Article/Artigo

Successful prevention of the transmission of vancomycin-resistant enterococci in a Brazilian public teaching hospital

Sucesso no controle da transmissão hospitalar de *Enterococos* resistentes a vancomicina em um hospital universitário público brasileiro

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ABSTRACT

Introduction: Vancomycin-resistant enterococci (VRE) can colonize or cause infections in high-risk patients and contaminate the environment. Our objective was to describe the epidemiological investigation of an outbreak of VRE, the interventions made, and their impact on its control. **Methods:** We conducted a retrospective, descriptive, non-comparative study by reviewing the charts of patients with a VRE-positive culture in the University Hospital of Campinas State University, comprising 380 beds, 40 of which were in intensive care units (ICUs), who were admitted from February 2008–January 2009. Interventions were divided into educational activity, reviewing the workflow processes, engineering measures, and administrative procedures. **Results:** There were 150 patients, 139 (92.7%) colonized and 11 (7.3%) infected. Seventy-three percent were cared for in non-ICUs ($p = 0.028$). Infection was more frequent in patients with a central-line ($p = 0.043$), mechanical ventilation ($p = 0.013$), urinary catheter ($p = 0.049$), or surgical drain ($p = 0.049$). Vancomycin, metronidazole, ciprofloxacin, and third-generation cephalosporin were previously used by 47 (31.3%), 31 (20.7%), 24 (16%), and 24 (16%) patients, respectively. Death was more frequent in infected (73%) than in colonized (17%) patients ($p < 0.001$). After the interventions, the attack rate fell from 1.49 to 0.33 ($p < 0.001$). **Conclusions:** Classical risk factors for VRE colonization or infection, e.g., being cared for in an ICU and previous use of vancomycin, were not found in this study. The conjunction of an educational program, strict adhesion to contact precautions, and reinforcement of environmental cleaning were able to prevent the dissemination of VRE.

Keywords: *Enterococcus*. Vancomycin resistance. Disease outbreaks. Epidemiology. Infection control.

RESUMO

Introdução: Enterococos resistentes a vancomicina (ERV) podem colonizar e causar infecção em pacientes de alto risco, bem como contaminar o ambiente. Nosso objetivo foi descrever a investigação epidemiológica de um surto de ERV, as intervenções realizadas e o impacto no controle do surto. **Métodos:** Estudo retrospectivo, descritivo, por revisão de prontuários de pacientes com cultura positiva para ERV em um hospital geral, público, universitário, admitidos entre fevereiro de 2008 e janeiro de 2009. As intervenções foram divididas em ações educacionais, revisão de processos de trabalho, medidas administrativas e de engenharia. **Resultados:** Foram avaliados 150 pacientes, 139 (92,7%) colonizados e 11 (7,3%) infectados por ERV. Setenta e três por cento estavam internados em unidades de cuidados não intensivos (p=0,028). Infecção por ERV foi mais frequente em pacientes usando cateter venoso central (p=0,043), ventilação mecânica (p=0,013), cateter urinário (p=0,049) ou drenos cirúrgicos (p=0,049). Vancomicina, metronidazol, ciprofloxacina ou cefalosporina de terceira geração foram utilizados previamente por 47 (31,3%), 31 (20,7%), 24 (16%) e 24 (16%) pacientes, respectivamente. Óbito foi mais frequente em pacientes infectados por ERV (73%) em relação aos colonizados (17%) (p<0,001). Após as intervenções, a taxa de ataque diminuiu de 1,49 para 0,33 (p<0,001). **Conclusões:** Fatores de risco clássicos para colonização ou infecção por ERV, como internação em unidade de terapia intensiva e uso prévio de vancomicina, não foram identificados neste estudo. Um conjunto de intervenções, tais como programa educacional, maior adesão às precauções de contato e reforço da limpeza ambiental apresentou impacto no controle da disseminação hospitalar do ERV.

Palavras-chaves: *Enterococcus*. Resistência à vancomicina. Surtos. Epidemiologia. Controle de infecção.

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INTRODUCTION

Vancomycin-resistant enterococci (VRE) are a major problem in many hospitals because of their ability to colonize or cause disease in high-risk patients, in addition to their ability to contaminate the hospital environment. The inappropriate use of glycopeptides in the hospital setting and the use of avoparcin and virginiamycin as growth promoters in chicken farms have been initially suggested as the trigger for the emergence of resistance in enterococci to glycopeptides[1–3]. Since *Enterococcus* spp. are part of the gastrointestinal microbiota, supercolonization by resistant strains can occur with relative ease[4]. The limited current evidence suggests that patients colonized with VRE cannot be colonized by non-resistant strains[5,6]. The contamination of the hospital environment and the ability of enterococci to survive outside the human body for prolonged periods are factors for the occurrence of cross-contamination, either through the hands of health care workers, equipment, or surfaces[7].

