Original Article

Usage-evaluation study on Vancomycin among hospitalized pediatric patients: Experience from two tertiary care centers of Eastern India

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ABSTRACT

Background: Vancomycin is a highly effective bactericidal antibiotic with excellent efficacy against resistant Gram-positive microorganisms. It is losing its antimicrobial efficacy due to its rampant usage in Food and Drug Administration/Centers for Diseases Control and Prevention as well as off-label clinical uses. To stop its emerging resistance, judicious use of vancomycin following antibiotic stewardship is required. **Aims:** This study aims to examine the rationality of vancomycin use with respect to its adherence to Hospital Infection Control Practices Advisory Committee guidelines as well as its dosing, duration, adverse effects, and final outcome. **Methodology:** A retrospective cross-sectional hospital record-based study was conducted at two medical colleges of Eastern India from January 1, 2020, till June 30, 2020, incorporating all admitted newborns and children till 12 years' age who received vancomycin for any clinical conditions. However, the patients with renal diseases or incomplete history were excluded from the study. **Results:** A cohort of 388 patients was included of which majority of them (41.2%) were in the age group of 2–12 years and males (56.9%). Sepsis (24.2%) and pneumonia (20.8%) were the most common indications for vancomycin prescription. Overall, appropriate usage of vancomycin was found in 57.2% of patients with maximum appropriate usage which was seen among neonates (64.5%). The areas of inappropriate usage were empirical therapy in febrile neutropenia, surgical prophylaxis, treatment of coagulase-negative Staphylococcal infection, and failure to withdraw vancomycin even after negative culture report for Gram-positive organisms. The final outcome in terms of clinical improvement was seen in 72.4% of patients irrespective of appropriate/inappropriate usage. **Conclusion:** Monitoring vancomycin usage should be followed in institutional practice to stop the emergence of resistance of vancomycin.

Key words: Antibiotics, Hospital infection control practices advisory committee, Methicillin-resistant *Staphylococcus aureus*, Vancomycin

Vancomycin is a high-molecular-weight complex glycopeptide and a primarily bactericidal narrow-spectrum antibiotic. Vancomycin plays a crucial role in treating life-threatening infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Enterococcus*, and *Streptococcus pneumoniae*, as well as patients allergic to β-lactam antibiotics [1-3]. But of late, there is a growing concern worldwide due to the emerging resistance of both *Enterococcus* and MRSA to vancomycin. The reason for this increasing microbial resistance is because of its inappropriate use in Food and Drug Administration/Centers for Diseases Control (CDC) and Prevention as well as off-label clinical cases. It has been found in a study that at least 50% of vancomycin prescriptions were unnecessary which contributes to drug resistance, superinfection, and unnecessary financial burden [4].

During the early nineties, the usage was so havoc in the USA that the Hospital Infection Control Practices Advisory Committee (HICPAC) which is a subchapter of CDC, published guidelines on rational usage of vancomycin in the year 1995 [5]. This guideline describes the appropriate and inappropriate usage of vancomycin while considering its empiric use. Henceforth, the HICPAC guidelines became widely accepted worldwide and adherence to the guideline and drug utilization evaluation (DUE) became the cornerstone of rational usage of vancomycin with the aim to prevent the emergence of resistance. Subsequently, several studies were published worldwide on the evaluation of usage pattern of vancomycin in their respective institute [6-12], but there was no definite study on its usage in the pediatric population in India.

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Thus, the purpose of this study is to evaluate how rationally vancomycin is being used in two leading medical colleges of Eastern India.

METHODOLOGY

A retrospective cross-sectional hospital record-based study on vancomycin usage was conducted on admitted patients in the Department of Pediatric Medicine and Neonatology in two tertiary centers in East India, namely, Medical College and Hospital, Kolkata, and Burdwan Medical College. The approval was obtained from both the Institutional Ethical Committee of both medical colleges and due consents were taken.

