on the indication, dose, and therapeutic level monitoring.

Methodology

Setting and design

A prospective observational study was conducted in a tertiary care hospital over a 3- month period (March to May 2015). The hospital is a 544-bed tertiary care center which includes a dialysis unit, drug rehabilitation unit, burn unit and an oncology unit. A data collection form was used to gather information on 93 patients receiving vancomycin for different treatment indications. All patients (adults and pediatrics) receiving at least one dose of vancomycin were included. Patients who received vancomycin for surgical prophylaxis or had a history of glycopeptide antibiotic allergy were excluded. Information collected included: patients' demographic data, allergies, history of present illness, past medical history, site(s) of infection, concurrent antibiotics, vancomycin dosage, frequency of administration, vancomycin trough concentration (if measured), bacterial culture and sensitivity results, as well as clinical subjective and objective data (temperature, white blood cell count, neutrophil count, and serum creatinine). Creatinine clearance (CrCl) was calculated for adult and pediatric patients according to Cockcroft-Gault and Schwartz equations, respectively.

Study outcomes were assessment of the appropriateness of vancomycin indication, dose, and therapeutic trough level. We evaluated the appropriate use of vancomycin both empirically and after culture results were available. Moreover, we examined the incidence of vancomycin-induced nephrotoxicity. The analysis included data collected from initiation of the first dose of vancomycin until patient's discharge. The most commonly used empiric vancomycin dose in adults was 1 gram given intravenously twice daily, regardless of the patient's weight. The most commonly used empiric vancomycin dose in pediatrics was 15 mg/kg of actual body weight intravenously every 6 hours. The dose was changed depending on measured trough concentrations at the discretion of each physician. The trough levels were most commonly measured 30 minutes to 1 hour before the fourth dose of vancomycin. Subsequent trough levels were measured as deemed necessary by the medical team. We relied on vancomycin package insert, published guidelines, and clinical judgment for our evaluation.

Target vancomycin trough concentration per indication are listed in Table 1. The hospital currently does not have a pre-defined antibiotic policy for the dosing and monitoring of vancomycin.

The study was approved by the hospital's Institutional Review Board and was performed in accordance with the Declaration of Helsinki and its later amendments.

Data Collection

We were provided with an electronic daily list of all patients who were prescribed vancomycin by the central pharmacy. We then identified patients who received vancomycin for a treatment indication using the hospital's computerized patient record system. Indication, dosing and therapeutic level monitoring of vancomycin were followed till discontinuation of the antibiotic and/or discharge of the patient from the hospital Culture results were also followed- up throughout the duration of treatment.

Statistical analysis

Data were processed and analyzed through the application of the software Statistical Package for Social Sciences (SPSS, version 23, IBM Corporation, Armonk, NY). Responses were tabulated and cross-tabulated, and percentages were calculated.

Table 1. Vancomycin target trough levels per indication.

Type of infection	Target trough level
Bacteremia	15-20 mg/L
Endocarditis	15-20 mg/L
Osteomyelitis	15-20 mg/L
Meningitis	15-20 mg/L
Hospital-acquired pneumonia	15-20 mg/L
Other infections	10-15 mg/L

Results

Over the three- month period of the study, vancomycin treatment was prescribed to 93 patients. The intensive care unit (ICU) had almost one third of the number of patients on vancomycin (31%). The rest were distributed over other units as follows: internal medicine (16%), oncology (14%), pediatrics (12%), cardiac care unit (11%), neonatal intensive care unit (7%), pediatric oncology (5%), and pediatric intensive care unit (4%). Vancomycin was used for the treatment of skin and soft tissue infections (28%, N = 26/93), nosocomial pneumonia (24%, N = 22/93), febrile neutropenia (18%, N = 17/93), diabetic foot infections (14%, N = 13/93), osteomyelitis (7%, N = 6/93), urinary tract infections (4%, N = 4/93), sepsis of unknown focus (3%, N = 3/93), endocarditis (1%, N = 1/93) and septic arthritis (1%, N = 1/93). The majority of our study participants were males (64.5%). The age range was 2 months to 95 years. The patients' weight ranged from 2 to 150 Kg. The baseline creatinine clearance for

Table 2. Summary of patients' characteristics.

Gender	**Male**	**60 (64.5%)**
	Female	33 (35.5%)
Age range	2 months - 95years	
Weight range (Kg)	2 - 150	
Diagnosis	Skin and soft tissue infection	26 (28%)
	Nosocomial pneumonia	22 (24%)
	Febrile neutropenia	17 (18%)
	Diabetic foot ulcer	13 (14%)
	Osteomyelitis	6 (7%)
	Urinary tract infections	4 (4%)
	Sepsis (unknown focus)	3 (3%)
	Endocarditis	1 (1%)
	Septic arthritis	1 (1%)
Wards	Intensive care unit (ICU)	29 (31%)
	Internal medicine (IM)	15 (16%)
	Oncology	13 (14%)
	Pediatrics	11 (12%)
	Cardiac care unit (CCU)	10 (11%)
	Neonatal ICU (NICU)	6 (7%)
	Pediatric oncology	5 (5%)
	Pediatric ICU (PICU)	4 (4%)

enrolled patients ranged between 10 ml/minute to 125 mL/minute. All patients were taking at least one other antibiotic concomitantly. A summary of patients' characteristics is shown in Table 2.