The first identification of VRE in Brazil occurred in a hospital at Curitiba, State of Paraná[8]. At our institution, a longitudinal prospective study showed that the prevalence of vancomycin-resistant *Enterococcus faecalis* among patients cared for in the intensive care units (ICUs) was 1.8% in 2004; vancomycin-resistant *E. faecium* was not found at that time[9]. However, in June 2007, a 31-year-old woman cared for at the gastroenterology ward was diagnosed with peritonitis, and a culture of her peritoneal fluid was found to be positive with vancomycin-resistant *E. faecium*. A subsequent surveillance program found 8 new patients colonized with VRE in the same unit and 53 secondary or tertiary cases in other wards. The infection control team started an epidemiological investigation and a *VRE Working Group* was designated to work on controlling the intra-hospital dissemination of VRE. The initial interventions were the interruption of new admissions for a period of 15 days, closing

the unit that was first affected, searching for new cases through the microbiological surveillance of patients and staff, and the application of contact precautions, along with continuing medical education. From July 2007 to January 2008, 1,919 swabs were collected, with 225 (11.7%) positive for VRE[10]. A significant reduction in the detection of new positive cultures from rectal swabs was observed in 2009 (1.5%) when compared to 2008 (4.2%) and 2007 (7.2%) ($p < 0.005$). The annual rate of patients colonized with VRE per 1,000 admissions significantly decreased from 20.3 in 2007 to 10.07 in 2008 and 3.82 in 2009 ($p < 0.001$)[10]. The purpose of this study was to describe the epidemiological investigation, the interventions made, and their impact on the control of the outbreak.

METHODS

Setting and study design

We conducted a retrospective, descriptive, non-comparative, pre- and post-interventional study to assess the impact of measures taken to control an outbreak of VRE colonization or infection at the Hospital de Clinicas, Universidade Estadual de Campinas, State of São Paulo, Brazil. The study was performed in a public university hospital, which is a tertiary referral center for a region containing ~4,000,000 inhabitants, comprising 380 beds, 40 of them in ICUs. The medical records of patients admitted between February 2008 and January 2009 were reviewed for demographic data, underlying conditions, wards, length of stay, risk factors for being colonized by VRE, specimens collected, enterococcal species isolated, and minimal inhibitory concentration (MIC) for vancomycin. The interventions were dynamics and concurrent, and were initiated immediately after identifying the first case in 2007, with a peak in February 2008. The interventions were analyzed with respect to their impact on the control of transmission of VRE and the prevention of new cases.

Definitions

Patients were considered as colonized if they were asymptomatic and had a rectal swab or stool culture positive for VRE. Patients were considered to be infected if they had a positive culture for VRE in blood or body fluids in the presence of clinical symptoms, in addition to leucocytosis or leucopenia. Invasive procedures were considered as risk factors if they were present prior to the isolation of VRE. Hematological malignancies and solid organ tumors were grouped into a single category (i.e., cancer). Chemotherapy was considered as a risk factor if it was administered until 3 weeks before the identification of VRE. The time to the primary identification of VRE was the difference between the date of admission and the date of the first VRE-positive culture. The attack rate was calculated by dividing the number of patients with a VRE-positive culture by the number of patients admitted in the same period.

Microbiological methods

The clinical specimens were collected using sterile swabs and transported in Stuart's medium (Stuart transport medium; Copan, Brescia, Italy) except for blood and other sterile fluids. Rectal swabs were collected from non-neutropenic individuals, whereas stool swabs were collected from neutropenic patients. Rectal and stool swabs were screened for VRE by inoculating them in bile-esculin agar (Enterococcosel Agar BBL®; BD Diagnostic Systems, Sparks, MD, USA) supplemented with 6 mg/L vancomycin (Sigma-Aldrich Co., St. Louis, MO, USA). All VRE isolates were identified by manual methods and confirmed by using the Vitek II system (bioMerieux Vitek, Inc., Hazelwood, MO, USA). The antimicrobial susceptibility tests were performed following the recommendations of the Clinical Laboratory Standards Institute (CLSI, USA), with OXOID® antibiotic disks (OXOID Ltd., Basingstoke, UK). The MICs of vancomycin and penicillin were determined using Etest® (AB Biodisk, Solna, Sweden), according to the manufacturer's instructions.

