Vancomycin Use in a Hospital with High Prevalence of Methicillin-Resistant *Staphylococcus aureus*: Comparison with Hospital Infection Control Practices Advisory Committe Guidelines (HICPAC)

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This study evaluates vancomycin prescribing patterns in a tertiary-care hospital, with high prevalence of methicillin-resistant *Staphylococcus aureus*, comparing with the guidelines proposed by the Hospital Infection Control Practices Advisory Committee. The study was conducted in a 930-bed tertiary-care hospital, during 40 days (March 10 to April 30, 2003). Data were collected of all patients given vancomycin, using a standardized chart-extraction form designed. Inappropriate use was subdivided in five categories: empiric therapy without 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 blood culture positive for coagulase-negative *staphylococcus*, if other blood cultures taken during the same time frame were negative; systemic or local prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters. Of 132 orders, 126 (95.4%) were considered to have been appropriate. Of these 126 prescriptions, 31 (24.6%) were administered for treatment of proven Gram-positive infections (78.1% of those were MRSA), 1 (0.8%) for beta-lactam allergy and 95 (75.4%) for empiric treatment of suspected Gram-positive infections. The majority of the patients (88.6%) have used antimicrobial recently (3 months). The mean pre-treatment hospitalization period was 14±15 days. Of the 132 treatments, 105 (79.5%) were nosocomial infections. In the institution analyzed, the vancomycin use was considered conscientious. Reduction in use of glycopeptide may be obtained by adaptations the CDC criteria, or by improvement of diagnostic criteria.

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

The heavy use and abuse of some antimicrobial agents have been directly linked to some of the more serious resistance problems challenging clinicians today [1,2]. The impact of antibiotic resistance on patients and society is overwhelming, as infections caused by resistant pathogens are associated with higher rates of morbidity and mortality [3]. Furthermore, microbial drug resistance has been done direct impact in health care costs.

Secondary resistance to vancomycin use is an important challenge. During the last decade, vancomycin-resistant enterococci (VRE) have become common causes of nosocomial infections in Western Europe and in United States [4-10]. The number of infections caused by this microorganism that have been reported to the Centers for Disease Control and Prevention's (CDC's) National Nosocomial Infections Surveillance system increases from 0.3% in 1989 to 7.9% in 1993 [11,12], more than 20-fold during the last decade [13]. This overall increases primarily in patients in intensive-care units (i.e., from 0.4% to 13.6%), although a trend toward an increased percentage of VRE infections in non-ICU patients was also noted [11-13]. The occurrence of VRE in NNIS hospitals was associated with larger hospital size (i.e., a hospital with at least 200 beds) and university affiliation [11,12]. In Brazil, the first case was reported in São Paulo [14]. Other cases occurred in several hospitals and, in 1998, the VRE spread for all country [15]. Controlled studies for disease severity found that vancomycin resistance was predictive of increased mortality [3,16,17].

VRE are feared because many strains are resistant to several commercially available antimicrobials and because of the potential transference of genetic factors responsible for vancomycin resistance to a variety of Gram-positive microorganisms, including *S. aureus* [4,11,18]. The occurrence of colonization with VRE and MRSA appears to be common among patients requiring intensive care [9,19]. Infections caused by strains of *Staphylococcus aureus* with reduced susceptibility to vancomycin (minimum inhibitory concentration = 8 μg/mL) were described in Japan and United States, each case occurred following a prolonged course of vancomycin therapy [20-22]. In the United States clinical infections with vancomycin resistant *Staphylococcus aureus* (VRSA) were reported, in 2002 [23-26]. Vancomycin resistance in *Staphylococci* is also a concern, and Vancomycin intermediate resistant *S. aureus* has been described in Brazil [27-29].

Because exposure to vancomycin has been identified as a strong risk factor for colonization and infection with VRE, the HICPAC guidelines recommend that healthcare centers adopt measures to ensure the prudent use of vancomycin and outline 5 clinical situations that justify the use of vancomycin and 12 situations in which its use should be discouraged [30-32]. Several American studies have measured the appropriateness of vancomycin use based on these guidelines, with estimates of appropriate use ranging from 20% to 40%, in absence of restriction policies [20,33-35].

