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Clinical Study

A new approach to Vancomycin utilization evaluation: A cross-sectional study in intensive care unit

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ABSTRACT

Objective: The risk of methicillin-resistant *Staphylococcus aureus* infections in Intensive Care Unit (ICU) is increasing in recent years with high rate of morbidity and mortality. Therefore, in this study, we aimed to evaluate the rationale use of vancomycin in ICU patients.

Methods: A total of 200 patients who received at least 48 h intravenous vancomycin were randomly selected from ICU wards, during 9 months. Vancomycin administration and related clinical and laboratory data were gathered from patients' charts and health information system to evaluate the appropriateness of different aspects of vancomycin use during all days which vancomycin were ordered.

Findings: During the study, 15,230 ± 1216 mg (mean ± standard error of the mean [SEM]) vancomycin was administered for 200 patients in the mean period of 9.79 ± 0.64 (SEM) days of ICU stay, for prophylaxis and empiric therapy. Results showed the appropriateness of vancomycin uses were 30.5%, 9%, and 5.5% in the first 24 h, after 72 h and during the whole time of treatment, respectively. In addition, infectious consultation was the only significantly different parameter between appropriate and inappropriate vancomycin administration groups ($P < 0.001$).

Conclusion: Although vancomycin utilization evaluation were mentioned in previous studies, but data related to ICU patients and during all days of vancomycin therapy are limited. High prevalence of inappropriate use of vancomycin in ICU is alarming for health systems and necessitates implementation of antibiotic policies.

Keywords: Intensive care unit; medication use evaluation; Vancomycin

INTRODUCTION

In Intensive Care Units (ICUs) the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections have considerably increased in recent years, which can lead to the development of sepsis or septic shock and subsequently high rate of morbidity and mortality.[1,2] Data from the previous studies showed 5–16% of critically ill patients were colonized with MRSA in ICUs,[1,3] with an average mortality rates of 50% for MRSA bacteremia.[2]

There are some underlying risk factors for MRSA infection in the ICU setting including recent hospitalization, surgery, long-term residence in a care facility centers, previous MRSA colonization or infection, chronic disease, immune suppression, previous antibiotic use, age (>65 years), enteral nutrition, dialysis, and indwelling percutaneous catheters and other medical devices.[1,4]

Vancomycin is the antibiotic of choice for treatment of documented or suspected MRSA infections while

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newer agents such as linezolid are now available.[2] Regarding to increasing the number of critically ill patients at high risk for MRSA colonization and infection, vancomycin utilization has been increased.[5] As a result, serious adverse effects of increased and inappropriate vancomycin utilization considered a great dilemma in health systems not only for financial and adverse reaction problems but also for limited options for treatment.[6-9]

Hence, rational utilization of vancomycin is an essential strategy in different hospital settings, especially in ICU; because inappropriate deprivation of critically ill patients from vancomycin treatment could cause the development of sepsis and on the other hand, irrational using of that could facilitate the emergence of pathogens resistant to vancomycin therapy.[8,10]

Therefore, some centers developed guidelines for vancomycin utilization and evaluated its use accordingly. However, many hospitals did not have any specific guideline and use other guides such as centers for disease control (CDC) guide for prescribing vancomycin.[11]

The previous studies from several countries reported 1–96% inappropriate use of vancomycin in various wards based on Hospital Infection Control Practices Advisory Committee (HICPAC) recommendations which provide guidance and advice to the CDC.[6,12-16]

However, there are not enough data regarding the appropriate use of vancomycin in critically ill patients. Hence, in this study, the prescribing patterns of vancomycin use were evaluated in ICU and consequently compared to HICPAC recommendations. Thereafter, the related factors of inappropriate use of vancomycin are also reported in our population study.

METHODS

We performed this cross-sectional study in one of the largest referral academic general, medical, and surgical ICUs affiliated with residency and fellowship program with more than 60 beds during 9 months. ICU adult patients were randomly selected from those received at least 48 h intravenous vancomycin in ICU and followed during ICU stay. We assign a consecutive number to each individual, and then random numbers produced by SPSS (SPSS, IBM, Somers, NY, USA) random number generator were used to select patients.

