

Vancomycin use in a Brazilian teaching hospital: comparison with the Hospital Infection Control Practices Advisory Committee Guidelines (HICPAC)

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This study describes vancomycin prescribing patterns in an average complexity hospital and compare the guidelines proposed by the Hospital Infection Control Practices Advisory Committee (HICPAC). The study was conducted in a 256-bed secondary-care hospital. Data were collected of all patients given vancomycin from March 2003 to February 2004, using a standardized chart-extraction form designed. Appropriate and inappropriate use was reviewed according to the Hospital Infection Control Practices Advisory Committee (HICPAC) guidelines on prudent vancomycin use. Out of 118 prescriptions, 95 (80.5%) were considered appropriate. Out of these 95 orders, 77 (81.1%) were administered for empiric treatment of suspected Gram-positive infections, 17 (17.9%) were administered for treatment of proven Gram-positive infections (76.5% identified as *Staphylococcus aureus*-like agents) and 1 (1.0%) for beta-lactam allergy. The majority of the patients (96.6%) had recently used an antimicrobial medication (3 months). The mean pre-treatment hospitalization period was 11±10 days. Out of the 118 treatments, 67 (56.8%) were for nosocomial infections. The more frequent indications for vancomycin use were pneumonia (48.3%) and primary sepsis (18.6%), accounting for more than 66% of all treatments. No restriction policy was suggested because vancomycin use was considered adequate in the majority of the treatment cases. The broad empiric use of this antimicrobial was greater than expected in the institution and its use should be revised.

Key-Words: Vancomycin, infection, guidelines, antimicrobial use.

The development of resistance to multiple drugs in Gram-positive pathogens is a serious clinical problem. Inadequate empiric therapy enhances the potential risk of developing resistance by 50% to 60% [1,2].

The increasing incidence of vancomycin enterococci (VRE) and the potential transfer of genetic factors responsible for vancomycin resistance to different Gram-positive microorganisms, including *Staphylococcus aureus* [3-7] is an international concern. Infections caused by strains of *Staphylococcus aureus* with reduced susceptibility to vancomycin (minimum inhibitory concentration = 8 µg/mL) have been described. In Japan and in the United States. All cases occurred following a prolonged course of vancomycin therapy [8-10]. In the United States cases of vancomycin resistant *Staphylococcus aureus* (VRSA) clinical infections were reported, in 2002 [7,11-13]. *S. aureus* intermediately resistant to Vancomycin has been described in Brazil [14-16].

Enterococcus sp. is the second most commonly isolated nosocomial pathogen. It is responsible for 8% of hospital acquired bloodstream infections [17,18]. The prevalence of vancomycin-resistant enterococcus (VRE) infections increased 20-fold over the past 10 years [19,20], especially in high-risk patient populations. Between 1989 and 1993, the proportion of enterococcal isolates resistant to vancomycin among in-patients increased from 0.3% to 7.9% and from 0.4% to 13.6% in intensive-care unit patients [21].

Over the last decade, vancomycin-resistant enterococci (VRE) have become a common cause of nosocomial infections in Western Europe and in the United States [4,20,22-26]. The occurrence of VRE in National Nosocomial Infections Surveillance (NNIS) hospitals has been associated with larger size hospitals (i.e., a hospital with at least 200 beds) and university affiliation [5,27]. The NNIS reported a vancomycin resistance rate of 26.3% for enterococci isolated from patients with nosocomial infections in intensive care units (ICUs) in 2000 [28,29]. In Brazil, the first case was reported in São Paulo [30]. Other cases occurred in different hospitals and, by 1998, VRE had spread throughout the country [31]. Disease severity controlled studies found that vancomycin resistance was predictive of increased mortality [32-34]. Comparing patients with vancomycin-susceptible isolates, patients with VRE bacteremia exhibit significantly increased mortality rates (17.2% vs. 36.0%) [18, 21].

In 1995, the Centers for Disease Control and Prevention (CDC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) issued guidelines to prevent the spread of vancomycin resistance [5]. Several studies demonstrated the benefit of stool scrutiny in decreasing the rate of VRE infections in healthcare facilities [4,22-25,32]. The objective of this study was to evaluate intravenous vancomycin use at a secondary-care teaching hospital and to estimate the proportion of intravenous vancomycin prescribed for an indication meeting the HICPAC guidelines, using actual information available in chart-review.

Material and Methods

The University Hospital provides services to the university community and local population and has a 10-bed intensive care unit and a 10-bed semi intensive care unit. It is

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a secondary-care teaching hospital, with 256 beds. The Pharmacy Service is centralized and attends hospitalized patients on an individual basis. Prescriptions are reviewed in each clinic by the pharmacist in charge. Drugs are dispensed to patients, for a maximum period of 24 hours (doses for oral or enteral administration are dispensed ready for use and doses for potential administration are dispensed without manipulation, with the identification of product and patient, dilution calculation and administration precautions).

