Drug Utilization Evaluation of Vancomycin Among Hospitalized Patients in Internal Medicine Wards of Tikur Anbessa Specialized Hospital

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Abstract: Background: Vancomycin use is considered inappropriate in most hospitals. A particular concern is the recent emergence vancomycin-resistant enterococci (VRE) which is related to the potential for nosocomial transmission, the lack of antibiotics to treat infections caused by this organism, and the possibility that the vancomycin-resistant genes present in VRE can be transferred to other gram-positive microorganisms such as S. aureus. The objective of this study was to evaluate the utilization of vancomycin among hospitalized patients in internal medicine wards of Tikur Anbessa Specialized Hospital (TASH). Methods: A retrospective cross-sectional chart review was carried out to evaluate the utilization of vancomycin among hospitalized patients with vancomycin therapy between April 2012 to 2013. Results: One hundred twenty five patients were enrolled in the study, consisting of 60 males and 65 females. The age range was 13 to 80 years. Of all courses, 88.8% were considered to be initially appropriate, but this decreased to 6.4% after vancomycin initiation. Continued empiric use of vancomycin without further evidence of gram-positive infections accounted for the majority of inappropriate use. The major dosing regimen employed was 1g every 12 h in 99 (79.2%) of treatments. Vancomycin dose was not adjusted or adjusted inadequately for 62 (96.5%) of the patients with increased serum creatinine. Furosemide was the most frequently identified potentially interactive drug. Conclusion: Although the initial indication for vancomycin use was generally appropriate, failure to continue this antibiotic as per HICPAC criteria and inappropriate dosing adjustment based on MDRD CrCl level were common challenges identified.

Keywords: Vancomycin, Drug Use Evaluation, Hicpac Guideline, Dosage, Interaction

1. Introduction

Vancomycin is a member of a class of antibiotics referred to as glycopeptides. These antibiotics interfere with peptidoglycan biosynthesis by binding to the terminal D-alanyl-D-alanine residue of the peptidoglycan precursor [1].

Vancomycin use is considered inappropriate in most hospitals. A particular concern is the recent emergence of VRE [2]. The number of infections caused by VRE that have been reported to the Center for Disease Control and Prevention's (CDC's) National Nosocomial Infections Surveillance system was 40% in 2012 among US Hospitals. VRE are estimated to be responsible for 10 to 30% of all nosocomial infections in US [3]. The mounting emergence of VRE has resulted in the development of guidelines for use by Hospital Infection Control Practices Advisory Committee (HICPAC) of CDC [4,5].

Indications for vancomycin use were classified as appropriate or inappropriate based on modified HICPAC criteria [6]. According to the guidelines, inappropriate use of vancomycin is subdivided into five; empiric therapy without risk factors, continued empiric use without further culture evidence of gram-positive infections, treatment of Methicillin susceptible *Staphylococcus aureus* (MSSA) infections without allergy history to beta-lactam antimicrobials, treatment in response to a single blood culture positive while other blood cultures taken during the same time-frame are negative, and use as systemic or local prophylaxis for infections [7].

According to a national survey conducted to map antimicrobial resistance in Ethiopia, VRE accounted for around

8.7% of all identified enterococci species [8]. Concern about VRE is related to the potential for nosocomial transmission, the lack of antibiotics to treat infections caused by this organism, and the possibility that the vancomycin-resistant genes present in VRE can be transferred to other gram-positive microorganisms such as *Staphylococcus aureus* [3].

Drug Utilization Evaluation (DUE) is an effective mechanism to identify individual variability in drug use and to promote interventions that will improve positive patient outcomes [9, 10, 11].

Vancomycin is an antibiotic of growing importance in the treatment of hospital acquired infections, with particular emphasis on its value in the fight against MRSA. However, its usage profile must be evaluated to assure maximum benefit and minimum risk. Such studies are lacking in Ethiopia thus it would be prudent to assess whether vancomycin is used appropriately in a cost effective manner so as to improve patient outcomes.