Daily surveillance was performed to collect required information from the patient's chart and health information system of hospital including demographic information (gender, age), vital signs, admission diagnosis, history of present illness, concurrent antibiotics and other nephrotoxic drugs, surgery, complete blood count, urine analysis, antimicrobial treatment in the previous 3 months, presence of mechanical ventilation and central catheters before the first dose of vancomycin, immunosuppressive medication, cultures and microbiology data, vancomycin dosage, route of administration, duration of vancomycin, and vancomycin-related adverse effects.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score[17] on the first day of ICU admission and mean of Sepsis Organ Failure Assessment (SOFA) score[18] during vancomycin administration in ICU were used to determine the severity of patients' illness for hospital mortality rate. There was not any specific hospital protocol for vancomycin consumption in our setting; so, CDC recommendations (HICPAC) were used as the guidance for its prescription [Table 1].[11] Moreover,

Table 1: Recommendation of centers for disease control for vancomycin use in adults

Situations in which the use of vancomycin are appropriate
Treatment of serious infection due to Gram-positive microorganisms which are resistant to β-lactams
Serious allergies to β-lactam antimicrobials in treatment of infections caused by Gram-positive microorganisms
Prophylaxis for endocarditis in patients at high risk
Prophylaxis of high-risk surgical procedures for MRSA or MRSE infections involving implantation of prosthetic materials or devices
Febrile neutropenic patients with evidence which suggests a Gram-positive infection and admitted into hospitals with high prevalence of MRSA infections
Antibiotics-associated colitis when there is a problem with metronidazole therapy or potentially life-threatening (oral vancomycin)
Situations in which the use of vancomycin should be discouraged
Prophylaxis for routine surgical procedures
Prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis
Prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters
Empiric antimicrobial therapy for a febrile neutropenic patient, other than patients who have initial evidence of Gram-positive microorganisms and patients who admitted in to hospitals with high prevalence of MRSA infections
Continued empirical therapy when cultures are negative for β-lactam-resistant Gram-positive microorganisms
Treatment for coagulase-negative staphylococcus based on only one single blood culture positive between multiple blood cultures
Treatment for β-lactam-sensitive Gram-positive microorganisms in patients with renal failure
Eradication of MRSA colonization
Primary antibiotic-associated colitis
Topical application or irrigation of vancomycin solution
Selective decontamination of the digestive tract

CDC=Centers for disease control, MRSA=Methicillin-resistant *Staphylococcus aureus*, MRSE=Methicillin-resistant *Staphylococcus epidermidis*

we considered recommendations of Sanford guide and review of the literature for some occasions that CDC guidelines did not satisfy for determination of appropriate prescription of vancomycin.[11,19] Appropriate vancomycin dosing regimen was also considered according to creatinine clearance calculated by Cockcroft and Gault equation.[20,21]

We classified indications for vancomycin use into three categories: Empiric (existence of clinical evidence of infection before or without information about culture results), prophylaxis (perioperative of surgical procedure), and therapeutic (based on clinical and culture result).[19,22]

In addition to indication, other aspects of vancomycin use such as dosing, rate of infusion (≥30 min for every 500 mg vancomycin), infusion concentration (≤5 mg/mL), duration of therapy were evaluated in this study.[23]

For our primary aim, we categorized patients in appropriate or inappropriate groups for different aspects including indication, dose, duration, concentration, and rate of vancomycin infusion. Descriptive statistics (mean ± standard error of the mean) were used to report these results.

Moreover, possible risk factors of inappropriate indication for vancomycin use such as patient demographic characteristics, APACHE II score, SOFA score, infectious consultation and physicians' services were assessed in our study.

Independent *t*-test and Mann–Whitney U-test were used to determine differences in continuous data between independent groups (patients with appropriate and inappropriate indication for vancomycin use) for parametric and nonparametric variables, respectively. However, Chi-square tests were applied for categorical data. If more than 20% of the categories had expected frequencies below five, the Fisher exact test was used. Data were entered into a computerized database to perform suitable analysis and calculation using SPSS for Windows, version 15 (SPSS, IBM, Somers, NY, USA).

RESULTS

During the study period, vancomycin utilization was assessed for 200 randomly selected ICU patients over 9 months. Averages duration of ICU and hospital stay of patients were 19.29 ± 1.65 days and 30.67 ± 2.15 days, respectively. According to our results, no previous reports of patients' allergy to beta-lactam antibiotics or exposure to daycare centers were detected. Demographic and baseline characteristics of studied population were listed in Table 2.