Study Population

The Study Population included Patients who received intravenous vancomycin between March 2003 and February 2004, as in-patients of a 256-bed, secondary-care teaching hospital. This hospital provides services to the university community and local population and has a 10-bed intensive care unit and a 10-bed semi intensive care unit.

Data Collection and Analysis

All new vancomycin prescriptions were evaluated. The order form identified new cases. A standard design chart-extraction form was used for entering the data. These data included underlying diagnosis, history of drug allergy, demographic characteristics, hospital location, indications for vancomycin use, including culture and sensitivity data, antimicrobial treatment in the preceding three months, nature of infection, suspension of treatment when necessary or possible and antimicrobial replacement, renal insufficiency and dosing regimen.

Appropriate Use Criteria

Use was considered appropriate if the clinical indication met the HICPAC criteria. In cases of empiric use in patients with risk factors due to hospital epidemiology – high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). Accordingly, the Hospital Infection Control Commission identified during the study period nine nosocomial infections caused by *Staphylococcus aureus*. Out of these, eight were MRSA.

Inappropriate Use was Subdivided

- Use of empiric therapy without the presence of risk factors;
- Continued empiric use for presumed infections in patients whose cultures were negative for beta-lactam-resistant Gram-positive microorganisms;
- Treatment of infections caused by beta-lactam-sensitive Gram-positive microorganisms, without allergy history to beta-lactam antimicrobials;
- Treatment in response to a single positive blood culture for coagulase-negative *staphylococcus*, if other blood cultures taken during the same time-frame are negative;
- Systemic or local prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.

Secondary Conformity Analysis Classification of Inappropriate Use

Vancomycin use was studied after the culture results became available. If cultures revealed methicillin-sensitive *staphylococci*, or another relevant pathogen, maintenance of vancomycin use was considered inappropriate.

Renal Function Monitoring and Dosing Regimen Correction

Renal function monitoring was reviewed (serum urea or creatinine). When these tests were performed at least twice a week, monitoring was considered adequate. The dosing regimen, including adjustment for renal insufficiency, was evaluated using the normogram [35].

Results

Vancomycin was prescribed 118 times during the year audited (March 2003 to February 2004). The average age was 49 ± 29 years. The mean pre-treatment hospitalization period was 11 ± 10 days. The most frequent indications for vancomycin use were pneumonia (48.3%), septicemia (18.6%), peritonitis (7.6%), catheter local infection (5.1%), surgical wound infection (4.2%), and meningitis (2.5%). The medical specialties that prescribed the drug most were: intensive care unit (37.3%), semi-intensive care unit (16.9%), medical clinic (13.6%), surgical clinic (11.0%) and pediatric intensive care unit (10.2%).

Out of the 118 treatments, 67 (56.8%) were nosocomial infections, 11 (9.3%) were healthcare-related infections and 40 (33.9%) community infections. The majority of the patients (96.6%) had used antimicrobials recently (3 months).

Vancomycin use was considered consistent with the HICPAC guidelines in 95 (80.5%) patients. Out of these, 77 (81.1%) for empiric treatment of suspected Gram-positive infections, 17 (17.9%) for treatment of proven Gram-positive infections (76.5% identified *Staphylococcus aureus*-like agents) and 1 (1.0%) for beta-lactam allergy (Table 1).

Out of the 95 treatments considered appropriate, 5 (5.3%) had cultures that justified the antimicrobial discontinuation but only 3 (3.2%) actually had the antimicrobial suspended. Among the 23 (19.5%) treatments considered inappropriate, 15 (65.2%) were community infections and 8 (34.8%) were treatments for agents that did not warrant that treatment.

Table 1. Results of vancomycin audit.

Use	N (%)
Appropriate	95 (80.5%)
Empiric therapy with risk factors	77 (81.1%)
Treatment of proven Gram-positive infections	17 (17.9%)
Beta-lactam allergy	1 (1.0%)
Inappropriate	23 (19.5%)
Empiric therapy without risk factors;	15 (65.2%)
Continued empiric use without further evidence of Gram-positive infection	8 (34.8%)

Among the 23 cases of inappropriate treatment, 7 (26.1%) began in a medical clinic, 6 (26.1%) in intensive care units, 4 (17.4%) in pediatric intensive care units, 3 (13.0%) in a surgical clinic, 2 (8.7%) in semi-intensive care units and 1 (4.3%) in a nursery.