2. Materials and Methods

The study was conducted in internal medicine wards of TASH which is located in Addis Ababa, Ethiopia. TASH was established in 1962 with the aim of improving the provision of health services in Ethiopia. A retrospective cross-sectional chart review was carried out to evaluate the utilization of vancomycin among hospitalized patients with vancomycin therapy in in internal medicine wards of TASH between April 2012 to 2013.

Medical records (charts) had been reviewed using individual patient data abstraction format. Both the initial indication as empiric therapy and vancomycin prescription following the availability of culture and sensitivity results was assessed. Information that was collected included demographic data, renal function parameters, admission diagnosis, type of infection, evidences for empiric vancomycin therapy, the judgment on whether vancomycin prescription was empirical or based on culture, history of allergies, concurrent antimicrobials and nephrotoxic drugs, vancomycin dosage, route of administration, duration of vancomycin therapy, culture and sensitivity test results. Key informant interview was conducted with physicians from infectious disease unit to gather information like the reason behind inappropriate vancomycin use and dosing; criteria used to start and continue empiric therapy, and commonly used guidelines for prudent vancomycin use.

Analysis was done using SPSS version 20.0. The descriptive statistic methods were used to summarize data. Determination of appropriateness of dose adjustment creatinine clearance was calculated using the modification of diet in renal disease (MDRD) formula. Information from Drug.com data base was used to identify potential interaction and Chi-square (X^2) had been used to identify possible association between ages, ward units, types of indications, and outcomes after therapy and time after initial therapy with appropriateness of vancomycin use. $P < 0.05$ was considered statistically significant.

3. Results

Between April 2012 and 2013, a total number of 125 patients (60 males and 65 females) received a total of 125 courses of vancomycin. There were 104 adults (mean ± S.D. age, 37 ± 14 years) and 18 patients above 65 years of age. The average length of hospital stay was 20.7 days; the average length of hospital stay prior to vancomycin use was 9 days. Of the patients studied, 54.4% died after 72 h of vancomycin therapy. No patient was allergic to β-lactam antimicrobials (Table 1).

Table 1. Socio-demographic and disease characteristics of the study participants.

Variables	Number (n=125)	Percentage (%)
Age of patients(yrs.)		
≤ 13	3	2.4%
13-65	104	83.2%
≥ 65	18	14.4%
Sex of patients		
Male	60	48%
Female	65	52%
Hospital stay		
< two weeks	46	36.8%
≥ two weeks	79	63.2%
Outcome		
Death	68	54.4%
Discharge	57	45.6%

The most frequent indications to the vancomycin use were pneumonia (54.40%) and primary sepsis (23.20%) (Fig1).

After starting vancomycin as an empiric therapy, the drug use was consistent with HICPAC guidelines only in 8 (6.4%) patients. Of these, majority 6 (75%) had discontinued empirical use for presumed infections in patients yielding subsequent culture negative results. Continued empiric use without further evidence of gram-positive infections accounted for 94.8% of inappropriate vancomycin use, according to CDC recommendations (Table 2).

Renal function was monitored to almost all of the patients, however, the doses were not adjusted correctly or not at all adjusted according to MDRD CrCl formula for 62 (96.9%) of patients that had renal failure (Table 3).
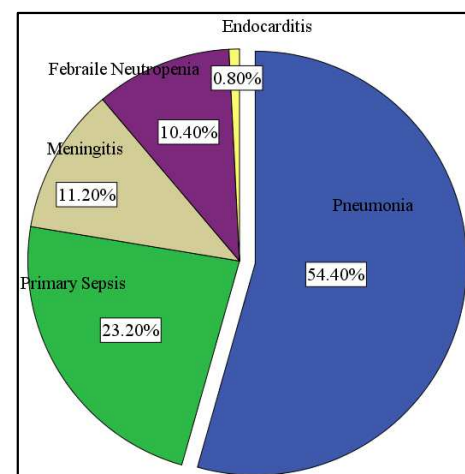
*Figure 1. Indications for vancomycin use among the study participants.*

Table 2. *Vancomycin use based on HICPAC guideline among the study participants.*

