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Eradication of vancomycin resistant *Enterococcus faecium* from a paediatric oncology unit and prevalence of colonization in hospitalized and community-based children

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SUMMARY

We previously reported an outbreak of vancomycin resistant enterococci (VRE) in a paediatric oncology unit in December 1995 which was associated with widespread environmental contamination of the unit with VRE. We undertook this study to evaluate the effectiveness of the infection control policy instituted subsequent to the outbreak and to investigate the underlying prevalence of VRE colonization in hospitalized, outpatient and community-based children. We sought to establish the molecular similarity of VRE isolates from the study. Stool specimens were obtained from outpatients at risk of VRE, hospital inpatients and from healthy community-based children. VRE colonization was eradicated from the inpatient unit within 11 months, but in outpatients, 16 months after the outbreak, 4 of 137 (2·9%) attending oncology outpatients, 5 of 65 (7·7%) with cystic fibrosis and 1 of 12 (8·3%) with liver disease were found to be colonized with VRE. The isolates were all *Enterococcus faecium*, Van A phenotype except one *E. casseliflavus* of the Van C phenotype. All were unique in *Sma*I DNA macrorestriction patterns with the exception of two isolates, which were similar to the original outbreak strain and three further isolates of a single strain but which differed from the outbreak strain. Of 315 hospital inpatients, 2·5% were colonized with VRE of the Van C resistance phenotype but VRE was not detected in 116 healthy, community-based children. We conclude that effective strategies can successfully control spread of VRE but despite a low prevalence of VRE colonization in hospital patients and in community-based children, outbreaks can occur when infection control practices are not optimal. Continued vigilance to detect VRE and limit spread within hospitals is therefore necessary.

INTRODUCTION

Vancomycin resistant enterococci (VRE) have emerged as important nosocomial pathogens since they were first described in 1988 [1, 2]. In the United States, their contribution to nosocomial infection increased from 0·3% in 1989 to 7·9% in 1993 [3]. Control of spread within clinical units has proved difficult [4–14] and eradication of these organisms from units is rare [5, 15, 16]. There are few reports of outbreaks in paediatric populations [17, 18–21] and the underlying prevalence of VRE colonisation in

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hospitalized, outpatient or healthy children is unknown.

Recently, we described a nosocomial outbreak of vancomycin resistant *Enterococcus faecium* in a paediatric oncology unit involving 16 patients. All were colonized with enterococci of the Van A phenotype (14 identified as *E. faecium*, 11 of the same strain) [17]. At the time, there was understaffing and widespread environmental contamination of the unit. Six of eight representative environmental strains were the same as the predominant strain colonizing patients.

We revisited this study with the aims (*a*) to evaluate the effectiveness of the strategy implemented to control inpatient colonization and eradicate environmental contamination in the unit, (*b*) to determine the prevalence of VRE in children attending the hospital and in community based children, and (*c*) to investigate the molecular similarity of VRE strains with high-level resistance to vancomycin (Van A phenotype).

METHODS

A control strategy was implemented in February 1996, 2 days after the second case of VRE infection was identified and 5 weeks after the first case. The strategy adhered closely to currently recommended guidelines [22] and included infection control measures, an educational programme and modification of existing antibiotic policy. Colonization status was as defined previously [17] and patients were cohorted accordingly. Colonized patients were isolated and gloves and plastic aprons (single use) were used for entry to their rooms. Long-sleeved gowns were used when direct patient contact was anticipated. Equipment was dedicated to single patient use where appropriate and records were highlighted for ease of recognition. Gloves and plastic aprons were used for contact with patients for whom colonization status was unknown and universal precautions were in place for VRE-negative patients. Minor operative procedures were performed in the oncology unit and intensive care was delivered on the unit where possible. Patients requiring surgery were scheduled at the end of the operating session and the theatre was cleaned and disinfected with Stericol (Lever Industrial, Runcorn, UK). All previously colonized children were placed in isolation immediately at each hospital readmission until negative status was confirmed.

The staff-patient ratio and household cleaning staff number was increased. The frequency of waste and soiled linen collections was doubled and an additional health-care worker was assigned to take responsibility for the cleaning and disinfection of medical equipment and other miscellaneous items. Removal of waste and cleaning of the unit was supervised closely and monitored daily by the hospital infection control team. The concentration of Stericol was increased from 1 to 2% as recommended for dirty situations [23] and rooms of colonized patients or patients of unknown status were disinfected after cleaning. Hypochlorite solution 0·1% (Semar, Ireland) was used to clean mattresses and all non-disposable equipment was heat-disinfected.