Interventions

Interventions were divided into 4 groups: educational activities, reviewing of workflow processes, engineering measures, and administrative procedures.

Educational activities consisted of classes for medical students, doctors, nurses, physiotherapists, and nutritionists, as well as lectures for the cleaning, maintenance, and clinical laboratory staff. The lectures focused on the ability of VRE to survive in the environment, their mode of transmission, and the precautions to be taken. Handouts emphasizing the importance of hand hygiene and contact precautions were distributed; a version specifically for the patients and visitors was written without medical terminology.

Regarding the care processes, we established *Special Contact Precautions for VRE,* i.e., the use of disposable gloves and gowns for any patient contact and daily bathing with chlorhexidine. Environmental cleaning was reinforced, comprising of cleaning the patients' bathrooms 3 times a day with sodium hypochlorite on the surfaces and scrubs with 70% alcohol on the furniture and equipment. A special ward of 18 beds was created in order to standardize the care of the patients.

Administrative measures consisted of the implementation of a VRE Team, which consisted of members of the Administration and the other services of the hospital, such as infection control, human resources, medical and nursing supervision, clinical laboratory, engineering division, and acquisition of medical supplies. The objective of the VRE team was to coordinate the interventions by focusing on 3 main areas. The first one was to encourage hand hygiene and contact precautions. To accomplish this objective, dispensers containing disposable bags of alcohol gel were distributed widely throughout all hospital areas, replacing the 70% reusable flasks that had been used previously. In addition, the paper towels used in the hospital were replaced by a better quality brand. To accomplish the special contact precautions for VRE, we reinforced the use of disposable gowns and gloves. The second aspect in the scope of the administrative measures was related to the identification of colonized/infected patients, with the aim of expediting their readmission. For this, a field was inserted into the electronic records of the patients in which the medical staff could provide information if the patient was colonized by VRE. To ensure patient safety, there was an emergency hiring of nurses and nursing assistants, since the special contact precautions for VRE resulted in an increased workload for the existing nursing staff.

Regarding engineering measures, 3 wards were redesigned due to the rupture of sewage pipes. As a result, all of the sewer lines at the hospital were checked for their integrity and repaired if necessary by an emergency maintenance task force.

Statistical analysis

The variables of interest were demographic data, underlying conditions, wards, length of stay, invasive procedures, and surgical interventions. The primary outcomes were colonization or infection

and death. Statistical analysis was conducted through the association of the categorical variables, applying the χ^2 test or Fisher's exact test, when indicated. The association between continuous variables was tested using the Mann-Whitney test. The significance level was assigned as 5% ($p \leq 0.05$).

RESULTS

From February 2008 to January 2009, we detected 150 VRE-positive patients among 13,700 admissions, representing 1.1% of all admissions. Of these, 94 (63%) were men. The median age was 50 years (range 7–91) ($p = 0.277$). The main underlying conditions were prior infection in 90 (60%) patients, cancer in 60 (40%), and hypertension in 49 (33%). There were no significant differences between patients in respect of being colonized or infected by VRE according to gender, age, or underlying conditions (**Table 1**). The main wards affected were Internal Medicine, Oncology-Hematology, Trauma and Emergency, and Gastroenterology, representing 73% of the infected patients, while only 9 (6%) cases were cared for in an ICU. Among the identified cases, VRE were isolated from rectal swabs in 139 (92.7%) cases and from sterile sites in 11 (7.3%) cases, that is, in 5 cases (3.4%) from blood, in 2 cases (1.3%) from peritoneal fluid, and in 1 case (0.7%) each from a central-line catheter, pleural effusion, urine, and surgical wound infection. These 11 patients were considered as infected while the remaining patients were considered as colonized. *E. faecium* was isolated from 147 (98%) patients, representing a substantial change in the hospital epidemiology since during the initial outbreak period; the majority of cases were caused by *E. faecalis* (data not shown). The MIC for vancomycin was determined for 131 (87%) strains; in 94 (71.8%) samples, the MIC value was ≥256 μg/mL. For teicoplanin, 84 strains were tested, with 78 (92.9%) also resistant to this antibiotic. The length of hospital

TABLE 1 - Demographic data and risk factors among 150 patients with colonization or infection by vancomycin-resistant enterococci at the University Hospital of Campinas State University, February 2008 to January 2009.

