

Incidence of vancomycin-resistant *Enterococcus* at a university hospital in Brazil

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Keywords

Strepto-Enterococcus. Vancomycin resistance. Epidemiologic measurements. University hospitals.

Abstract

Objective

Vancomycin-resistant *Enterococcus* (VRE) is today one of the principal microorganisms implicated in nosocomial infections. Thus, a study was carried out with the objective of evaluating its epidemiology at a tertiary-level teaching hospital.

Methods

This was a three-year retrospective epidemiological study conducted from 2000 to 2002. Samples of VRE-positive clinical cultures at a 660-bed university hospital were analyzed. The incidence of VRE and the main anatomical sites and hospital units from which it was isolated were defined. Differences between the variables over the three years of the study were verified, and these were considered significant when $p < 0.05$.

Results

There was a progressive increase in the vancomycin resistance in the clinical cultures that were positive for *Enterococcus spp.*, over the three years of the study. In 2000, 9.5% of the samples were vancomycin-resistant, and this increased to 14.7% in 2001 and 15.8% in 2002. The hospital units with the largest numbers of isolates were, respectively, the emergency ward (19.5%) and the general intensive care unit (15%). The anatomical sites with the highest amounts of isolates included: urine (36%) and blood (20%).

Conclusions

With the progressive increase in the incidence of vancomycin resistance and the VRE rate, it is concluded that more effective control measures are needed for deterring the dissemination of VRE.

INTRODUCTION

Vancomycin-resistant *Enterococcus* (VRE) is one of the principal pathogens that cause hospital infections. Today, its presence in urinary infections, surgical site infections and bacteremia is notable.¹⁰ *Enterococcus* spp. is a normal inhabitant of the gastrointestinal tract, and 16 species have been described. Two species are predominant: *E. faecalis* and *E. faecium*. The *Enterococcus* genus presents intrinsic resistance to various antimicrobial agents and also progressive acquired resistance to antimicrobial

agents that are commonly utilized for treating enterococcal infections (e.g. ampicillin and aminoglycosides).⁸ Vancomycin resistance is much more recent²¹ and basically occurs through the production of peptidoglycan precursors in the cell wall that weakly bond to vancomycin, thereby impeding its action of blocking cell wall synthesis.¹² Since it was first isolated in Brazil in 1996,⁷ vancomycin-resistant *Enterococcus* has become a frequent concern among hospital epidemiologists because of its potential for dissemination through contact. This has led to the implementation of measures for avoiding

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its dissemination within the hospital environment. These measures basically consist of barrier precautions and guidance on the use of antimicrobial agents, with the particular aim of reducing the use of vancomycin, cephalosporins and antianaerobic antibiotics such as carbapenems, metronidazole and clindamycin.

Winston et al,²³ in a study on the epidemiology of VRE, found that among 181 patients with positive cultures for VRE, a large majority came from urine cultures (69%), and the species was *E. faecium* in 100% of the cases. Rosenberg et al¹⁹ described the increase in the incidence of VRE in clinical samples in several hospitals in São Francisco, California, between 1994 and 1998. There are no reports of studies in Brazil that have observed the epidemiology of clinical cultures that are positive for VRE; hence the importance of the present study. Sader et al²⁰ recently published an analysis of a microbiological surveillance study in Brazil that showed a rate of vancomycin resistance of around 7% in 2001.

Vancomycin-resistant *Enterococcus* was first isolated in a surveillance culture from a patient with acute lymphocytic leukemia, in 1998.⁶ Subsequently, it started to be frequently isolated in clinical cultures, with rapid dissemination through several sectors of the hospital. In view of this, a surveillance program was begun in two intensive care units (general ICU and pneumonology ICU), in which the patients with colonization were diagnosed by means of collecting rectal swabs. This program had the objective of isolating these patients from contact and minimizing the risk of transmission to other patients.

The *Enterococcus* spp. isolated in Brazilian hospitals is basically *E. faecalis*, which still has a good sensitivity profile in relation to ampicillin, differing from the American model in which there are significant and growing quantities of *E. faecium* with a much wider resistance profile.¹³ There are already reports of resistance to recently launched antimicrobial agents with activity against *Enterococcus* spp, such as linezolid and quinupristin-dalfopristin.^{8,11} In Brazil,

it is common to use ampicillin alone or in association with gentamycin or streptomycin.

The objective of the present study was to assess the incidence distribution within hospitals of clinical cultures positive for vancomycin-resistant *Enterococcus*, and also the principal sites from which it is isolated.

METHODS

This was a retrospective epidemiological study based on the evaluation of clinical cultures positive for VRE. It was carried out in a 660-bed university teaching hospital between January 2000 and December 2002.

The samples were seeded in specific culturing media, after identification as *Enterococcus* spp. by means of bile-esculin. The disk diffusion test using Mueller-Hinton (MH) agar was performed to confirm the vancomycin resistance using a conventional method.¹⁶ The *Enterococcus* species in the sample were not identified.

