

## Appropriate use of vancomycin in an educational tertiary care hospital in Tehran, Iran

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### Abstract

**Background:** Inappropriate prescription of vancomycin has been shown to be associated with induction of antibiotic resistance. The objective of this study was to determine the incidence of inappropriate use of vancomycin in a tertiary care hospital in Iran.

**Methods:** A descriptive cross-sectional investigation was performed from September 2004 to March 2005 in all units of a general teaching Medical Center in Tehran. All adults and children who had vancomycin initiated in this medical center were enrolled in the study and the appropriateness of vancomycin use was determined according to Centers for Disease Control (CDC) guidelines.

**Results:** Forty-four percent of vancomycin use was inappropriate with the highest incidence of inappropriate use occurring in surgical units. The most common inappropriate indication for vancomycin was routine surgical prophylaxis.

**Conclusion:** Inappropriate use of vancomycin is very common in a tertiary care hospital in Iran and could potentially be decreased by educating physicians about the CDC guidelines. These educational programs should target physicians in surgical units.

**Keywords:** vancomycin resistance, inappropriate usage

### Introduction

Vancomycin-resistant enterococci (VRE) were first reported in Europe in 1986, followed by reports from the United States in 1988 where from 1989 to 1993, the percentage of nosocomial enterococcal infections caused by VRE increased from 0.3% to 7.9% [1]. Hospital studies have demonstrated the association between oral or parenteral administration of vancomycin and VRE colonization [2]. In May 1996, the first documented infection with vancomycin-intermediate *Staphylococcus aureus* was reported in a patient in Japan [3], followed by such report in the United States in 1997 [4]. In 2002, the first

two vancomycin-resistant *S. aureus* cases were reported in patients from the United States [4,5].

Inappropriate use of vancomycin has been investigated in many studies [6,7,8]. A vancomycin use report from a 225-bed tertiary care pediatric teaching hospital during a 6-month period (September 1995 to March 1996) identified 118 patient courses of vancomycin administered. Appropriate vancomycin usage was based on the CDC HICPAC criteria, but was modified to accept empiric use for presumed central line infection, presumed pneumococcal meningitis, or pneumococcal infections in critically ill patients, and initial treatment of selected febrile patients with sickle cell anemia. Van-

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comycin use was inappropriate in 64 (54%) of 118 patients. Reductions in inappropriate use (64% in the first 2 months of the study to 50% in the last 4 months of the study) occurred following a letter sent to physicians describing the modified CDC guidelines [6].

Three additional studies of vancomycin use have been reported from Children's Health Care of Atlanta at Egleston. In all of them, the rate of inappropriate use for vancomycin was high and had especially been used as a prophylactic measure [7].

In a recent study, adherence to the Hospital Infection Control Practice Advisory Committee (HICPAC) guidelines on vancomycin prescription in a large university-affiliated hospital in Shiraz, Iran was evaluated. From August to December 2003, 200 hospitalized patients received vancomycin. For only 12 (6%) of these patients was vancomycin prescribed appropriately according to HICPAC guidelines. The main reasons why vancomycin use did not comply with HICPAC recommendations were: surgical prophylaxis in patients with negative cultures for resistant Gram-positive organisms, no investigation of vancomycin serum levels in patients receiving > 48 hours of vancomycin, vancomycin serum levels not repeated in patients receiving > 1 week of vancomycin, no appropriate adjustment of dosage with respect to serum levels in patients receiving vancomycin [8].

The objective of this study was to determine the rate of compliance with CDC guidelines in a tertiary care hospital in Iran, which may lead to practical interventions to improve compliance with these guidelines.

### Methods

This descriptive, cross-sectional study was performed from September 1, 2004 to March 31, 2005 in all units of a general teaching hospital, an 800-bed hospital located in the center of Tehran, Iran. Two research assistants prospectively reviewed all orders on a daily basis and

identified patients for whom vancomycin was prescribed. Patients for whom the vancomycin prescription was initiated in other hospitals were excluded from the study. Data was recorded on eligible patients including age, gender, history of allergy to beta lactam antibiotics and underlying diseases including immunoglobulin production or function disorders (primary immunodeficiencies), neutropenia defined as an absolute neutrophil count (ANC) of less than 500 per cubic millimeter, human immunodeficiency virus infection, active collagen-vascular diseases, recent use of corticosteroids defined as greater than 1.5 milligram per kilogram per day for more than two weeks or pulse corticosteroids within the previous two months, or malignancies requiring chemotherapy. The need for mechanical ventilation and/or the presence of prosthetic devices including intravascular catheters, urinary catheters and cerebrospinal (CSF) shunts prior to initiation of vancomycin was recorded. Relevant culture results available before the initiation of vancomycin were recorded. Finally, the primary diagnosis and the presumptive indication for which vancomycin was initiated was recorded. Severe infection was defined as those infections with systemic inflammatory response syndrome (SIRS) or multiple organ failure as well as low blood pressure. The appropriateness of use of vancomycin was then determined by applying the CDC guidelines [1] to determine the compatibility of vancomycin prescription with such criteria. The Hospital Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) published recommendations for appropriate use of vancomycin in 1995 that have been implemented in many medical centers worldwide [1]. According to these guidelines, situations in which the use of vancomycin is appropriate include:

- For treatment of serious infections caused by beta-lactam-resistant gram-positive microorganisms. Vancomycin may be less rapidly bactericidal than are beta-lactam agents for be-

ta-lactam- susceptible staphylococci.