Assessment of Indication

The indication for the use of vancomycin in the 93 patients was evaluated (Table 3). The use of vancomycin both empirically and after culture results was appropriate in 78.5 % of the patients (N = 73/93). In patients who had positive results of cultures, indication of vancomycin was appropriate in 85.7% (N = 24/28). Among the different units, the oncology unit had 100% appropriateness with respect to indication (N = 13/13). The unit with the lowest percentage (33.33%, N = 2/6) for vancomycin appropriate use was the neonatal intensive care unit (NICU).

Assessment of Dose

Almost half of the patients, 51.6 % (N = 48/93), received an inappropriate dose of vancomycin per actual body weight, creatinine clearance, and indication (Table 3). The percentage of patients with baseline renal impairment, defined as a creatinine clearance of less than 50 ml/minute upon the initiation of vancomycin, was 18.3% (N = 17/93). The pediatrics unit had the most appropriate doses (81.8%, N = 9/11) per indication. The unit with the lowest percentage of appropriate dosing was the NICU (16.7%, N = 1/6). None of the patients received a loading dose.

Assessment of frequency of trough monitoring

6 of the 93 patients in this study were not evaluated for vancomycin trough monitoring since they did not fulfill the criteria (these patients took less than 3 or 4 doses of vancomycin and then were switched to other antimicrobial agents). Of the remaining 87 patients, 69.0 % (N = 60/87) had inappropriate vancomycin trough level monitoring (Table 4). About one third, 28.7 % (N = 25/87), did not have any trough level ordered. The oncology unit had the highest rate of appropriate monitoring for vancomycin trough level (66.7%, N = 8/12), and the ICU had the lowest (14.8%, N = 4/27).

Assessment of target trough concentration

There were 166 troughs measured for the 93 patients. Only 15.7 % were within the target level for the corresponding indication (Table 4). The unit having the most troughs within target range was the cardiac care unit (CCU) (42.9%, N = 15/35). Three units had none of their trough levels within target range per indication: the pediatrics unit, pediatric oncology unit, and the pediatric intensive care unit (PICU). The lowest level was recorded in the oncology unit (0 mg/L) and the highest was in the CCU (69.8 mg/L).

Assessment of incidence of vancomycin-induced nephrotoxicity

Among all study participants, 31.2% (N = 29/93) had a worsening renal function while on vancomycin therapy. 18.3% (N = 17/93) of the patients had baseline renal dysfunction (defined as CrCl less than 50 mL/min). One patient developed vancomycin-induced acute kidney injury on top of their pre-existing chronic kidney disease.

Discussion

Evaluation of the appropriate use of vancomycin in healthcare settings is important to assess the institution's adherence to best medical practice. Studies that describe morbidity, mortality and adverse drug reactions due to inappropriate use of vancomycin have shown the need for standard policies for its therapeutic drug monitoring [6]. The guidelines issued by the IDSA on the treatment of MRSA infections in adults and children [1] and on the therapeutic monitoring of vancomycin in adult patients [6] guide clinicians on the appropriate use of vancomycin. We report here the

Table 3. Appropriateness of indication and dose of vancomycin.

	Appropriate	Inappropriate
Vancomycin indication	73/93 (78.5%)	20/93 (21.5%)
Vancomycin dose	45/93 (48.4%)	48/93 (51.6%)

Table 4. Appropriateness of frequency of trough monitoring and target trough concentration of vancomycin.

	Appropriate	Inappropriate
Frequency of trough monitoring	27/87 (31.0%)	60/87 (69.0%)
Target trough concentration	26/166 (15.7%)	140/166 (84.3%)

results of the evaluation of vancomycin use in our tertiary care hospital and this study was presented as a poster at the American Society of Health-System Pharmacists summer meeting in Denver, USA [15].