Initial treatment type	N (%)
Empirical	125(100%)
Microbiologically documented	0(0%)
Vancomycin use	N (%)
Consistent with HICPAC guideline	8(6.4%)
Discontinued empirical use for presumed infections in patients yielding subsequent culture negative results	6(75%)
Continued empiric use for presumed infections in patients yielding subsequent cultures positive for β-lactam-resistant gram-positive organisms	1(12.5%)
Discontinued empirical use for in patients yielding subsequent cultures positive for β-lactam-susceptible gram-positive organisms without β-lactam allergy	1(12.5%)
Inconsistent with HICPAC guideline	117(93.6%)
Empiric therapy without risk factors	3(2.6%)
Continued empiric use without further evidence of Gram-positive infections	111(94.8%)

Table 3. *Appropriateness of vancomycin dosing adjustment according to MDRD CrCl equation among study participants with renal disease.*

Adjustment		N (%)
Not required		61 (48.8%)
Required		64 (51.2%)
	Correctly adjusted	2 (3.1%)
	Incorrectly adjusted	22 (34.4%)
	No adjustment made	40 (62.5%)

When dose used was disaggregated by CrCl, 1 g every 12 h was commonly employed in patients with normal or near-normal renal function (CrCl >65 ml/min) and this was found to be appropriately used in almost all patients in this category. Inappropriate dose used among these patients was small and largely attributed to under dosing. In patients with low renal function, although an attempt was made to adjust the dose, the adjustment was incorrect in majority of the cases. Doses used for the treatment of greater proportion of patients with moderately decreased CrCl (30-59 ml/min) were not adjusted (Fig 2).
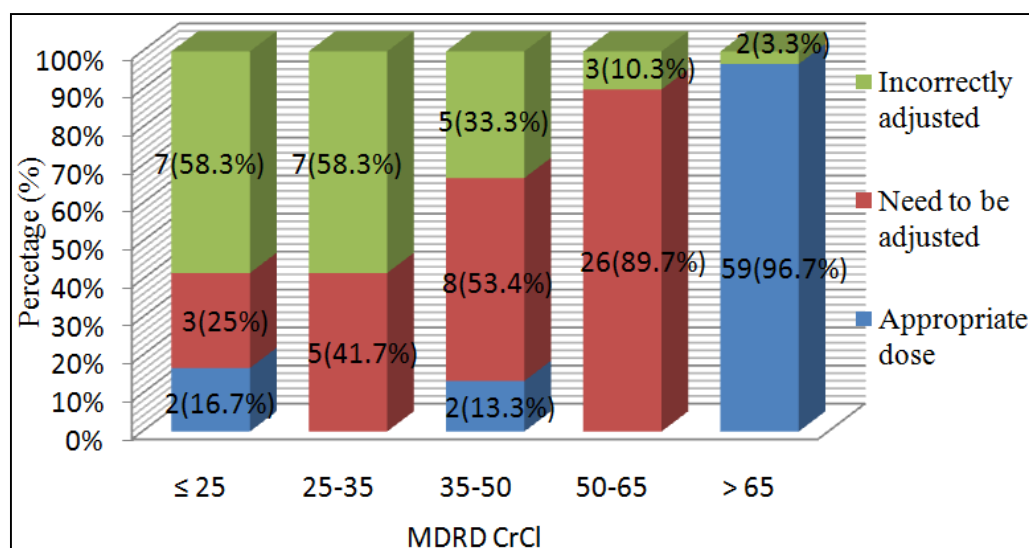
Figure 2. *Vancomycin dosing pattern based on MDRD CrCl calculations among study participants with renal disease.*

Table 4. *Bivariate analyses of risk factors for inconsistent vancomycin use, according to the CDC criteria (HICPAC), among study participants.*

Variables		Use of vancomycin as per HICPAC guidelines		P-value
		Inappropriate	Appropriate	
Age of patients	< 65	100	8	0.000
	≥ 65	17	0	
Internal medicine units	ICU	26	1	0.20045
	Non-ICU	91	7	
Type of indication	Pneumonia	63	5	0.10027
	Others	54	3	
Time after therapy initiation	Before 24hrs	14	111	0.000
	After 72hrs	117	8	

Out of the total charts reviewed in the present study, 52 contained at least one potential drug-drug interaction (D-DI) and four potential D-DIs were counted 57 times without any special vancomycin dose adjustment. Furosemide (Lasix) and

Tenofovir (TDF) were the most frequently and the only major interactive drugs identified. Renal diseases account for 45 out of 58 potential drug-diseases interactions

After several factors were analyzed, it was found out only age and time after initiation of the drug to have association with inappropriate use of vancomycin (Table 4).