Characteristics	Colonization (n = 11)	Infection (n = 139)	Total (n)	P
Age (years)				
median (range)	52 (7-91)	58 (27-80)		0.277
Gender				
male	85	9	94	0.148
female	54	2	56	
Wards				
internal medicine/vascular surgery	29	2	31	0.208
oncology-hematology	25	5	30	
trauma/emergency	26	1	27	
gastroenterology	20	2	22	
others	39	1	40	
Underlying conditions				
infection at admission	85	5	90	0.238
cancer	53	7	60	0.117
hypertension	45	4	49	0.510
acute renal failure	26	2	28	0.663
diabetes mellitus	26	1	27	0.375
chronic renal failure	9	0	9	0.493
previous SOT	8	0	8	0.535
previous HSCT	4	0	4	0.735
AIDS	2	0	2	0.858
Invasive procedures				
central-line catheter	103	11	114	0.004
urinary catheter	71	9	80	0.049
ventilator use	47	8	55	0.013
previous surgery	41	3	44	0.589
chemotherapy	8	5	33	0.064
hemodialysis	26	4	26	0.231
hemodialysis catheter	24	4	28	0.124
surgical drain	17	4	21	0.049
parenteral nutrition	8	2	10	0.159

SOT: solid organ transplant; **HSCT:** hematological stem cell transplant; **AIDS:** acquired immunodeficiency syndrome.

stay ranged from 1–171 days, and the median was 22.5 days, with no significant difference between colonized or infected patients (p = 0.53). The median time for the first VRE identification was 14 days (min: 1 day; max: 147 days), with no significant difference between colonized or infected individuals (p = 0.715). Patients with an infection were more frequently observed among those receiving mechanical ventilation (p = 0.013), central-line catheter (p = 0.043), indwelling urinary catheter (p = 0.049), or surgical drain (p = 0.049). The majority of patients, regardless of whether they were colonized or infected, did not use antibiotics before the identification of VRE; vancomycin was used by 47 (31.3%) patients, while imipenem was used by 44 (29.3%) patients. The other drugs used were metronidazole (31 patients; 20.7%), ciprofloxacin (24 patients; 16%), third-generation cephalosporin (24 patients; 16%), azithromycin (20 patients; 13.3%), amoxicillin (20 patients; 13.3%), piperacillin plus tazobactam (19 patients; 12.7%), ampicillin plus sulbactam (18 patients; 12%), and first-generation cephalosporin (15 patients; 10%). There were 31 deaths; the proportion of death was significantly higher in the infected patients (73%; 8/11) than in the colonized individuals (16%; 23/139) (p < 0.001). The ongoing monitoring of the outbreak showed a significant decrease in the number of identified cases, with 40 new patients colonized in the 11 months following the interventions, representing an attack rate of 0.33% compared with the previous attack rate of 1.49% (p < 0.001) (**Figure 1**). No newly infected patients were identified in the post-intervention period.

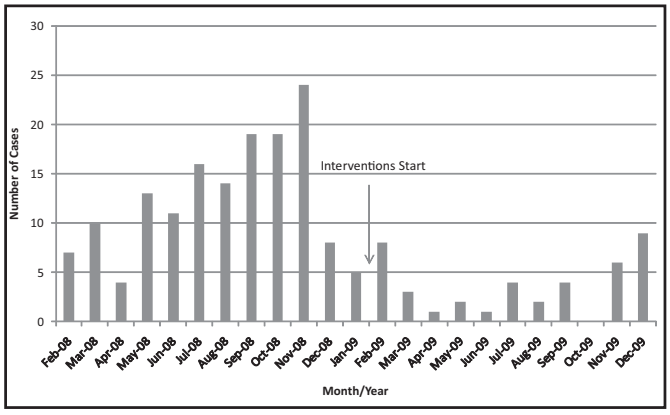

FIGURE 1 - Distribution of new cases of vancomycin-resistant enterococcal colonization or infection in the University Hospital of Campinas State University, during February 2008–January 2010.