- For treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials.

- When antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life threatening.

- Prophylaxis, as recommended by the American Heart Association, for endocarditis following certain procedures in patients at high risk for endocarditis.

- Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices (e.g. cardiac and vascular procedures and total hip replacement) at institutions that have a high rate of infections caused by Methicillin-resistant *S. aureus* (MRSA) or Methicillin-resistant *S. epidermidis* (MRSE). A single dose of vancomycin administered immediately before surgery is sufficient unless the procedure lasts greater than 6 hours, in which case

the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses [2,5].

When necessary, an interview with prescribing physician(s) was performed to clarify the reason for initiation of vancomycin. As the guidelines of Hospital Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) are usually respected in all textbooks and other scientific resources, we hypothesized that after a few years upon CDC guidelines publication, they must have some impact on practice in all fields. Hence, no comment or education was offered before the prescription. To evaluate the relationship between the appropriateness of use of vancomycin and the prescribing service or age of the patient, statistical analysis using the chi-square test was applied with P values below 0.05 as significant.

| Diagnosis                                 | N   | %   |
|---|-----|-----|
| CNS infections (other than brain abscess) | 49  | 15  |
| Very severe infections <sup>1</sup>       | 40  | 12  |
| CNS tumors                                | 36  | 11  |
| ICH/IVH                                   | 30  | 9   |
| Aspiration pneumonia                      | 15  | 5   |
| Other pneumonia                           | 15  | 5   |
| HMD                                       | 12  | 4   |
| Fever and neutropenia                     | 12  | 4   |
| Wound infection                           | 10  | 3   |
| Surgical repair of disc herniation        | 9   | 3   |
| Bone/joint infections                     | 7   | 2   |
| Post-dialysis                             | 5   | 1   |
| Vascular catheter infection               | 4   | 1   |
| Brain abscess                             | 4   | 1   |
| Others                                    | 78  | 24  |
| Total                                     | 326 | 100 |

<sup>1</sup>: Defined as toxic appearance, comatose state, renal failure, Acute Respiratory Distress Syndrome (ARDS) or Disseminated Intravascular Coagulation (DIC)

CNS: central nervous system

HMD: hyaline membrane disease

ICH: intracranial hemorrhage

IVH: intraventricular hemorrhage

Table 1. Suspected diagnoses in cases where vancomycin was prescribed.

## Results

A total of 342 patients received vancomycin during the 7-month period, of which 16 were excluded from the study as vancomycin was initially prescribed in other hospitals. Of the remaining 326 cases, 58% were male and the age range of the patients was from 1 day to 90 years (mean 32 years). Six of the 326 cases (1.8%)

had a history of allergy to penicillin or penicillin derivatives. Ninety-one cases (27.9%) had underlying medical conditions including a prosthetic heart valve (n=2), hip prosthesis (n=1), other prosthesis (n=2), primary immunodeficiencies (n=2), use of corticosteroids as previously defined (n=27), neutropenia (n=21), active collagen-vascular diseases (n=10), and