4. Discussion

Vancomycin is used in the treatment of serious infections caused by susceptible organisms resistant to β-lactam antibiotics like MRSA or in individuals with serious allergy to penicillin [9]. The most frequent indications to vancomycin use in our study were pneumonia (54%) followed by primary sepsis. In previous studies, Febrile neutropenia and primary sepsis were the two common indications to which vancomycin were most frequently used and they accounted for 87.9% and 74.5%, respectively, of the total number of

reasons for vancomycin used [12,13]. According to the result obtained through interview with physicians from infectious disease unit, the high prevalence of vancomycin use for pneumonia is suggestive of pneumonia to be the most common hospital acquired infection in the internal medicine wards of the hospital.

Although rational use is mandatory, high prevalence of MRSA may raise the consumption of glycopeptide for empiric therapy in hospitals. All of the patients in this study received empiric treatment for suspected gram-positive infections. This is higher than rates reported by other researchers which range from 71% and 98 % [7,12,13]. This outcome is suggestive of high prevalence of MRSA in TASH [8], probably necessitated a high empiric vancomycin use and independence of vancomycin initiation and continuation with culture results because of accessibility and quality issue.

Inappropriate use of vancomycin is a major contributing factor in the emergence of VRE [14, 15]. Generally vancomycin use was considered inconsistent with HICPAC guidelines in 117 (93.6%) patients. Of the total inappropriate vancomycin use, 94.8% were due to continued empiric use without further evidence of gram-positive infections by culture results. This is higher than rates reported by other researchers which varied between 46% and 95.4% [7,12,13]. According to the key informant interview, continuation of vancomycin empiric therapy in the hospital doesn't depend on the microbiological data due to availability and quality issue. The key informant interview also highlighted that few of the physicians in the hospital were aware of the HICPAC recommendations.

Glomerular filtration rate (GFR) is the best index of kidney function. Mathematical estimations of GFR, based on serum creatinine, are clinically useful methods to follow renal function [16]. Absence of patient weight in the medical chart limited us to calculate CrCl based on Cockcroft Gault (CG) equation which is used by most researchers for vancomycin dosing evaluation. As use of CG and MDRD provided discordant estimations [16], the results of dose adjustment based on MDRD CrCl in our study was compared with the previous studies which were evaluated based on similar equation. According to MDRD CrCl calculation, vancomycin dose was not corrected or corrected inadequately for 96.5% of patients that had renal failure. This is also higher than rates reported by other researchers which range from 11.5% to 60% [7,12,13]. These findings suggest that vancomycin dosing among patients with renal impairment in our hospital was not calculated based on CrCl results even though the physicians' interview revealed GFR is used to adjust vancomycin dose in internal medicine wards of TASH.

Bivariate analysis showed that the risk factors associated with inappropriate vancomycin use, according to the CDC criteria, were patients above 65 years old, time after 72 h of empiric vancomycin therapy. In our analysis, patients those who were hospitalized in units other than ICUs did not have risk factors associated with inappropriate use of vancomycin as compared to ICU patients. The high incidence of inappropriate vancomycin use after 72 h of therapy in our study is associated with continued empiric use without

further evidence of gram-positive infections. According to a previous study, patients aged less than 60, non-ICU patients and those who did not present neutropenia were the principal groups at risk of inappropriate use as per the CDC criteria [2].

5. Conclusion

Although the initial indication for vancomycin use was generally appropriate, failure to continue this antibiotic as per HICPAC criteria and inappropriate dosing adjustment based on MDRD CrCl level were common challenges identified in internal medicine wards of TASH.

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