Table 2: Clinical and demographic characteristics of patients receiving vancomycin in intensive care unit at Alzahra university hospital

Characteristics	Total (*n*=200) (%)
Age (years)	54.26±1.42
Gender	
Male	118 (59)
Female	82 (41)
Reason for ICU admission	
Surgical	77 (38.5)
Medical	89 (44.5)
Trauma	34 (17)
Admission APACHE II score	14.10±0.45
Mean of SOFA score during ICU admission	4.72±0.20
Immunosuppressive illness or therapy	6 (12)
Renal impairment	
AKI	30 (15)
CKD	33 (16.5)
Dialysis	12 (6)
Previous antibiotic therapy‡	35 (17.5)
Fever at the first day of admission	41 (20.5)
Fever at the last day of admission§	21 (10.5)
CV line**	83 (41.5)
Mechanical ventilation**	103 (51.5)

‡They were included beta-lactam, macrolide, or fluoroquinolone therapy within the past three to 6 months, §Fever in ICU was defined as temperature ≥38.3,[24] **At the 1st day of vancomycin prescription, Continuous variables are expressed as mean±SEM, Categorical variables are expressed as *n* (%). ICU=Intensive Care Unit, APACHE II=Acute Physiology and Chronic Health Evaluation II, SOFA=Sepsis Organ Failure Assessment, AKI=Acute kidney injury, CV=Central venous, SEM=Standard error of the mean

Based on HICPAC guidelines, the appropriateness of vancomycin indications were 30.5%, 9%, and 5.5% in the first 24 h, after 72 h and during the whole time of vancomycin therapy in ICU, respectively. In addition, more data regarding different aspects of vancomycin use are mentioned in Table 3.

The most prevalent services that prescribed vancomycin in our study were surgery (63.5%), internal medicine (10.5%), respiratory (5.5%), and infectious department (5%). Neurosurgeons were the most frequent prescriber of vancomycin for neurosurgery prophylaxis (31% of all patients).

The average total dose of vancomycin administration was 15,230 ± 1216 mg during the mean of 9.79 ± 0.64 days of ICU stay for the study population. Duration of vancomycin administration for empiric therapy was significantly more than prophylaxis (11.41 ± 0.86 days vs. 7.72 ± 0.90 days, respectively, P = 0.004). In a similar manner, more doses of vancomycin were administered for empiric therapy than prophylaxis (16,094 ± 1636 mg vs. 14,126 ± 1822 mg, respectively).

In our study, there was not any patient that received vancomycin according to the result of culture. Not

Table 3: Evaluation of vancomycin use

Vancomycin use parameters	Total (*n*=200) (%)
Indications	
Prophylactic	87 (43.5)
Empirical therapy	113 (56.5)
Documented	0 (0)
Culture at the initiation of vancomycin[†]	99 (49.5)
No bacterial growth	41 (20.5)
Gram-negative bacteria	40 (20)
MSSA	3 (1.5)
MRSA	10 (5)
Other	5 (2.5)
Appropriate dosing administration	174 (87)
Appropriate dose adjustment according to renal function	180 (90)
Over dose[‡]; duration of being over dose	6 (3); 0.82±0.24
Under dose[§]; duration of being under dose	14 (7); 0.34±0.15
Appropriate concentration of infusion	23 (11.5)
Appropriate duration of infusion	21 (10.5)
Appropriate indication after 24 (h)	61 (30.5)
Appropriate prophylaxis after 24	0 (0)
Appropriate empirical therapy after 24	61 (30.5)
Appropriate documented therapy after 24	0 (0)
Appropriate indication after 72 (h)	18 (9)
Appropriate prophylaxis after 72	0 (0)
Appropriate empirical therapy after 72	18 (9)
Appropriate documented therapy after 72	0 (0)
Appropriate treatment duration	12 (6)

[†]Any type of culture received at the initiation of vancomycin use (blood, urine, CSF, bronchial fluid, synovial fluid, pleural fluid, tracheal tube, catheter, and chest tube), [‡]Patients who received higher doses than recommended according to renal function (inappropriate dose), [§]Patients who received lower doses than recommended according to renal function (inappropriate dose), Continuous variables are expressed as mean±SEM, Categorical variables are expressed as *n* (%). MSSA=Methicillin-sensitive *Staphylococcus aureus*, MRSA=Methicillin-resistant *Staphylococcus aureus*, SEM=Standard error of the mean, CSF=Cerebrospinal fluid

only culture had not been received for 101 patients at the initiation of vancomycin, but also the results of cultures in only 10 patients were MRSA. The results of cultures were mentioned in Table 3.