All the patients falling in the age group "birth to 12 years," admitted in the above-mentioned institutions, and received parenteral vancomycin from January 1, 2020, till June 30, 2020, were included in the study. However, the patients on oral vancomycin, those having pre-existing kidney diseases, incomplete/missing records, or those being referred from a different hospital with ongoing vancomycin therapy were excluded from the study.

The study was conducted on predesigned worksheets comprising the following variables: Demography, indications of vancomycin administration, adherence to HICPAC guidelines, culture reports with antibiogram, vancomycin dosage, treatment duration, renal function test, adverse reactions, and final outcome [6]. Appropriate usage was considered if vancomycin prescriptions were done either following positive antibiogram report or adherence to HICPAC guidelines in case of empirical usage along with the proper dosage and duration of treatment. Adherence to HICPAC guidelines while considering empirical vancomycin usage includes the following clinical indications of (1) treatment of β-lactam resistant Gram-positive life-threatening infections, (2) serious allergy to β-lactam antibiotics for Gram-positive microbial infections, (3) antibiotic-associated colitis failed to respond to metronidazole, and (4) prophylaxis for endocarditis following certain procedures in patients at high risk for endocarditis.

Non-adherence to HICPAC guidelines was considered if the drug was used either as routine surgical prophylaxis other than life-threatening allergy to beta-lactams or empiric therapy for febrile neutropenia other than strong suspicion of Gram-positive infection or treatment of single blood culture-positive coagulase-negative *Staphylococcus* or continued empiric use even after negative cultures for Gram-positive microorganisms. A detailed note was taken to find out clinical indications of vancomycin usage and to label it appropriate/inappropriate usage, along with its dose, duration, irrational combination, adverse effects, and the final outcome of patients.

Statistical analysis was done using SPSS software version 26. Data were put on a Microsoft Excel spreadsheet and qualitative data were expressed in frequency and percentage. The difference in proportion was analyzed using the Chi-square test. $p<0.05$ (≤ 0.05) is considered statistically significant.

RESULTS

We recorded a total of 388 patients who received parenteral vancomycin in any of the above-mentioned medical colleges during the study period, of which 221 (56.9%) were male and 167 (43.04%) were female patients. There was a remarkably low admission from April 2020 onward with the onset of the countrywide lockdown due to the COVID-19 pandemic outbreak and our study included only non-COVID 19 patients. The study population consists of 93 (23.9%) neonates, 135 (34.7%) infants, and 160 (41.2%) older children of the 2–12 years age group. Sepsis was the most common indication for vancomycin usage (24.2%), followed by pneumonia (20.8%), meningitis and CNS infection (19.2%), and febrile neutropenia (13.4%), as shown in Table 1. Chronic osteomyelitis (9.3%), urinary tract infection (6.1%), and enteric fever (4.9%) were other few important indications found in its usage.

Approximately 57.5% of the usage of vancomycin was found appropriate with the rest 42.5% being inappropriately used. We found that the most appropriate usage of Vancomycin (64.51%) was in the neonatal age group and almost equal in both the infant (2–24 months) and older children (2–12 years) age group which were 51.8% and 57.5%, respectively. On further analysis of appropriate usage of vancomycin in the neonatal age group, we found that 28% of the total usage was for the treatment of serious infection caused by β-lactam resistant Gram-positive microorganism, 10.7% were appropriately discontinued on negative culture report, and the usage was supported by an antibiogram in 23.65% of cases. The most common inappropriate usage in neonates was found where vancomycin administration was continued in patients even after a negative culture report for β-lactam resistant Gram-positive organisms and it was around 19.3% of total usage, and the rest were inappropriate doses as well as the duration of treatment and inappropriate antibiotic combination.

In both infants and older children of 2–12 years' age group, empirical use of vancomycin for serious infections due to β-lactam resistant Gram-positive organisms was the most common indication for appropriate use of the drug which was 21.4% and 19.3%, respectively, in each age group followed by the usage for surgical prophylaxis and antibiogram supported prescriptions (Table 2). In both infants and children of 2–12 years age group, the leading cause of inappropriate vancomycin usage was empirical therapy of febrile neutropenia (39.4%), empiric surgical prophylaxis (19%), treatment of coagulase-negative

Table 1: Indication wise case distributions of vancomycin usage

Indications	Number (%)
Sepsis	94 (24.2)
Pneumonia	81 (20.8)
Meningitis and CNS infections	74 (19)
Febrile neutropenia	50 (13.4)
Osteomyelitis	28 (9.3)
UTI	23 (6.1)
Enteric fever	18 (4.6)
Others	20 (5.1)

Staphylococcus on a single positive blood culture (6.7%), and usage in patients without allergy to β-lactam antibiotics (4.1%).