| Unit <sup>1</sup>   | Number of vancomycin prescriptions | Appropriate vancomycin prescriptions (%) | Surgical prophylaxis in absence of beta lactam allergy (CDC 1) | Continued empiric use despite no beta lactam resistant organisms in cultures (CDC 4) | Prophylaxis of patients on dialysis (CDC 10) | Others   |
|---------------------|------------------------------------|--|--|--|--|----------|
| SICU-Neurosurgery   | 72                                 | 13 (18%)                                 | 56   | 3  | -  | -        |
| PICU                | 54                                 | 38 (70%)                                 | 6  | 10   | -  | -        |
| Internal Medicine   | 35                                 | 27 (77%)                                 | -  | 7  | -  | 1        |
| Neurosurgery        | 26                                 | 11 (42%)                                 | 14   | 1  | -  | -        |
| NICU                | 24                                 | 9 (38%)                                  | 1  | 14   | -  | -        |
| MICU                | 21                                 | 19 (90%)                                 | -  | 1  | 1  | -        |
| Pediatrics          | 20                                 | 19 (95%)                                 | 1  | -  | -  | -        |
| Hematology/Oncology | 18                                 | 11 (61%)                                 | 1  | 2  | -  | 4        |
| Nephrology          | 15                                 | 11 (73%)                                 | -  | 1  | 2  | 1        |
| General Surgery     | 14                                 | 5 (36%)                                  | 1  | 7  | 1  | -        |
| Orthopedics         | 9                                  | 8 (89%)                                  | -  | 1  | -  | -        |
| Neurology           | 4                                  | 3 (75%)                                  | -  | 1  | -  | -        |
| SICU - Surgery      | 4                                  | 3 (75%)                                  | 1  | -  | -  | -        |
| ENT                 | 4                                  | 1 (25%)                                  | 2  | 1  | -  | -        |
| SICU-ENT            | 1                                  | 0 (0%)                                   | 1  | -  | -  | -        |
| SICU- Neurology     | 1                                  | 0 (0%)                                   | -  | 1  | -  | -        |
| Ophthalmology       | 1                                  | 1 (100%)                                 |  |  |  |          |
| CCU                 | 1                                  | 1 (100%)                                 |  |  |  |          |
| SICU – Orthopedics  | 1                                  | 1 (100%)                                 |  |  |  |          |
| Dermatology         | 1                                  | 1 (100%)                                 |  |  |  |          |
| <b>Total</b>        | <b>326</b>                         | <b>182 (56%)</b>                         | <b>84</b>  | <b>50</b>  | <b>4</b>                                     | <b>6</b> |

1: The Psychiatry and Obstetrics/Gynecology Units were omitted as vancomycin was never prescribed.

CDC: Centers for Disease Control

ENT: Ear, Nose and Throat

MICU: Medical Intensive Care Unit

NICU: Neonatal Intensive Care Unit

PICU: Pediatric Intensive Care Unit

SICU: Surgical Intensive Care Unit

Table 2. Compatibility of use of vancomycin with CDC guidelines (1) with units ranked according to total number of patients treated with vancomycin and inappropriate indications indicated as per CDC guidelines.

malignancy currently requiring chemotherapy (n=26). In 84 cases (25.8%), the patient was on a mechanical ventilator prior to receiving the first dose of vancomycin and in 23 cases (6.4%), there were indwelling devices including an umbilical vein catheter (n=2), central venous catheter (n=9) or CSF shunt (n=12). Use of other antibiotics within 4 weeks prior to initiation of vancomycin was documented in 166 cases. The presumptive diagnoses for which vancomycin was prescribed are as shown in Table 1 with the most common diagnoses being neurologic problems or very severe infections.

In 182 cases (56%), vancomycin prescription was compatible with the CDC guidelines (Table 2). Use of vancomycin was usually appropriate in pediatric units (other than in the neonatal intensive care unit (NICU)) and in internal medicine units while use was often inappropriate in the surgical units. Vancomycin prescription in surgical units was less likely to be compatible with CDC criteria than in other units ( $P<0.001$ ). In some units including gynecology, dermatology, ophthalmology, the coronary care unit and psychiatry, vancomycin usage was too infrequent to be assessed. Surgical prophylaxis in the absence of beta lactam allergy and continued empiric treatment despite no identification of beta lactam resistant pathogens were the most common inappropriate indication for use of vancomycin (Table 2). In 17 of the 326 cases, vancomycin was started after relevant culture results were available, but use was in accordance with CDC guidelines in only

6 of these cases (2 cases of MRSA and 4 cases of MRSE infection).

Figure 1 shows the relationship between age of the patient and the compatibility of vancomycin use with CDC guidelines. There was a significant difference in the rate of appropriate vancomycin used in the different age groups ( $P<0.05$ ), with appropriate use being most common at the extremes of age.

### Conclusion

Almost half of vancomycin use in a large tertiary care hospital in Iran was inappropriate according to CDC guidelines. About one-third of all vancomycin use was on the neurosurgery service with the highest percentage of inappropriate vancomycin use being in the neurosurgical intensive care unit. One problem appeared to be the use of vancomycin as routine prophylaxis in almost all surgical procedures in which dura was incised despite the absence of data to support this practice. The unit with the second highest rate of vancomycin prescription was the pediatric intensive care unit (PICU), in which the most common diagnoses for patients prescribed vancomycin were central nervous system (CNS) infections, very severe infections, aspiration pneumonia and febrile neutropenia. However, vancomycin was usually prescribed appropriately in PICU, possibly as pediatricians are more accustomed than are other physicians to following protocols. As it was mentioned in the methods, all severe infections including meningitis and pneumonias were