The clinical reasons for empirical therapy were most identified as serious infection with suspicious of MRSA (22.5%) and pneumonia (21%). Carbapenems (98.2% meropenem), cephalosporines (81.9% ceftazidime), and fluoroquinolones (83.1% ciprofloxacin) were the most antibiotics prescribed concurrently with vancomycin in our study (57%, 47%, and 32.5%, respectively). Moreover, 5.5% of patients received nephrotoxic drugs including colistin (3.5%), aminoglycosides (1.5%), and amphotericin B (0.5%) concurrent with vancomycin use. Although among three patients who experienced nephrotoxicity reaction of vancomycin only one patient received colistin concurrently. In addition, sensitivity reaction of vancomycin was reported only in one patient.

According to analyses, we found that only frequencies of infectious consultations were significantly different between appropriate and inappropriate vancomycin administration groups ($P < 0.001$). In this manner, infectious specialists' consults were conducted for only 24% of those with inappropriate vancomycin use, while 50% of vancomycin prescriptions were according to infection consultations in appropriate use group.

DISCUSSION

Spread of multi-resistant organisms has a significant role in infectious disease outcome and patients' morbidity and mortality. One of the most important factors causing resistance is an inappropriate use of antimicrobial agents.[13] Vancomycin was commercialized more than 50 years and since few years later has been used widely.[13,15] In 1995, HICPAC recommendations were published to control the excessive and inappropriate use of vancomycin.[11] Many studies performed to evaluate vancomycin prescription according to the guidelines which listing appropriate and inappropriate situations for vancomycin use.[6,12-16,19]

In the current study, we show poor compliance to guideline for vancomycin use, especially for prophylaxis indications with only 5.5% appropriateness according to HICPAC. However, reports of several performed studies in the past decade showed, up to 88% appropriate use of vancomycin based on CDC recommendation.[6,14-16]

These differences between studies may be related to the most indications of prescribed vancomycin which were evaluated during the study. For example, empirical therapy was the most reason of vancomycin indication in our study. It could be predictable because ICU patients may be at high risk of mortality and morbidity if too severe restrictions of vancomycin use were applied. However, de-escalation protocol should be put under consideration to prevent overuse of antibiotics and emergence of resistant microorganism.[15]

However, because of high prevalence of admitted neurosurgical patients in our setting, we identified surgical prophylaxis as the major source of inappropriate use of vancomycin, but, empirical therapy considered as the most frequent reason of inappropriate vancomycin administration in recent studies.[13-16] This controversy may be related to the different reasons' prevalence of vancomycin administrations.

In our study, the second reason for inappropriate use of vancomycin was continuation of empirical therapy

despite negative culture results for MRSA. This result is similar to the previous study which evaluated vancomycin prescription among 365 patients in a tertiary care hospital in 2013.[14] Excessive use of vancomycin is really alarming because of increasing resistant organisms.

In 2003, Hails *et al*. reported 16.2% prevalence of MRSA among the patients admitted to 217 ICUs of England hospitals.[3] However, there is not enough related data in Iranian ICUs but, the prevalence of MRSA in Iran has been shown more than 50% in systematic review conducted in 2012.[25]

In the mentioned study, the relative frequency of MRSA was 20.48% in Isfahan, while in our study, only 5% of cases were infected with MRSA. This may be related to higher prevalence of inappropriate vancomycin use in non-ICU than ICU setting.[15]

An issue highlighted in the present study is that the appropriateness of vancomycin indication decreased over the time of ICU stay. It could be justified by the reason that empirical vancomycin use was not corrected according to bacteriological culture with an antibiotic stop order at 72 h after initiation of vancomycin. Another conducted study was also showed de-escalation of vancomycin was not performed adequately during the study.[15] Lack of confidence to the culture results and critical condition of patients could be considered as the frequent reasons to continue inappropriate use of vancomycin in our study which also have been observed in some other developing countries.[14,26]

Since meropenem and ceftazidime were usually administered with vancomycin for empirical and neurosurgery prophylaxis respectively in our ICU, it could be expected that they were the must prescribed antibiotics with vancomycin. In addition, fluoroquinolones (especially ciprofloxacin) were added to empirical treatment regimen in more serious conditions and consequently reached the third position between co-administered antibiotic with vancomycin.

As infectious consultation was the only factor that significantly had a positive effect on appropriate vancomycin prescription, it seems necessary to consult of infectious specialists before and after 72 h of vancomycin initiation.

Although we evaluated different aspects of vancomycin administrations, but further studies should be carried out to include therapeutic drug monitoring procedure for preparing adequate, nontoxic dose of vancomycin in critically ill patients especially those with renal impairment.

