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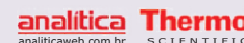
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Vancomycin-resistant enterococcus outbreak in a pediatric intensive care unit: report of successful interventions for control and prevention

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Abstract

The objective of this study is to retrospectively report the results of interventions for controlling a vancomycin-resistant enterococcus (VRE) outbreak in a tertiary-care pediatric intensive care unit (PICU) of a University Hospital. After identification of the outbreak, interventions were made at the following levels: patient care, microbiological surveillance, and medical and nursing staff training. Data were collected from computer-based databases and from the electronic prescription system. Vancomycin use progressively increased after March 2008, peaking in August 2009. Five cases of VRE infection were identified, with 3 deaths. After the interventions, we noted a significant reduction in vancomycin prescription and use (75% reduction), and the last case of VRE infection was identified 4 months later. The survivors remained colonized until hospital discharge. After interventions there was a transient increase in PICU length-of-stay and mortality. Since then, the use of vancomycin has remained relatively constant and strict, no other cases of VRE infection or colonization have been identified and length-of-stay and mortality returned to baseline. In conclusion, we showed that a bundle intervention aiming at a strict control of vancomycin use and full compliance with the Hospital Infection Control Practices Advisory Committee guidelines, along with contact precautions and hand-hygiene promotion, can be effective in reducing vancomycin use and the emergence and spread of vancomycin-resistant bacteria in a tertiary-care PICU.

Key words: Infections; Antibiotics misuse; Drug resistance; Vancomycin-resistant enterococcus

Introduction

Vancomycin overuse has been a concern for many years because of its role in selecting vancomycin-resistant enterococci (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA) (1,2). In fact, correlations between antimicrobial consumption and resistance have already been demonstrated (3). VRE are usually resistant to other antimicrobials, are easily transmitted in the hospital setting and may transfer vancomycin resistance to other Gram-positive organisms (4). In fact, VRSA has been already

reported, carrying the enterococcal vanA gene complex, with altered cell wall composition and high resistance to both oxacillin and vancomycin (5).

In response to the increasing vancomycin misuse, in 1995, the United States Centers for Disease Control and Prevention - Hospital Infection Control Practices Advisory Committee (CDC-HICPAC) released the Recommendations for Preventing the Spread of Vancomycin Resistance, which contain instructions for prudent vancomycin use,

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role of microbiology laboratories in detection, reporting and control of VRE, as well as preventing and controlling nosocomial transmission of VRE (6). Since then, several groups have evaluated vancomycin use at their own institutions, and the reported prevalence of inappropriate use varied widely (20-100%) in adults and children, primarily due to empirical therapy (1,2,4,7-14). Recently, some of the HICPAC guidelines have been modified to reflect the need to empirically cover novel penicillin-resistant pneumococci and methicillin-resistant *S. aureus* (MRSA) (2).

Despite the HICPAC guidelines, multidrug-resistant bacterial infections have increased among Pediatric (PICU) and Neonatal (NICU) Intensive Care Units with impact on major outcomes such as mortality, length-of-stay and costs (15,16).

In our institution, since 1998, the protocol for prophylaxis of bacterial infection in children undergoing open heart surgery has included vancomycin for those admitted 2 days or more before surgery, and vancomycin has been initiated against any suspected nosocomial infection in the postoperative period. Until recently, there were no guidelines about discontinuation of vancomycin use. In September 2008, the first VRE-colonized patient was identified in our hospital on the oncology ward. In August 2009, we identified the first (index) case of VRE infection in a pediatric patient in our institution, followed by 4 other cases, resulting in three deaths. This led to a series of meetings with the Infection Control Service (ICS) team, which resulted in the implementation of several practices to achieve full adherence to HICPAC guidelines. Therefore, the objective of this study was to report the results of these interventions in vancomycin use and VRE infections at our institution.