Statistical analysis using the chi-squared test was performed to verify the significance of the variables over the three years of the study. Differences were considered significant when $p < 0.05$.

The present study was approved by the research ethics committee of Escola Paulista de Medicina, Federal University of São Paulo (Unifesp).

RESULTS

Over the study period, 240 cultures positive for VRE were observed, of which 44 were in 2000, 88 in 2001 and 108 in 2002. Thus, there was a 100% increase in 2001 in relation to 2000 and 22% increase in 2002 in relation to 2001. Table 1 shows the principal sites from which VRE was isolated each year, and the number of cultures per site. The progressive increase in isolation from urine samples was statistically significant ($p < 0.0001$). The reduction in its incidence in isolates from surgical wounds over the three years of the study was also significant ($p < 0.0001$).

Table 1 - Numbers of isolates positive for vancomycin-resistant *Enterococcus*, according to year of the study and site.

Site/Year (No. of cultures)	2000 (44)	2001 (88)	2002 (108)	p
Blood culture	11 (25%)	18 (20%)	21 (19%)	NS
Urine culture	8 (18%)	35 (40%)	45 (42%)	$P < 0.0001$
Surgical wound	7 (16%)	7 (8%)	5 (4%)	$P < 0.0001$
Central catheter	4 (9%)	9 (10%)	6 (5%)	NS
Scar	4 (9%)	5 (6%)	2 (2%)	NS
Others	10 (23%)	14 (16%)	29 (27%)	NS
Total	44	88	108	

VRE: vancomycin-resistant *Enterococcus*
NS: Not significant

In 2000, VRE was isolated from 17 units of the hospital, while in 2001 it was isolated from 26 units, thus characterizing an increase of 52%. In 2002, it was isolated from 25 units. Table 2 shows the units from which VRE was isolated, and also the numbers of cultures from each unit.

In 2000, the incidence of vancomycin resistance in clinical cultures was 9.5%, increasing to 14.7% in 2001 and to 15.8% in 2002.

The unit that presented the greatest numbers of cultures positive for VRE was the emergency ward, with 47 cultures (19.5%), followed by the general intensive care unit, with 36 cultures (15%) and by nephrology with 15 cultures (6.2%). There were statistically significant differences in the numbers of isolates in the emergency ward ($p < 0.0001$), pneumonology intensive care unit ($p < 0.0001$) and vascular surgery ($p < 0.0001$) over the period studied.

The percentages of VRE in cultures positive for *Enterococcus* spp were 9.5% in 2000, 14.7% in 2001 and 15.8% in 2002. The numbers of VRE per 1000 patients-day were, respectively, 0.21 in 2000, 0.46 in 2001 and 0.6 in 2002. The numbers of VRE per 1000 clinical cultures were, respectively, 3.1 in 2000, 5.9 in 2001 and 7.3 in 2002.

DISCUSSION

Vancomycin-resistant *Enterococcus* today is one of the principal pathogens causing hospital infections. It presents wide dissemination in large-sized hospitals, and notably in those with teaching activities, like the one where the present study was made. Between 1989 and 1997 in the United States, there was an increase from 0.4% to 23.2% among intensive care unit patients, and from 0.3% to 15.4% in other units.⁴ Colonization or infection by VRE has been associated with a variety of factors, including the length of hospitalization, underlying disease (particularly renal insufficiency and neutropenia) and liver transplantation.¹ Patients colonized by VRE

carry the organism in their intestinal flora and may remain colonized for prolonged periods (up to two years).¹⁰ Vancomycin resistance has been classified into five phenotypes: VanA to VanE. Of these, only the phenotype VanC is intrinsically present, in two species (*E. gallinarum* and *E. casseliflavus*): all the others are acquired in the two principal species (*E. faecalis* and *E. faecium*).¹⁰ After introduction into a given hospital, *Enterococcus* presents a great capacity for dissemination, affecting various sectors and creating an endemicity profile that makes subsequent eradication attempts very difficult.¹⁵ Lai et al¹² reported that, with the utilization of all the recommended interventions, it was possible to reduce the numbers of VRE cases, but not to eradicate them. However, there was better control over the use of vancomycin and an increase in the expenses on gloves and gowns.

In the university hospital of the present study, the data present a progressive increase in the incidence of VRE over the three years, to reach a level of 15.8% of the strains of *Enterococcus* spp. presenting vancomycin resistance in 2002. This indicates a worrying situation, given that the SENTRY surveillance study, which included Brazilian data, showed a VRE rate of only 2% for Latin America.¹⁸

The present study also describes a progressive increase in the numbers of cultures positive for VRE, in relation to the numbers of patients hospitalized over the period of the study (patients-day). There was a year-by-year increase in the number of cultures positive for VRE despite the reduction in the number of patients-day per year of the study. There was also a year-by-year increase in the number of cultures positive for VRE, in relation to the average number of cultures per year performed at the central laboratory (data presented per 1,000 cultures/year), which was 3.1/1,000 cultures/year in 2000 and rose to 7.3/1,000 cultures/year in 2002.