Many antibiotic policies should be implemented to improve antimicrobial use such as vancomycin prescription pattern in ICU by the automatic stop order at 72 h, implementation of hospital guideline and adherence to that to restrict antibiotic prescription, developing of educational programs, close cooperation of clinical pharmacist and physicians.

AUTHORS' CONTRIBUTION

AM carried out the literature review, performed data collection and data entry process, and helped to draft the manuscript. SA participated in the study design and manuscript reviewing and editing. SF participated in the literature review and study design, performed final revision of the manuscript, and supervised the whole project.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abad CL, Pulia MS, Krupp A, Safdar N. Reducing transmission of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* in the ICU – An update on prevention and infection control practices. JCOM 2014;21:218-32.
2. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: Robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 2011;55:2704-9.
3. Hails J, Kwaku F, Wilson AP, Bellingan G, Singer M. Large variation in MRSA policies, procedures and prevalence in English intensive care units: A questionnaire analysis. Intensive Care Med 2003;29:481-3.
4. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, *et al*. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying panton-valentine leukocidin genes: Worldwide emergence. Emerg Infect Dis 2003;9:978-84.
5. Swartling M, Gupta R, Dudas V, Guglielmo BJ. Short term impact of guidelines on vancomycin dosing and therapeutic drug monitoring. Int J Clin Pharm 2012;34:282-5.
6. Dib JG, Al-Tawfiq JA, Al Abdulmohsin S, Mohammed K, Jenden PD. Improvement in vancomycin utilization in adults in a Saudi Arabian Medical Center using the Hospital Infection Control Practices Advisory Committee guidelines and simple educational activity. J Infect Public Health 2009;2:141-6.
7. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr., Craig W, Billeter M, *et al*. Therapeutic monitoring of vancomycin in

adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82-98.
8. Powell SL, Liebelt E. Appropriate use of vancomycin in a pediatric emergency department through the use of a standardized electronic guideline. J Pediatr Nurs 2015;30:494-7.
9. Jung E, Byun S, Lee H, Moon SY, Lee H. Vancomycin-resistant *Enterococcus* colonization in the intensive care unit: Clinical outcomes and attributable costs of hospitalization. Am J Infect Control 2014;42:1062-6.
10. Fridkin SK, Gaynes RP. Antimicrobial resistance in intensive care units. Clin Chest Med 1999;20:303-16, viii.
11. Recommendations for preventing the spread of vancomycin resistance: Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). Am J Infect Control 1995;23:87-94.
12. Wright SW, Wrenn KD. Appropriateness of vancomycin use in the emergency department. Ann Emerg Med 1998;32:531-6.
13. Askarian M, Assadian O, Safaee G, Golkar A, Namazi S, Movahed MR. Vancomycin use in a large teaching hospital in Shiraz, Islamic Republic of Iran, 2003. East Mediterr Health J 2007;13:1195-201.
14. Al Za'abi M, Shafiq S, Riyami DA, Ali AB. Utilization pattern of vancomycin in a university teaching hospital in Oman: Comparison with international guidelines. Trop J Pharm Res 2013;12:117-21.
15. Alfandari S, Levent T, Descamps D, Hendricx S, Bonenfant C, Taines V, *et al.* Evaluation of glycopeptide use in nine French hospitals. Med Mal Infect 2010;40:232-7.
16. Roustit M, François P, Sellier E, Roch N, Vittoz JP, Foroni L, *et al.* Evaluation of glycopeptide prescription and therapeutic drug monitoring at a university hospital. Scand J Infect Dis 2010;42:177-84.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-29.
18. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, *et al.* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793-800.
19. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195-283.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
21. Gilbert DN, Eliopoulos GM, Chambers HF, Saag MS. The Sanford Guide to Antimicrobial Therapy. 45th ed. Antimicrobial Therapy; 2015.
22. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc 2011;86:156-67.
23. American Pharmacists Association. Drug Information Handbook: A Comprehensive Resource for all Clinicians and Healthcare Professionals. 24th ed. US: Lexi-Comp; 2015.
24. Rehman T, Deboisblanc BP. Persistent fever in the ICU. Chest 2014;145:158-65.
25. Askari E, Soleymani F, Arianpoor A, Tabatabai SM, Amini A, Naderinasab M. Epidemiology of mecA-methicillin resistant *Staphylococcus aureus* (MRSA) in Iran: A systematic review and meta-analysis. Iran J Basic Med Sci 2012;15:1010-9.
26. Istúriz RE, Carbon C. Antibiotic use in developing countries. Infect Control Hosp Epidemiol 2000;21:394-7.