Material and Methods

Study design

This is a retrospective report on the results of systematic interventions in a PICU at Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HC-FMRP-USP), a tertiary-care university hospital, carried out between August and September 2009. This unit assists patients undergoing major surgical procedures, mostly open heart surgery and neurosurgery, and patients from pediatric oncology wards with clinical or surgical complications.

Vancomycin use before the interventions

From 1998 to August 2009, our protocol for prophylaxis of bacterial infection in children undergoing open heart surgery was a) cephazolin (80 mg/kg loading dose plus 40 mg/kg every 8 h) for patients admitted within 48 h before surgery, or b) vancomycin (10 mg/kg every 6 h) plus amikacin (7.5 mg/kg every 12 h) for those admitted 2 days or more before surgery. These regimens were maintained for 48 h after surgery. In addition, when sternum closure

was delayed, antibiotics were continued until 24 h after sternum closure. When a postoperative bacterial infection was suspected, vancomycin, plus a 3rd- or 4th-generation cephalosporin, were started and maintained for at least 7 days even when cultures resulted negative or identified a microorganism other than MRSA. Blood cultures were collected as single samples.

Interventions

After the identification of the first VRE infection, we started a series of meetings with the ICS staff to plan interventions at the following three levels: patient care, microbiological surveillance, and medical and nursing staff training. 1) Patient care: full compliance with the HICPAC guidelines for adequate use of vancomycin, bathing with a 2% chlorhexidine solution the night before surgery and on the day of surgery, changes in surgical prophylaxis (use of cephazolin for children admitted up to 5 days before surgery and those with negative routine screening cultures, MRSA decolonization with chlorhexidine bathing plus a nasal argentine sulfadiazine solution for 5 days for patients colonized with MRSA, adjustments of dose and timing of prophylactic antibiotics, maintenance of prophylaxis only for 24 h even in patients with an open chest, new loading doses right before chest closure), changes in treatment of postoperative infections (starting vancomycin only if deep surgical site- or central venous catheter-related infection or isolated MRSA or severe infections with sepsis was present and discontinuation if no MRSA was identified within the first 72 h), collection of paired samples for blood cultures, geographic cohorting of patients with documented MRSA or VRE, and contact precautions and dedicated patient equipment. 2) Staff training: lectures on HICPAC guidelines, antibiotics stewardship, antisepsis for blood culture sample collection, emphasizing the importance of the antibiotic loading dose given immediately before the beginning of surgery, attention to extra doses of intraoperative antibiotics, careful hand degermation with 2% chlorhexidine at unit entry plus hand cleaning with gel alcohol, aseptic techniques for invasive procedures, routine environmental cleaning and disinfection, and avoiding hypothermia and hyperglycemia. 3) Microbiological surveillance: routine collection of surveillance cultures from patients transferred from other hospitals (blood, urine, tracheal, or nasal specimens, rectal swabs), routine collection of blood cultures and tracheal aspirates or nasal swabs from patients colonized with MRSA, and routine collection of blood cultures and rectal swabs from patients colonized with VRE.

Data collection

Data were collected from the ICS computer-based database and from the electronic prescription system, including: number of admissions, mean length-of-stay, mortality, prescriptions of vancomycin, dose of vancomycin used, and number and agents of infections, including VRE. The

National Nosocomial Infections Surveillance (NNIS) system was used for nosocomial infection surveillance and report (17). VRE nosocomial infections were diagnosed according to CDC/NHSN criteria (18).

Statistical analysis

Data are reported as raw numbers and proportions, or as means \pm SD. There was no hypothesis test.

Results

In 2008, after the identification of the first VRE-colonized patient (rectal swab), VRE was isolated from 14 other patients (one from the surgical site and 13 from rectal swabs), and 12 were considered infected. All these patients were adults, and VRE was never found in pediatric patients until August 2009. In 2009, VRE was isolated from 29 adult plus 5 pediatric patients at many hospital sites, and 24 were considered infected. Only vancomycin-resistant *Enterococcus faecium* (VREfm) was isolated from all patients using automated methods with manual confirmation.