Cereda et al,⁵ studying 250 strains from the same hospital as in the present study that were isolated in

Table 2 - Numbers of cultures positive for vancomycin-resistant *Enterococcus*, according to years of the study and hospital

Unit/Year (No. of cultures)	2000 (44)	2001 (88)	2002 (108)	p
Emergency ward	8 (18%)	10 (11%)	29 (27%)	P<0.0001
General ICU	6 (14%)	14 (16%)	16 (15%)	NS
Pneumology ICU	8 (18%)	3 (3%)	3 (3%)	P<0.0001
Vascular surgery	4 (9%)	2 (2%)	0 (0%)	P<0.0001
Nephrology	4 (9%)	8 (9%)	3 (3%)	NS
Neurosurgery	1 (2%)	5 (6%)	6 (5%)	NS
Pediatrics	1 (2%)	4 (5%)	7 (6%)	NS
Others	12 (27%)	42 (48%)	44 (41%)	P<0.0001
Total	44	88	108	

ICU: intensive care unit

1994 and 1995, did not find any vancomycin resistance. However eight isolates (3.2%) with intermediate sensitivity were found, thus already presaging the subsequent development of resistance, which was first found in 1998, in a surveillance culture performed on a patient with acute lymphoid leukemia who was submitted to a bone marrow transplant.⁶ After this initial isolation of VRE, weekly surveillance culturing was instituted in 2000, in the two intensive care units where the greatest numbers of cases had arisen up to that time (general ICU and pneumonology ICU). Weekly culturing was performed on the gastrointestinal tract, by means of rectal swabs taken from the patients who had stayed for more than five days in the two intensive care units. If the cultures were positive for VRE, the patients were isolated until their discharge.

The present report also confirms that there is greater incidence of VRE in critical care units. It was seen that the emergency ward, which functions as a semi-intensive care unit, was the unit that presented the greatest incidence of cases during the study period, along with the general intensive care unit. Urine (36.6%) and the bloodstream (20.8%) were the two sites most involved in positivity for VRE, followed by surgical wounds (7.9%) and catheter tips (7.9%), as described in the literature.¹⁰

The pneumonology intensive care unit presented a progressive reduction in incidence. This was one of the intensive care units where surveillance was being done by means of collecting rectal swabs and where patients with cultures positive for VRE were being isolated. On the other hand, in the general intensive care unit, where surveillance swabs were also being taken, a progressive increase in cases over the three years of the study was observed. Units with progressive increases in cases need to be carefully watched, and the collection of surveillance cultures from patients close to the index case is indicated, in order to attempt to avoid further dissemination of the VRE, especially in outbreak situations.

After VRE appeared in the hospital of the present study, measures based on the recommendations from the Centers for Disease Control (CDC), Atlanta, United States, were implemented. In these recommendations, the rational use of vancomycin, surveillance of units at risk, with isolation of patients who have become infected and colonized, and the important role of the laboratory in identifying resist-

ance, are emphasized.³ Byers et al,² starting from an outbreak of VRE, showed that by implementing the measures recommended by the CDC, they were able to reduce the dissemination of the pathogen through the hospital. They also found that proximity to a non-isolated case was an important risk factor for VRE acquisition, as was a history of trauma or use of metronidazole.

Surveillance measures are extremely important for containing VRE. Studies have shown that the incidence of colonized patients in a given hospital is ten times greater than the number of infected patients. This contributes towards very rapid transmission to other patients, because if patients are not identified using surveillance methods, it is impossible to implement contact barriers.¹⁴

Over the last few years, there has been a concern that *Enterococcus* might transmit vancomycin resistance to *Staphylococcus aureus*, which is a much more prevalent and pathogenic organism. Such transmission has been achieved *in vitro*,¹⁷ and it became reality in 2002, with the isolation of vancomycin-resistant *S. aureus* in two patients who also presented VRE of VanA phenotype.^{21,22}

Because of the large numbers of VRE cases, surveillance measures need to be implemented in the emergency ward, with the aim of reducing the incidence of VRE and also its dissemination to other units in the hospital. It must be borne in mind that this unit functions as the gateway for patients going to other sectors of the hospital.

In summary, vancomycin-resistant *Enterococcus* is a pathogen with progressive incidence in our environment, as has already occurred in other countries. It is important to identify and control it, particularly by means of barrier precautions and appropriate use of antimicrobial agents. Surveillance cultures are an important resource, in association with the above measures, for attempting to avoid greater dissemination of VRE in units at risk, such as intensive care units, transplantation and hemodialysis units and immunodepressed patient units.

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