

An outbreak of vancomycin-resistant *Enterococcus faecium* in an acute care pediatric hospital: Lessons from environmental screening and a case-control study

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BACKGROUND: The present study describes a vancomycin-resistant enterococci (VRE) outbreak investigation and a case-control study to identify risk factors for VRE acquisition in a tertiary care pediatric hospital.

OBJECTIVE: To report an outbreak investigation and a case-control study to identify risk factors for VRE colonization or infection in hospitalized children.

METHODS: Screening for VRE cases was performed by culture or polymerase chain reaction. A case-control study of VRE-colonized patients was undertaken. Environmental screening was performed using standard culture and susceptibility methods, with pulsed-field gel electrophoresis to determine relationships between VRE isolates. Statistical analysis was performed using SAS version 9.0 (SAS Institute Inc, USA).

RESULTS: Thirty-four VRE-positive cases were identified on 10 wards between February 28, 2005, and May 27, 2005. Pulsed-field gel electrophoresis analysis confirmed a single outbreak strain that was also isolated from a video game found on one affected ward. Multivariate analysis identified cephalosporin use as the major risk factor for VRE colonization.

CONCLUSIONS: In the present study outbreak, VRE colonization was significantly associated with cephalosporin use. Because shared recreational items and environmental surfaces may be colonized by VRE, they warrant particular attention in housekeeping protocols, particularly in pediatric institutions.

Key Words: Cephalosporins; Outbreak; Pediatrics; Risk factor; VRE

The increasing emergence and spread of vancomycin-resistant enterococci (VRE) is a worldwide concern impacting health care-associated morbidity, mortality and the cost of care (1). VRE are relatively resistant to most currently used antibiotics and can be easily transmitted within the acute care hospital setting if infection control practices are suboptimal. Transmission of VRE to other patients usually occurs as a result of fecal contamination of the environment and subsequent spread via the hands

Une écloison d'*Enterococcus faecium* résistant à la vancomycine dans un hôpital pédiatrique de soins de courte durée : Leçons tirées du dépistage environnemental et d'une étude cas-témoin

HISTORIQUE : La présente étude décrit l'enquête sur une écloison d'entérocoque résistant à la vancomycine (ERV) et une étude cas-témoin pour repérer les facteurs de risque d'acquisition d'ERV dans un hôpital pédiatrique de soins tertiaires.

OBJECTIF : Faire un compte rendu de l'enquête sur une écloison et une étude cas-témoin pour repérer les facteurs de risque de colonisation ou d'infection par l'ERV chez des enfants hospitalisés.

MÉTHODOLOGIE : Le dépistage des cas d'ERV s'est effectué par culture ou réaction en chaîne de la polymérase. Les auteurs ont entrepris une étude cas-témoin des patients colonisés par l'ERV. Ils ont procédé à un dépistage environnemental au moyen de cultures standard et de méthodes de susceptibilité, avec une électrophorèse en champ pulsé pour déterminer le lien entre les isolats d'ERV. Ils ont effectué l'analyse statistique au moyen du logiciel SAS version 9.0 (SAS Institute Inc., États-Unis).

RÉSULTATS : Les auteurs ont repéré 34 cas positifs à l'ERV dans dix services hospitaliers entre le 28 février et le 27 mai 2005. L'analyse par électrophorèse en champ pulsé a confirmé une seule souche d'écloison, également isolée sur le jeu vidéo d'un service hospitalier touché. L'analyse multivariée a établi que l'utilisation de céphalosporine était le principal facteur de risque de colonisation par l'ERV.

CONCLUSIONS : Dans l'écloison à l'étude, la colonisation par l'ERV s'associait de manière significative à l'utilisation de céphalosporine. Puisque le partage de jeux et les surfaces environnementales peuvent être colonisées par l'ERV, il faut en tenir particulièrement compte dans les protocoles d'entretien ménager, notamment dans les établissements pédiatriques.

of health care workers or others. Resistance to vancomycin is found primarily in *Enterococcus faecium* or *Enterococcus faecalis*; it is mainly transmitted by the *vanA* and *vanB* genes.