The average treatment duration was 12±10 days. The major dosing regimen employed was 1 gram every 12 hours and 500 milligrams every 6 hours, in 52 (44.1%) and 7 (5.9%) treatments, respectively. The other dosing regimens were specifically adjusted for renal insufficiency. Five patients, 60 years old or over, used a dosing regimen of 1 gram every 24 hours, despite the absence of renal insufficiency. This is justified by the slow metabolism [35]. Out of 23 children, 2 (8.7%) received a dose of the antimicrobial that was greater than necessary.

When the report on renal insufficiency was assessed, before or during the treatment with the antimicrobial, forty-four patients (37.3%) reported suffering from insufficiency before the treatment and 17 (14.4%) after its use. The function was monitored in 123 (93.4%) patients and the dose wasn't corrected for 2 (5.9%) patients who presented renal insufficiency (Table 2). Among the patients not monitored, 5 (35.7%) were children.

Table 2. Adjustment of posology, according to renal function.

Adjustment	N (%)
Not required	57 (48.3%)
Required	61 (51.7%)
Correctly adjusted	57 (93.4%)
Incorrectly adjusted	2 (3.3%)
No correction performed	2 (3.3%)

Discussion

In March 2003 another study on the use of vancomycin in a Brazilian tertiary hospital was initiated by one of the authors of this paper. It is of notice that in both hospitals, MRSA prevalence is high, which justifies the empiric use of vancomycin in the treatment of hospital infections. MRSA prevalence in HU is 41% and 92 (78%) patients received empiric treatment for suspected Gram-positive infections, which is consistent with the results of the study in the other Brazilian hospital (78% of the empiric treatment with vancomycin) [36].

The empiric use in other studies [8,27,37] varied between 33% and 71%, among all patients that received vancomycin. Success rates in the management of Gram-positive infections (post surgical patients, ventilator-associated pneumonia, peritonitis, bacteremia and meningitis) were enhanced by early therapy with active agents against the organisms later identified by the appropriate culture. Inadequate therapy is closely correlated with adverse patient outcomes, including increased rates of hospital mortality [35,38,39].

Only one study confirmed an MRSA proportion considered high, more than 20% MRSA [40]. The empiric use was responsible for 81.1% of the prescriptions considered

adequate, because of hospital epidemiology (Table 1). In a Brazilian tertiary hospital, the empiric treatment was responsible for 81.1% of appropriate vancomycin use (because of hospital epidemiology) and 65.2% was inappropriate [36]. In other studies, the empiric treatment with vancomycin was considered the second largest category of inappropriate use (26%), and in others two studies it was considered the first, with 67% of inappropriate use [8,27,37].

For instance, the HICPAC guidelines state that vancomycin is an appropriate treatment for infections caused by Gram-positive microorganisms in patients with serious allergies to beta-lactam antibiotics; we considered as "appropriate", the only case of allergy that was reported in a patient's chart although the severity of the allergy was not specified.

According to Morgan et al. (1997), the average treatment duration was 4.7 days, influenced by the prophylactic use [27]. The prophylactic use is very common in the United States, but less frequent in Brazil. Failure to discontinue the documented inadequate treatments indicates that greater attention to a review of the medical conduct is required. No correction of dosing regimen occurs when there is renal insufficiency concern, mainly because the hospital attends an older population.

Surveillance of the posological scheme was inappropriate. Vancomycin misuse may be associated with clinical failure, toxicity or super-infections, such as Gram-negative bacteremia in children [41]. The higher dose regimen in children demonstrates failures in this antimicrobial prescription and dispensation system, considering an ordinarily corrected order by the clinic pharmacist. Vancomycin use was strongly associated with Gram-negative bacteremia in children [41]. An explanation was that severe infectious diseases, predominantly caused by Gram-negative bacteria, induce the use of central venous catheters, which in turn induces the use of vancomycin. However, the association between vancomycin and Gram-negative bacteremia is still regarded as strong when the study was restricted to children without central venous catheter [41].

Studies suggest that, even in the absence of restriction policies, vancomycin use is not more than 40% of the guidelines recommendations [36,38,39,42]. Other studies have shown that antibiotic control measures can reduce total vancomycin use [18,39]. Additionally, the implementation of pharmacy policies designed to reduce the number of initial orders of vancomycin were associated with a reduction of the inappropriate use of this antimicrobial and rate of VRE infections in healthcare facilities [1,8,20,22-25,35]. Hospital pharmacies represent an even more important control point for this drug [4].

In the institution analyzed, vancomycin use was considered cautious. We believe that other antimicrobials require more attention and no restriction policy was suggested. But, due to the large empiric use of these antimicrobials there is a consensus that vancomycin use should be monitored.

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