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There are newer therapies than vancomycin to *Staphylococcus* treatment (linezolid, daptomycin and quinupristin-dalfopristin), but new therapies may raise costs. Daily prices of intravenous therapy of linezolid and quinupristin-dalfopristin are substantially higher than vancomycin, achieving $140 and $320, respectively [36].

The goals of this study were to evaluate intravenous vancomycin use at a tertiary-care teaching hospital; to estimate the proportion of intravenous vancomycin prescribed for an indication meeting the HICPAC guidelines, using objective information available by chart-review; to evaluate the impact of information dissemination and antibiotic control measures on both total vancomycin use and the appropriateness of its use; and to define clinical correlates or patterns of inappropriate vancomycin use that might help guide future interventions [37].

Materials and Methods

This was a prospective study conducted during 40 days (March 10 to April 30, 2003) at the Hospital of Servidor Público Estadual of São Paulo, 930 beds, and tertiary-care teaching hospital. *Staphylococcus aureus* is the third most prevalent pathogen causing nosocomial infections at our institution. Resistance to methicilin is high, more than 64% of the isolates are methicilin-resistant *S. aureus* (MRSA) and this resistance rises up to 86% at the intensive care unit (ICU), according to Table 1. All new prescriptions of vancomycin were evaluated. The order form identified new cases. We used a standardized chart-extraction form designed and the data were included. These data included underlying diagnosis, history of drug allergy, demographic characteristics, hospital location, indication for vancomycin use, including culture and sensitivity data, antimicrobial treatment in the preceding three months, infection's nature, treatment suspension when necessary or possible antimicrobial substitution, presence of renal failure and dosing regimen.

Table 1. Prevalence of MRSA, among *S.aureus* isolates in HSPE (2003)

Sample	All wards	ICU
All	64.7	86.1
Blood	67.9	76.6
Intravenous catheter	80.2	95.6

Inclusion Criteria

All patients receiving intravenous vancomycin during the period of the study were included.

Appropriate Use Criteria

Use was considered appropriate if clinical indication met the HICPAC criteria. Cases in which the use was empiric in patients with risk factors has been justified by hospital epidemiology – high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA).

Inappropriate use was subdivided into:

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

Secondary Conformity Analysis Classification of Inappropriate Use

We also studied vancomycin use after the culture results were available. If cultures disclosed methicillin-sensitive *staphylococci*, or another relevant pathogen, we defined that vancomycin use was inappropriate.

Renal Function Monitoring and Dosing Regimen Correction

We evaluated if the renal function was monitored appropriately (serum urea or creatinine). When these tests were performed at least twice a week, we considered the monitorization adequate. Dosing regimen, including adjustment for renal failure, was evaluated using the normogram [38].

Results

Vancomycin was prescribed 132 times during the 40 days audit (March 10 to April 30, 2003). The media age was 58±21 years, indicating the hospital care of aged people. The mean pre-treatment hospitalization period was 14±15 days. The most frequent indications to the vancomycin use were pneumonia (30.3%), primary sepsis (12.9%), surgical wound infection (11.4%), catheter local infection (9.1%) and meningitis (8.3%). The specialist physicians that mostly prescribed the drug were from: intensive care unit (15.9%), neurosurgery (14.4%), nephrology (9.8%) and emergency intensive care unit (7.6%). Of the 132 prescriptions, 105 (79.5%) were nosocomial infections and 10 (7.5%) were healthcare-related infections. The majority of the patients (88.6%) have used antimicrobial recently (3 months) and the same was observed to 92 (87.6%) patients what had nosocomial infections and among those who had community infections, 14 (87.5%).

Vancomycin use was considered consistent with HICPAC guidelines in 126 (95.4%) patients. Of these, 31 (24.6%) were administered for treatment of proven Gram-positive infections (78.1% identified MRSA), 1 (0.8%) for beta-lactam allergy and 95 (75.4%) for empiric treatment of suspected Gram-positive infections (Table 2).