DISCUSSION

Our study pointed to an important role of environmental contamination and the use of invasive devices as the main associated factors for the occurrence of the outbreak, as emphasized by others[11,12]. Our study showed that 73% of the VRE-positive patients were hospitalized in 4 main wards, suggesting the importance of environmental contamination. The 4 wards providing specialty care were Internal Medicine and Vascular Surgery, Oncology-Hematology, Gastroenterology, and Emergency and Trauma, and they were characterized as low-risk units, with fewer patients in their ICUs and low rates of use of invasive devices and antibiotics. The characteristics of most our patients differ from those in the medical literature, which reports a higher incidence of VRE in critically ill patients in ICUs. In addition, these 4 main inpatient units had problems with their sewage system, following the rupture of a pipeline and likely environmental contamination. The problems with the sewage system had a temporal relationship with the identification of VRE-positive patients in these 4 wards.

In order to determine the role of the environment in the colonization of VRE, Dress et al. collected cultures from patients (once a week) and from the environment (twice weekly) in 2 ICUs. The authors showed that the presence of a VRE-colonized patient in the previous 2 weeks or a previous positive environmental culture were highly predictive for VRE acquisition by the subsequent occupant of the room[13]. In our study, the majority of the patients (73%) were cared for in just 4 wards and, conversely to the reported literature[14–16], with the exception of the Trauma unit, these wards were not involved in intensive care. Furthermore, these same wards had previous problems with the sewage system, including disruption of the sewer lines, which may have contributed to the outbreak. Calffe et al. assessed the impact of measures such as the use of surveillance cultures for the early identification of new cases and the implementation of contact precautions for patients with VRE-positive cultures in a tertiary hospital after identifying an outbreak of VRE during a 5-year period. The authors showed that VRE colonization was limited to 0.82% of admissions at a 600-bed tertiary hospital, but identified a prevalence of 100% for VRE colonization in the ICU[17]. A study conducted at Johns Hopkins University by Pelz et al. concluded that VRE infections have become increasingly common, particularly among critically ill patients. The authors searched a nationwide database for VRE acquisition and found that while VRE isolates increased from 0.3% in 1989 to 7.9% in 1993 among all admissions, VRE isolates in ICUs increased by 13.6% over the same period[18].

There are a large number of studies showing the impact of antibiotic use on the prevalence of VRE[19–22]. The majority of these reports show the previous use of antibiotics, e.g., vancomycin, carbapenem, metronidazole, clindamycin, and cephalosporin, as independent risk factor for the acquisition of VRE. However, in our study, the previous use of antimicrobials did not have impact on colonization or infection by VRE since 98% of our VRE-positive patients did not use clindamycin and 90%, 84%, 84%, 79%, 70%, and 68% of patients did not use first- or third-generation cephalosporin, ciprofloxacin, metronidazole, imipenem, or vancomycin, respectively, before VRE acquisition. Other common risk factors, such as cancer or other immunosuppressive diseases, were not clearly associated with colonization or infection in our study (p = 0.064), although cancer prevailed in VRE-infected patients in relation to the colonized. The literature shows that VRE-colonized patients who experience febrile neutropenia are at a higher risk of developing a VRE infection than the general hospitalized population, probably because of the higher levels of immunosuppressants and broad-spectrum antimicrobials used in these patients[23].

There was a higher mortality among the VRE-infected than VRE-colonized patients (p < 0.005). Developing a VRE infection was unusual, since the infection rate was 7.3%, but the higher mortality observed in the infected individuals raises concerns about the impact of being colonized as an important step that can lead to death. We cannot prove this, but we believe that environmental contamination was the pivotal event causing this particular outbreak, mostly because the main risk factors for VRE acquisition usually reported in the literature were not seen among our patients. Furthermore, the majority of cases occurred at ~1 week after a sewage rupture in these

wards. Finally, after the establishment of a task force, which reviewed and rebuilt the sewer lines, the identification of new VRE-positive cases dropped to the levels that were seen before this event, with no new cases identified among the at-risk population.

This study has some limitations. The first one is its retrospective design, with the data obtained through the review of medical charts. Second, the interventions were implemented concurrently, dynamically, and according to the need to control the outbreak; hence, it is not possible to assess the role of each intervention separately. Surveillance cultures, whether of patients or from the environment, are dependent on the quantity of VRE in the stool samples or surfaces; thus, this outbreak of VRE may be higher than our data suggest. Finally, it was not possible to perform molecular epidemiological analysis; therefore, it was not possible to prove that patients harbored the same strain of VRE found in the environment. For this same reason, it was not possible to ascertain if there was clonal or clustered spread among the patients. Despite this, our results show that the measures taken to reduce environmental contamination, as well as prevent the cross transmission of the microorganism, e.g., hand hygiene and contact precautions, were effective at stopping the dissemination of VRE, leading to the control of the outbreak.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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