Since 1998, our unit has admitted 3065 patients (mean of 236 patients per year) or 2230 patients-day per year (mean of the last 4 years), with an incidence density of nosocomial infection of 23 episodes/patient-day and overall mortality rate of 11.8% (both in 2009). The use of vancomycin was about 200 mg/patients-day during 2007, and in March 2008 we noted a progressive increase in vancomycin use, peaking in July 2008 and August 2009 (Figure 1). At that time, the first case of VRE infection was identified, followed by 4 other cases (Table 1), which resulted in 3 deaths (1 infected and 2 colonized). In all cases, only VREfm was isolated. VRE was not isolated from any other pediatric unit within our hospital.

Upon identification of the first case, the interventions were made. We then noted a significant 75% reduction in vancomycin prescription and use and 4 months later the last case of VREfm infection was identified. The survivors remained colonized until hospital discharge.

After the interventions, we noticed a transient increase in PICU length-of-stay and mortality (Figure 1). Since then, the use of vancomycin has remained relatively constant and strict, and despite the identification of 44 new cases of VRE-infected or colonized patients in our hospital, no other cases of VRE infection or colonization have been identified in our unit, and length-of-stay and mortality have returned to baseline.

Discussion

We have shown a significant reduction of vancomycin prescription and use and the control of vancomycin-resistant enterococcus spread in a Brazilian tertiary PICU after implementation of strict policies for vancomycin use and full compliance with HICPAC guidelines.

Decreasing the risk of infections with multidrug-resistant organisms by reducing overuse and misuse of antimicrobials is a major challenge to clinicians (1). Vancomycin misuse creates a selective pressure for the emergence of resistant bacteria, as we experienced. The proportion on VREfm increased over 10 years around the world,