The control of VRE within acute care facilities requires an understanding of the selective forces driving the horizontal transmission of these organisms because most outbreaks have been shown to be clonally related. Several authors have found that risk factors for the acquisition of VRE include contact

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TABLE 1
Univariate analysis indicates multiple risk factors for
vancomycin-resistant enterococci colonization

Risk factor	P	χ^2	OR	OR (95% CI)
Antibiotic use >4 days	0.01	3.8	3.7	1.3–10.5
End stage renal disease	0.12	2.4	6.0	0.6–57.7
Trimethoprim- sulfamethoxazole	0.05	4.0	3.5	1.0–11.0
Stay on ward X	0.03	4.8	6.0	1.2–29.7
Image-guided therapy	0.05	3.7	3.0	1.0–9.0
Use of any cephalosporin	0.01	7.3	3.5	1.4–8.8
Developmental delay	0.16	2.0	0.5	0.2–1.3
Current length of stay	0.23	1.4	1.0	1.0–1.0
Aminoglycoside use	0.75	0.1	1.2	0.5–3.0
Cystic fibrosis	0.99	0.0001	1000	0.01–1000
Clinic visits	0.55	0.35	1.0	1.0–1.0
Diarrhea	0.15	2.1	0.5	0.2–1.3
Immunosuppressive drug	0.37	0.8	1.5	0.6–3.7
Use of vancomycin	0.13	2.3	2.2	0.8–5.9
Use of piperacillin- tazobactam	0.53	0.4	0.7	0.3–1.9

with infected or colonized patients or items used by those patients; immunosuppression; use of antibiotics, particularly vancomycin and cephalosporins; exposure to specific invasive procedures or indicators of overall health (1-3). The environment has been shown to be heavily contaminated with VRE in outbreaks of colonization or infection in children (4,5), which explains the identification of 'exposure to an environment previously occupied by a VRE-positive patient' as a risk factor for acquisition (6). The primary aim of the present study was to describe an outbreak investigation and a case-control study with an emphasis on the identification of risk factors for VRE colonization or infection in hospitalized children.

PATIENTS, SETTING AND METHODOLOGY

The Hospital for Sick Children (HSC) in Toronto is a 300-bed tertiary care pediatric hospital serving the Canadian province of Ontario (population 12.5 million); it admits referred patients from across Canada. The first known case (colonized or infected) of VRE at the HSC was identified in the spring of 2005.

Before the outbreak, routine screening for VRE was performed on stool samples sent for *Clostridium difficile* toxin assay (7,8). Once the outbreak was identified, screening of known contacts and all patients on affected wards was performed at intervals. VRE-positive patients were placed in contact precautions, and extensive environmental cleaning was undertaken. When possible, the movement of VRE-positive patients was controlled, and contaminated items were embargoed. Aggressive contact tracing and screening of stools for VRE by culture or, in cases of time constraint, by polymerase chain reaction for *vanA/vanB* resistance determinants (Lightcycler VRE Detection Kit, Roche Molecular Systems Inc, USA) were performed on patients with a suspected epidemiological link to the index patient (8). Environmental surveillance from wards

linked to VRE-positive patients was done by swabbing (Amies media with charcoal) environmental sites at the height of the outbreak in selected rooms of selected wards. Randomly chosen high-touch surfaces (ie, toilet facilities, beds, walls, common equipment, door handles, floors, televisions and remote controls, shelves, books, toys, carts, keyboards and computer equipment) in all rooms and common areas of wards with VRE-positive patients were swabbed. Swabs were incubated for 24 h in brain heart infusion broth at 35°C. The broth (100 µL) was then inoculated onto mEnterococcus agar medium and incubated for 72 h at 35°C. Cultures were examined daily for growth, and suspect colonies were identified according to standard protocols (9). Antibiotic susceptibility testing and interpretation were undertaken using the Clinical and Laboratory Standards Institute-approved methodologies and breakpoint guidelines (7). Pulsed-field gel electrophoresis (PFGE) was carried out and interpreted according to Tenover et al's criteria (10).

The health records department undertook computerized control matching to identify controls while maintaining patient confidentiality. For the case-control study, a case was defined as any patient with culture-verified VRE colonization of the rectum or stool between January 1, 2005, and May 27, 2005. Control patients were the next two direct admissions to an affected ward who were VRE-negative with the closest duration of length of stay to the matched VRE-positive patient. A review of the literature led to the creation of a chart review screening tool, which was a checklist of risk factors for VRE colonization identified from previously published literature (1-3,6) used for the investigation of the outbreak. Potential risk factors for VRE colonization or infection included patient age, previous hospitalization, immunosuppression, antibiotic use, use of specific therapeutic agents, invasive devices and specific procedures. Other risk factors tested in this study are listed in Table 1.