Regarding the duration of treatment, 12.8% received vancomycin for more than 3 weeks and those were the cases of pleural effusion, brain abscess, and osteomyelitis, whereas 30.15% received vancomycin for 2–3 weeks and 42.2% received for 1–2 weeks, respectively (Table 3). Culture of body fluids was sent in 86.7% of cases of which, antibiogram showed vancomycin sensitivity in 17.2% of cases. Renal function was assessed in most of the cases, with the documentation of at least one creatinine study in the 1st week of vancomycin therapy which was done in 91.9% of cases but a 2nd time creatinine assessment rate dropped down to 32.1% of cases. Appropriate dosing was recorded in 86.4% of cases with renal dose adjustment wherever required. Serious nephrotoxicity as an adverse effect was found in 17 (4.38%) cases where dose titration or withdrawal of therapy was done appropriately and anaphylaxis was found in 11 (2.8%) cases and they were all probably due to rapid transfusion. The final outcome was the improvement in 72.4% of cases irrespective of appropriate and inappropriate usage and failed therapy in the form of either death or shifting to a different antibiotic was found in 22.6% of cases (Table 3). Nineteen patients were transferred to different institutes so not considered in outcome evaluation.

DISCUSSION

Vancomycin is a widely used antibiotic for life-threatening infections but very few pediatric centers follow its judicious use, though a pediatric-specific recommendation for its usage is still unavailable.

In our study, we found that the predominant use of vancomycin was therapeutic which is identical to Middle East's studies, whereas, North American studies reported that prophylactic usage of vancomycin was more than its therapeutic usage, which may be due to less incidence of infectious diseases in North American countries [7]. Sepsis (24.3%) and pneumonia (20.8%) were the two most common indications for vancomycin administration in this study, which was similar to the study of Salih *et al*. [8] in Sudan and Za'abi *et al*. in Oman [7] though, You JH *et al*. in a study at Hong Kong [9] found febrile neutropenia as the most common indication for vancomycin prescription which was identical to another study in Iran by Vazin *et al*. [10].

Culture of body fluid was advised in 86.7% of cases of our study, which was close to an Omani study (98%), whereas, studies by Salehifer *et al*. and Tagwa *et al*. recorded a predominant empirical vancomycin usage with a low blood culture rate of 30.1% and 20.5%, respectively [11]. Our study demonstrated 15.1% of vancomycin prescriptions followed proper antibiogram with the rest 84.9% was empirical, an observation similar to other studies in adults where vancomycin empiric usage was between 69% and 79% and even nearly 100% in few studies in Middle East nations [12,13].

Adherence to HICPAC guidelines and appropriate usage of vancomycin was recorded in 57.2% of vancomycin prescriptions in our study, which was low as compared to a study by Alfandari

Table 2: Distribution pattern of appropriate usage of vancomycin

Age groups	1–28 days	29 days–2 years	2 years–12 years
Antibiogram positive	22	17	19
Vancomycin stopped following culture negative for Gram-positive organism	10	6	9
Serious infection by β-lactam-resistant Gram-positive infection	28	29	37
Serious allergy to β-lactam antibiotics in Gram-positive infection	0	4	7
Surgical prophylaxis	0	14	20