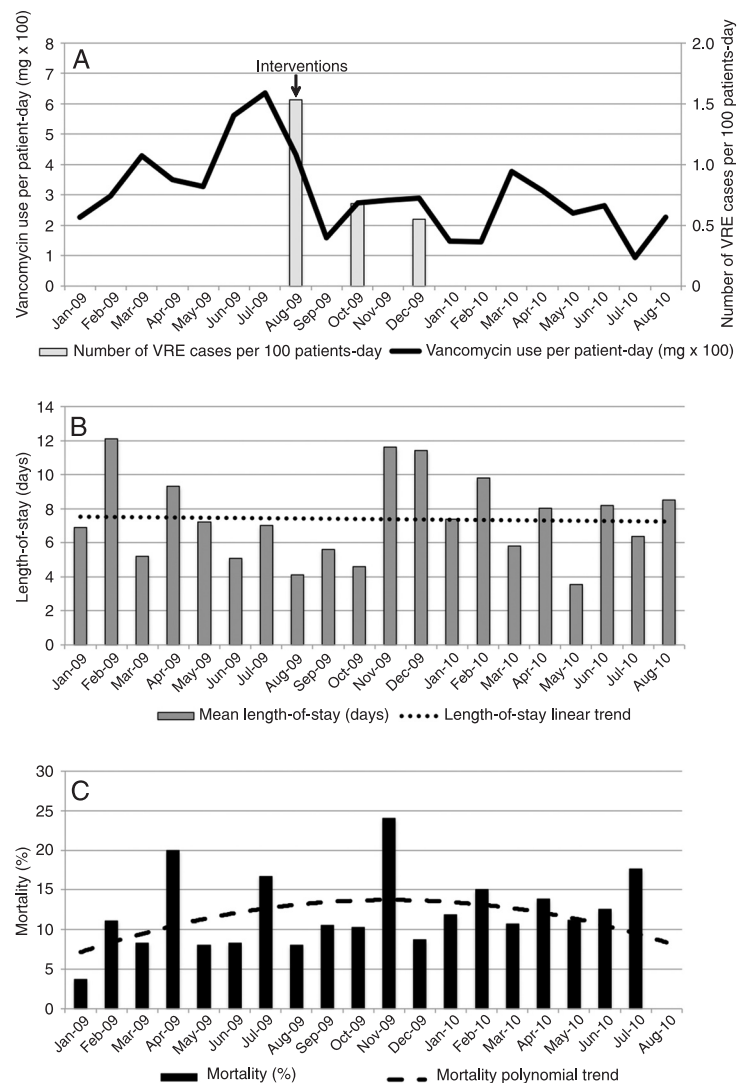


Figure 1. A, Vancomycin use per patient-day (mg x 100), number of vancomycin-resistant enterococci (VRE) cases per 100 patients-day; B, mean length-of-stay (with linear trend), and C, mortality (with polynomial trend) from January 2009 to August 2010.

Table 1. Main characteristics of patients infected or colonized with vancomycin-resistant enterococci.

Patient	Gender	Age (months)	Diagnosis	Vancomycin use	Date of VREfm identification	Site of identification	Outcome	Hospital length-of-stay
1	Female	8.9	Down syndrome, tetralogy of Fallot (operated)	49 days	08-10-2009	Mediastinum (infection)	Discharge	127 days
2	Female	6.5	Down syndrome, atrial septal defect plus patent ductus arteriosus (both operated)	20 days	08-14-2009	Blood stream (infection)	Discharge	41 days
3	Male	3.1	Situs inversus totalis, biliary atresia, congenital complete atrioventricular block, complex heart malformations (palliated)	19 days	08-28-2009	Rectal swab (colonization)	Death	154 days
4	Male	5	Bell's paralysis, total atrioventricular septal defect (operated), vesicoureteral reflux	1 day	10-19-2009	Rectal swab (colonization)	Death	41 days
5	Female	2	Ventricular septal defect, atrial septal defect, patent ductus arteriosus, deep vein thrombosis, renal failure requiring peritoneal dialysis	3 days	12-07-2009	Peritoneal fluid (infection)	Death	27 days

VREfm = vancomycin-resistant *Enterococcus faecium*.

whereas vancomycin-resistant *E. faecalis* (VREfc) remained constant. In Brazil, VREfc predominated until 1999, when dissemination of VREfm increased (19). Only VREfm was present in our patients.

Efforts should be directed at medical education on HICPAC guidelines and institutional policies for strict vancomycin use in order to control the emergence of resistant bacteria, as well as to reduce patient morbidity and mortality and healthcare costs (1,9). In the presence of a VRE outbreak, recommendations include testing enterococcal isolates for vancomycin resistance, fecal screening to detect patients colonized with VRE and intensifying control programs and staff education (20). Reports on measures for the control of vancomycin use in a tertiary-care hospital, including lectures to medical staff, dissemination of HICPAC guidelines and computer-based automatic stop vancomycin order after 72 h and electronic alerts, have shown a 22% reduction in vancomycin prescriptions, but most prescriptions were still inappropriate according to HICPAC guidelines (21). After the interventions, we showed a 75% reduction in vancomycin use in our unit.

Several other reports have been published on successful efforts to control outbreaks of VRE in many settings, including general wards, hematology units, and general, neurosurgical and neonatal intensive care units (16,19,22-27).

These interventions included creation of VRE control teams, cohorting of VRE carriers, active surveillance cultures for VRE, environmental cultures and cleaning, reinforcement of hand hygiene, and antibiotic control policies and education for the entire hospital staff (15,19,22,24,25,27). One report of lack of effectiveness of such interventions in VRE control has associated it to the emergence of the ST203 *E. faecium* clone with the acquired *vanB* locus (26).

The present report has some limitations. First, we did not evaluate the effects of interventions on morbidity or costs of hospitalization. Second, in addition to close monitoring of vancomycin use, rates of compliance with VRE isolation precautions and hand washing were not actively and systematically assessed.

In conclusion, we showed that a bundle intervention aiming at the strict control of vancomycin use and full compliance with the HICPAC guidelines, along with contact precautions and hand-hygiene promotion can be effective in reducing vancomycin use and the emergence and spread of vancomycin-resistant bacteria in a tertiary-care PICU.

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