Before initiation of the chart review, the study was approved by the HSC Research Ethics Board. Univariate and multivariate statistical analyses were performed using SAS version 9.0 (SAS Institute Inc, USA). Multivariate analysis used an analysis of maximum likelihood estimates, OR point estimates and the Wald confidence intervals for adjusted ORs. Variables tested by multivariate analysis included antibiotic use for more than four days, image-guided therapy (IGT) and the use of any cephalosporin.

RESULTS

Epidemiological and microbiological characteristics

Following the identification of the index case of VRE on a hematology-oncology ward, 33 patients who had been hospitalized on 10 wards were further identified between February 28, 2005, and May 27, 2005 (Figure 1). No new VRE cases were identified in the last 30 days of the outbreak. Intensified outbreak screening and time-course analysis indicated that the majority of VRE-positive patients (29 of 34 [85%]) were identified between days 19 and 41 of the outbreak. Of the over 1800 potential contacts, most had already been discharged. The one-third remaining in hospital were screened for VRE colonization. There were no episodes of clinical infection in patients colonized with VRE, and all cases were identified as 'VRE carriers' from culture and/or polymerase chain reaction of either rectal swabs or stool samples. All VRE isolates were identified as *E faecium* and were shown to carry the *vanA* resistance determinant. Strain typing of VRE by PFGE detected a single clone associated with all patients.

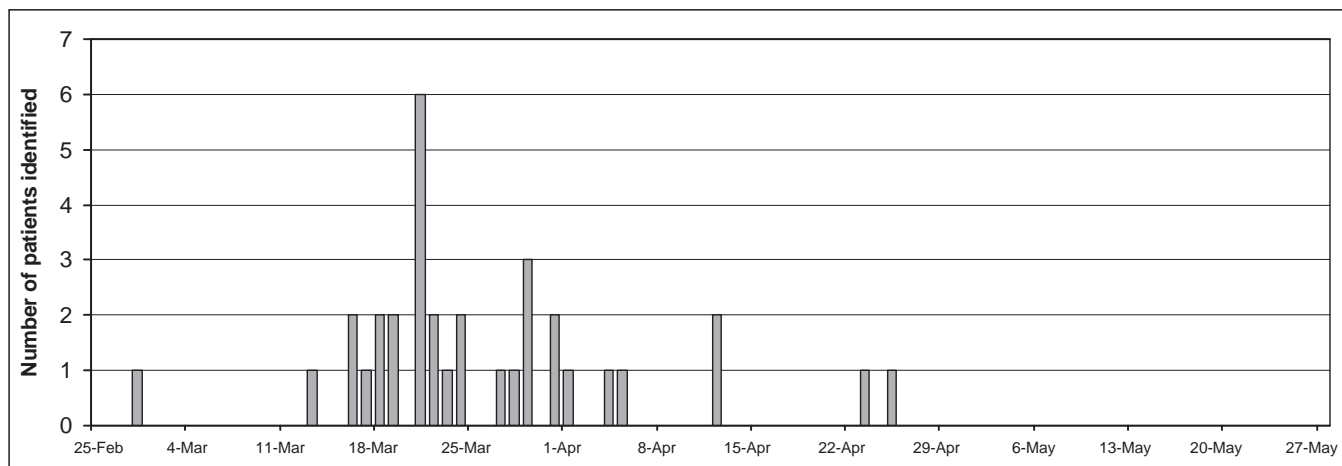


Figure 1) Epidemiological curve of vancomycin-resistant enterococci outbreak in an acute care pediatric hospital. Apr April; Feb February; Mar March

Environmental findings

The only environmental site from which VRE were detected (one of 192) was the surface of a video game system in the playroom of an affected ward. The VRE strain isolated from the video game was indistinguishable from 29 patient strains by PFGE, and was closely related (two-band difference) to the remaining patient strains.