Table 3: Demography and usage pattern of vancomycin

Age groups	1–28 days (%)	29 days–2 years (%)	2 years–12 years (%)
Demography (*P*=0.001)	93 (23.9)	135 (34.7)	160 (41.2)
Usage (*P*=0.01)			
Appropriate	60 (64.5)	70 (51.8)	92 (57.5)
Inappropriate	33 (35.4)	65 (48.1)	68 (42.5)
Antibiogram recommended use	22 (23.6)	17 (12.5)	19 (11.8)
Treatment duration			
<7 days	29	17	11
7–14 days	39	56	69
15–21 days	20	44	53
>21 days	5	18	27
Outcome (*P*=0.056)			
Improved	62 (66.6)	112 (82.9)	109 (68.1)
Referred	0	7 (5.1)	12 (7.5)
Failed	31 (33.4)	16 (11.8)	39 (24.3)

et al. (71%) and De Melo *et al*. (95%) [14,15]. However, our rate of appropriateness was near to the results found by Tagwa *et al*. (67.7%) in Sudan. In an Iranian study by Askarian *et al*., out of 200 vancomycin prescriptions, only 12 (6%) were appropriate [16], which was very low as compared to our study, whereas, in another Iranian study by Dehegan *et al*., the appropriateness of vancomycin prescription was 56.9% with no sex difference but a significant difference was found among the various age groups of patients [17].

We noticed that the appropriateness of vancomycin was higher in the neonatal age group (64.5%) as compared to infants (51.85%) and higher age group children (57.5%). The distribution of appropriateness in this study was as follows: Discontinuation of vancomycin on negative microbial culture report in 25 cases (11%), a life-threatening infection caused by β-lactam resistant Gram-positive organism in 94 patients (42%), treatment of patients allergic to β-lactam antibiotics in 11 cases (5%), surgical prophylaxis in 34 cases (15.4%), and culture positive with suggestive antibiogram in 52 (26%). The appropriateness distribution as found by an Omani study conducted by Za'abi *et al*. was the stoppage of vancomycin on negative microbial culture report (63%), followed by patients with life-threatening Gram-positive β-lactam-resistant bacteria (18%), and the patient allergic to β-lactam antibiotics (10%).

Inappropriate usage of vancomycin was noted overall in 42.7% of cases, which includes failure to discontinue vancomycin even after a negative microbial culture for β-lactam-resistant Gram-positive bacteria, perhaps due to more trust on vancomycin by treating pediatricians, as it covers many Gram-positive microorganisms, and in many cases, microbial culture may fail to detect MRSA. The other inappropriate uses were inappropriate combinations such as simultaneous usage of vancomycin and linezolid/flucloxacillin, particularly among febrile neutropenia patients, severe pneumonia suspecting Pontine–Valentine leukocidin producing organisms. Nephrotoxicity and anaphylaxis are the two most common side effects of vancomycin usage and it was recorded in 4.38% and 2.8%, respectively, in our study. An appropriate dosing, daily monitoring of serum creatinine, estimated creatinine clearance, and avoiding nephrotoxic drug combinations with vancomycin can prevent its toxicity. Nephrotoxicity was reported in 4.7% by Tagwa *et al*. in their study and they found that creatinine estimation was done at least once in 81% of patients which was 91.9% in the present study and 93.4% in a study by De Melo and Riberio *et al*. [18]. Inappropriate dosing was noted in 14.6% of cases but as there was no facility for drug level estimation so therapeutic monitoring which is the cornerstone of DUF of vancomycin could not be done in the present study.

The strength of the study is its in-depth analysis of vancomycin usage pattern on a larger cohort and bicentric evaluation having both urban and rural populations. However, there are shortfalls and the most important one was the lack of vancomycin serum level monitoring in each and every patient as therapeutic drug monitoring predicts the best efficacy versus toxicity of vancomycin and also its drug interaction with other nephrotoxic drugs [19].

CONCLUSION

Vancomycin was the drug of choice for MRSA for over four decades, but with its injudicious and rampant usage, it is failing to prove its adequate efficacy even in cases where culture and drug sensitivity report recommends its use. The relevance of this study is to highlight that while treating life-threatening infections at intensive care units, we often forgot to practice antibiotic stewardship. Routine usage of vancomycin in surgical prophylaxis/febrile neutropenia and evidence lacking faith over vancomycin in every life-threatening infection paves it irrational usage.

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