This prospective medication use evaluation has revealed several aspects of inappropriate utilization of vancomycin in our institution. Vancomycin was used for the appropriate indication in 78.5% of the patients . Findings revealed inappropriate prolonged empirical use of vancomycin without de-escalation in some of the patients (when indicated) after culture results were reported. The unit with the highest rate of inappropriate use was the NICU and may reflect a reluctance of physicians to de-escalate antibiotic therapy due to the critical illness of the patients. A similar previous study showed a lower rate of 34.7% for the appropriate use of vancomycin [14]. That study only assessed the appropriate use of vancomycin per indication. We assessed the indication, dose, monitoring and goal trough concentrations. The dosing of vancomycin was inappropriate in almost half of the cases. It is important to note that many patients did not have their weight recorded on the electronic chart thereby mandating the estimation of the patient's actual body weight. The most common inappropriate dosing occurred with empiric doses of vancomycin 1 gram given intravenously twice daily, regardless of the patient's weight. In pediatric patients the most common dose was 15 mg/kg every 6 hours. Another reason was that in several patient cases, doses were not adjusted according to the measured trough levels and/or level of renal impairment. Guidelines have emphasized the importance of not only having the correct initial dose of vancomycin, but also the significance of inter-patient variability and the need for proper follow up after trough levels are measured [1].

This study also evaluated the monitoring of trough levels per patient. The results show that 25 of the 87 patients (28.8%) recruited did not have any trough concentration measured.. Only around one third of the 87 patients had appropriate sampling time. Factors that may have contributed to this low rate of adherence to guidelines included: delayed ordering of vancomycin trough levels (after the fourth dose), inadequate monitoring in patients with renal failure and inadequate sampling time for hemodialysis patient. The unit with the most inappropriate monitoring of vancomycin trough levels was the ICU . A study on the pharmacokinetic and pharmacodynamic analysis of vancomycin in ICU patients revealed that there is a 33% risk of not achieving the recommended AUC_{24h}/MIC breakpoint for *Staphylococcus aureus* due to clearance variability in ICU patients (related to renal function, APACHE II score, age and serum albumin concentration) [16]. Consequently, appropriate monitoring of vancomycin therapy in critically ill patients is crucial.

The majority of patients (84.3%; N = 140/166) receiving vancomycin had inappropriate trough level concentrations according to indication. Three units (pediatrics, the pediatric oncology, and the PICU) had none of the trough levels within target range with a tendency to achieve trough levels significantly lower than recommended, 5.63 ± 3.64 mg/L, and 4.09 ± 1.11 mg/L for the pediatric unit and the pediatric oncology unit respectively. Subtherapeutic levels are associated with clinical failure and an increased risk of developing vancomycin- intermediate *Staphylococcus* aureus [1]. The highest percentage (42.9%, N = 15/35) of therapeutic trough levels within goal for indication was in the CCU which is still not optimal. The guidelines on therapeutic monitoring of vancomycin published by the American Society of Health-System Pharmacists emphasizes the correlation of trough levels with both efficacy and toxicity [6].

In our study, 35.3% (N = 6/17) of the patients with baseline renal impairment developed further worsening in renal function. A strong association between renal toxicity and hospital mortality is demonstrated in multiple clinical trials. A retrospective analysis by Jefferes *et al.* showed a triple (45% versus 15%) mortality rate in a subgroup of patients receiving vancomycin treatment and suffering from renal toxicity. The study also revealed a longer hospital stay (44.8 days versus 28.7 days) for patients with nephrotoxicity which also resulted in an increase in hospital costs [17].

Appropriate vancomycin prescribing, dosing and monitoring correlates with morbidity and mortality in hospitalized patients. The presence of a clinical pharmacist as part of an inter-disciplinary team has been associated with a decrease in the number of adverse drug reactions, medication errors, improvement in medication adherence, and a decreased length of hospital stay [18]. In particular, the presence of an infectious diseases specialized clinical pharmacist resulted in a significantly decreased in the inappropriate use of vancomycin from 39% to 16.8% ($p = 0.005$) in one study [17]. Several studies have also shown that an antimicrobial restriction policy decreases significantly inappropriate vancomycin use from 59% to 30% [19-22]. Actions such as educational programs, automatic stop orders at 72 hours, and computer alerts

electronically mailed to the ordering physician can be utilized to standardize vancomycin use [23].

There are several limitations to this study. First it is an observational study, so the cause effect relationship cannot be assured. Second, the study took place in one academic tertiary care center which limits the ability to generalize the results. Third, data collection was done through the institution's computerized system; consequently, there were no interventions directly performed on the hospital wards . Finally, for the assessment of the appropriate dose of vancomycin, some of the patients did not have a recorded weight thereby mandating its estimation.

Conclusion

This study evaluated vancomycin prescribing patterns at a Lebanese tertiary care hospital and evaluated the compliance with guidelines. Results of this study demonstrated a high level of inappropriate use of vancomycin; mostly attributed to incorrect dosing and/ or inappropriate trough level monitoring. Interventions that improve vancomycin prescribing and monitoring are recommended.

Authors' contributions

WK made substantial contributions to conception, design, analysis and interpretation of data and has been involved in drafting the manuscript and revising it critically for important intellectual content. GK made substantial contributions to the analysis and interpretation of data and has been involved in drafting the manuscript. NC made substantial contributions in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript and are accountable for all aspects of the work.

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