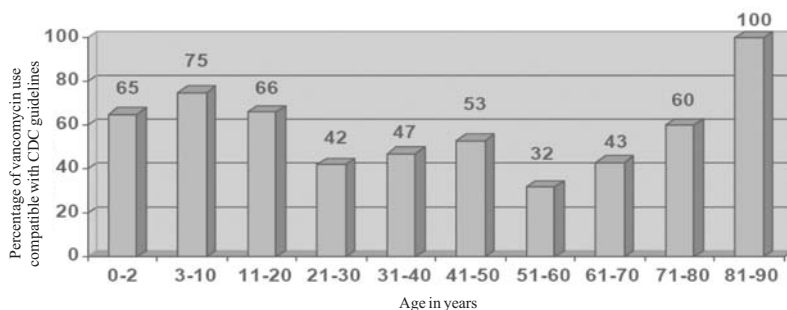


Fig. 1. Relationship between the age of the patient and the compatibility of vancomycin use with Centers for Disease Control guidelines.



considered appropriate indications. Also in all circumstances in which the possibility of ventilator associated pneumonia was considered as a probable or presumptive diagnosis, the indication was considered appropriate.

However, vancomycin was also commonly used in the NICU where about two-third of prescriptions were not compatible with the CDC guidelines. Although MRSA bacteremia is prevalent in the NICU and is appropriately managed with vancomycin, inappropriate use of vancomycin for neonatal infections such as early onset sepsis, CNS infections, pneumonia and hyaline membrane disease was common. Vancomycin was sometimes used 2 days per week in patients undergoing hemodialysis for prevention of hemodialysis catheter-related infections, despite evidence that administration of vancomycin during the first dialysis session or repeatedly every sixth day does not offer any protection against catheter-related infections [9].

Despite the high rate of inappropriate use of vancomycin in the NICU, there was an interesting relationship between age of the patient and the appropriateness of use of vancomycin with the drug being prescribed more judiciously at the extremes of age. This is difficult to explain in the young children, but in the elderly may be because physicians are less aggressive in treating elderly patients so use less empiric antibiotics than in younger adults.

In the current study, inappropriate use of vancomycin was seldom related to antibiotic allergy (<2%), compared to a previous study where allergy to beta-lactam antibiotics was the reason for vancomycin prescription in 6 % of all cases [7]. Over-diagnosis of beta-lactam allergy is a commonly recognized phenomenon, but may be less of a problem in Iran than in other countries. Even when culture results were available, vancomycin was often prescribed inappropriately. This might be due to improper selection of culture sites, uncertainty regarding the culture results, or fear of malpractice resulting in reluctance to discontinue empiric antibiotic regimens.

Previous studies described inappropriate use of vancomycin ranging from 17% to 79% in adults and from 38% to 100% in children [10, 11] versus our rate of 44% in a combined population. This wide variability could relate to local practices and to variable severity of illness. Although the CDC guidelines do not recommend empiric use of vancomycin in septic patients, the increasing incidence of gram positive infections (including MRSA) in immunocompromised hosts and in intensive care unit patients since the publication of the guidelines in 1995 may eventually result in broadening of the CDC indications for use of vancomycin including empiric use for severe sepsis, suspected pneumococcal meningitis [8,10] or CNS shunt infections.

As we realized that sensitizing the physicians before or after their practice may have some impact on their routine practice, we did not evaluate the awareness of physicians for such guideline this might be considered as a limitation. Another limitation was accessing all charts at the hospital as there was initially some resistance for such surveillance. However, we resolved this upon cooperation with higher executives at the hospital and clarification of importance of study for head of departments.

We did not measure the duration of vancomycin use in this study and this might be another limitation of the study. Although in most circumstances, the prescription was done by the physicians in charge or with their consult, it would have been ideal to record the duration of vancomycin use to determine the true magnitude of inappropriate use. One study demonstrated that the incidence of inappropriate use was higher for prolonged (>72 hours) than for shorter courses of Vancomycin [10].

In conclusion, this study demonstrates the potential value of surveillance and control of the use of vancomycin combined with physician educational programs in Iran. One of the ways

to improve the compliance with CDC guidelines is to ensure that physicians are familiar with the guidelines, as one of the reasons for inappropriate use of vancomycin is lack of knowledge of the guidelines [12]. Reduction in inappropriate use of vancomycin was reported following a letter sent to physicians describing the modified CDC guidelines [13] and when physicians received feedback within 24 hours as to whether a patient had an indication for use of vancomycin according to the guidelines [9]. Use of an antibiotic order form in a pediatric hospital did not decrease inappropriate use, but compliance with completing the form was not compulsory and inaccurate data was often recorded [14]. Perhaps mandatory completion of such a form in an accurate manner combined with an educational approach would be beneficial. A more labor-intensive approach that has been used in some hospitals and should be compared to other interventions is to require verbal approval of use of vancomycin by an infectious diseases physician [14]. In this hospital, such interventions should be targeted towards physicians in the surgical units. As CDC criteria are still the cornerstone for studies on appropriateness of vancomycin usage [15] periodic surveillance for its prescription will be mandatory.

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