Case-control matching and univariate analysis

Case-control matching was possible for 33 of 34 cases of VRE colonization. Using univariate analysis, significant risk factors that were identified included the use of antibiotics for more than four days, the use of trimethoprim-sulfamethoxazole, stay on one ward which had the highest incidence of VRE cases, having undergone IGT and the use of any cephalosporin (Table 1).

Multivariate analysis

Multivariate ANOVA indicated that VRE colonization was predominantly associated with the use of any cephalosporin ($P=0.03$, $\chi^2=5.0$, $OR=3.1$, $OR\ 95\% \text{ CI } 1.1 \text{ to } 8.3$). Multivariate ANOVA did not find an association between VRE and antibiotic use of more than four days ($P=0.09$, $\chi^2=2.9$, $OR=2.6$, $OR\ 95\% \text{ CI } 0.9 \text{ to } 7.9$), or having undergone IGT ($P=0.14$, $\chi^2=2.2$, $OR=2.6$, $OR\ 95\% \text{ CI } 0.7 \text{ to } 9.3$).

DISCUSSION

The present study is the first published description of a VRE outbreak investigation in a Canadian pediatric acute care institution, although reports in children's hospitals have been reported worldwide. Similar to this outbreak, which was first identified in a hematology-oncology population, most previously described outbreaks and surveillance studies of VRE in pediatric hospitals have identified hematology-oncology patients as key reservoirs of VRE; reports of outbreaks in children in neonatal intensive care units have also been reported (4,5,11,12). For example, following the introduction of surveillance screening in the United Kingdom, Gray and George (4) found colonization with VRE in 38.3% of hematology-oncology patients and in 11.1% of hepatology-gastroenterology patients, but in only 2.3% of children in the pediatric intensive care unit and 1.5% of children in the renal unit. Other characteristics of the outbreak described here are similar to those previously reported in terms of

risk factors, duration, number of patients involved and the use of control measures.

Pediatric VRE outbreaks in other institutions have been associated with antibiotic use; for example, one outbreak of 14 patients (19% of those screened) on an oncology ward was associated with prolonged treatment with teicoplanin, ceftazidime or amikacin (5). In this report, the authors identified cephalosporin use as the key risk factor for VRE colonization. It is postulated that cephalosporin use may give VRE a selective advantage in the intestinal tract, thereby increasing the load of VRE that is transmitted between patients either by inanimate objects or the hands of health care workers (13). Findings like this have led to the idea that antibiotic stewardship may play a role in limiting the spread of VRE in hospitals by controlling antibiotic prescribing and/or the class of antibiotics used (13). However, this remains unproven, as does the hypothesis that certain antibiotics may actually be used to prevent a selective advantage for VRE colonization (14).

Other outbreaks in pediatric institutions have described much heavier environmental contamination than we observed in our outbreak (ie, 25% to 70% of samples testing positive) (4,5). If the environment was an important factor in transmission in our study, we might have missed the heavily contaminated areas due to the commencement of enhanced cleaning by the time environmental screening was performed. Alternatively, mobile or shared elements, such as the video game system, might have played a larger role in our outbreak than in others. Previous studies indicated that VRE can survive for prolonged periods of time on inanimate surfaces (15), and that occupancy of an environment previously used to house a VRE-positive patient is a risk factor for VRE acquisition (6). Thus, environmental decontamination is important in controlling outbreaks of VRE. In one study (5), the use of stringent infection control measures successfully reduced environmental contamination rates from 25% of samples in week 1 to none in week 11, which was the length of time it took to control the outbreak. Although the impact of individual control measures in our outbreak was not formally evaluated, the use of active surveillance, enhanced infection control measures and molecular testing were in line with previously reported efforts to control VRE outbreaks, and were clearly successful in ours (5,16,17).

Since our investigation, patients admitted to the hematology-oncology ward are actively screened for VRE and isolated with contact precautions if positive. We have had no evidence of further nosocomial spread of colonized patients admitted to hospital and no further outbreaks. Good antibiotic stewardship and judicious antibiotic use is reinforced by our institution's antibiotic utilization committee. Currently, in the course of housekeeping and environmental disinfection, particular attention is paid to frequently touched surfaces and objects, including mobile toys

and games. In a pediatric setting, the latter are of particular importance because despite policies to the contrary, it is hard to control access to these highly desired objects.

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