The mean treatment time was 13±10 days. Out of 126 treatments considered appropriate, 8 (7.1%) had culture that justified the antimicrobial suspension but only one (12.5%)

Table 2. Results of vancomycin audit

Use	N (%)
Appropriate	126 (95.4%)
Inappropriate	6 (4.6%)
a. Empiric therapy without risk factors	1 (16.7%)
b. Continued empiric use without further evidence of Gram-positive infection	1 (16.7%)
c. Treatment of beta-lactam-sensitive microorganisms	3 (50.0%)
d. Treatment of a single blood culture positive for CNS	1 (16.7%)
e. Systemic or local prophylaxis	0 (0.0%)

has had the antimicrobial suspended. The major dosing regimen employed was 1g every 12 hours, in 75 (56.8%) of treatments. The other dosing regimens were adapted to renal failure, especially. Three patients, who were 60 years old or more, utilized dosing regimen of 1 gram every 24 hours, despite of not having renal failure. This is justified by the slow metabolism [38]. Of four kids, 1 (25%) received a sub dose of the antimicrobial.

We also evaluated the adjustment of posology, according to the renal function. Forty patients (30.3%) had the diagnosis of renal disfunction before vancomycin was started and 12 (10.1%) after its use. The function was monitored to 123 (93.4%) patients and the dose was not corrected or corrected inadequatly for 6 (11.5%) of patients that had renal failure (Table 3).

Table 3. Adjustment of posology, according to renal function

Adjustment	N (%)
Not required	80 (60.61%)
Required	52 (39.39%)
Correctly adjusted	46 (88.45%)
Incorrectly adjusted	2 (3.85%)
No correction performed	4 (7.70%)

Discussion

Vancomycin resistance is a relevant concern; ad glycopeptide restriction is one of the most important goals of the infection control committee. Although rational use is mandatory, high prevalence of MRSA may raise the consumption of glycopeptides in hospitals.

Our study discloses the situation. Our hospital has a high prevalence of methicillin resistance among *staphylococci*, which supports a high use of glycopeptides. Ninety-five patients (72.0%), among all patients, received empiric treatment of suspected Gram-positive infections. In previous studies, the reported empiric use varied between 33% and 71%, among all patients that received vancomycin [12,20,34]. Success rates in the management of Gram-positive infections (post surgical patients, ventilator-associated pneumonia, peritonitis, bacteremia and meningitis) are improved by early therapy with active agents against the organisms which are subsequently identified by appropriate culture. Subsequently testing and provision of inadequate therapy is closely correlated with adverse patient outcomes, including increased rates of hospital mortality [39-42].

Solomkin et al. (2004) affirmed that hospitals with more than 20% of MRSA should use vancomycin in empiric treatment [43]. The empiric use was responsible for 75.4% of prescriptions considered adequate, because of hospital epidemiology (Table 1). 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 [12,20,34]. For instance, the HICPAC guidelines state that vancomycin is the appropriate treatment for infections caused by Gram-positive microorganisms in patients who have serious allergies to beta-lactam antibiotics; we considered "appropriate" the unique case of allergy that was cited in patient's chart, though the allergy severity wasn't specified.

According to Morgan and collaborators (1997), the media of the treatment duration was 4.7 days, influenced prophylactic use [12]. The prophylactic use is very common in the United Sates, but not frequently reported in Brazil.

These findings suggest that adoption of the HICPAC criteria for vancomycin audit in hospitals with high prevalence of methicillin-resistance may be inappropriate. Specific criteria may be created, which includes restriction of glycopeptides for community-acquired infection (unless prevalence of community-acquired MRSA is high [29]), screening of high and low risk patients or units, improvement of diagnostic criteria of nosocomial infection and reduction of time of therapy. Diagnostic criteria are especially important, specially ventilator-associated pneumonia, where nosologic and etiologic diagnosis is inaccurate.

We also reported that surveillance of the posological scheme was inappropriate. Vancomycin misuse may be associated to clinical failure, toxicity or super infections, such as Gram-negative bacteremia in children [44]. These findings suggest that education, guidelines and the participation of a clinical pharmacist may improve not only the quality of vancomycin indications, but also the dosing scheme of the drug.

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