An individualized educational programme was commenced for all patients and parents, medical, nursing, portering and household staff. Written information was given to the above groups and small discussion groups were held as well as delivery of information using the forum of the weekly hospital clinical conference. The unit empiric therapy for fever in the neutropenic host was modified to restrict the use of ceftazidime and glycopeptides and to introduce piperacillin/tazobactam and amikacin as first line therapy. Vancomycin is very rarely prescribed in the unit and teicoplanin is the glycopeptide of choice. Metronidazole is reserved for the treatment of *Clostridium difficile*-associated diarrhoea.

Evaluation of the control strategy

Following the outbreak a stool specimen was obtained from all patients on admission to the unit. Monthly stool specimens were obtained from surviving colonized patients.

Patients were categorized as VRE-positive if VRE was identified in at least two stool samples or negative when three consecutive stool cultures at least 2 weeks apart failed to yield VRE. Extensive environmental screening of the unit was performed.

Screening of patients and community-based children

Screening of oncology patients and other at-risk outpatients was conducted in July 1997. All surviving children who had been admitted on at least one occasion to the oncology unit during the previous year (1 July 1996 to 1 July 1997) were identified for VRE screening. Children receiving palliative care at home were excluded. All children were undergoing regular

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outpatient review and many had had multiple admissions to the unit. Other outpatients deemed to be at risk of VRE colonization as a result of their frequent use of antibiotics included patients with cystic fibrosis (CF), patients on immunosuppressive therapy following liver transplant or chronic active hepatitis, and human immunodeficiency virus (HIV) infected patients attending the hospital. Stool specimens were requested by mail and on receipt of the specimen, telephone contact was made with the parents of each child and the hospital record was reviewed. Details of age, sex, address, diagnosis, length of hospitalization and antibiotic use (both at home and in hospital) in the preceding 3 months were obtained. Where VRE was isolated from a stool, repeat stools from that child were requested on a monthly basis until three consecutive negative stools had been obtained. Stool specimens were also requested from all family members of colonized patients.

Our Lady's Hospital for Sick Children is a tertiary referral hospital for the Republic of Ireland with a 280-bed capacity and an average of 18000 admissions per year. Inpatient wards include two intensive care units (ICU) and oncology, surgical, cardiac, neonatal and general medical wards. Two hospital prevalence surveys were conducted 6 months apart, each spanning a 5-day period (May and October 1997). Following informed consent, stool specimens were requested from all resident inpatients on day 1 and from all new admissions during the following 4 days. On receipt of a stool specimen, details of age, sex, diagnosis, surgery, hospital antibiotic use and hospitalization history during the preceding 3 months were obtained from patient records.

A request for a stool specimen from each child ($\leqslant$ 15 years of age) of staff members was enclosed with hospital pay cheques in December 1997. Stool containers and questionnaire forms were made available throughout the hospital.

Stools were inoculated into Enterococcosel broth (Microbiology Systems, Cockeysville, MD, USA), a selective enrichment broth with bile-esculin and sodium azide, supplemented with vancomycin (6 mg/l), clindamycin (8 mg/l), colistin (50 mg/l) and amphotericin B (4 mg/l) to suppress the growth of other bowel flora. After 48 h of incubation at 37 °C, broths (100 μl) were subcultured on a selective Slanetz and Bartley agar plate (Oxoid, Basingstoke, UK) modified with the same antibiotics. Plates were incubated at 37 °C for 48 h. All isolates were identified using standard methods [24, 25] and the API-20 or Rapid ID 32 Streptococcus systems (BioMerieux, Marcy L'Etoile, France) and identification was confirmed by specific PCR [26]. Initial disk sensitivity testing was performed on Isosensitest agar (Oxoid, Basingstoke, UK) with ampicillin 10 μm, vancomycin 5 and 30 μm teicoplanin 30 μm and gentamicin 200 μm disks following the NCCLS method [27]. MIC was determined on Isosensitest agar using E-test (Epsilometer) antibiotic strips (AB Biodiscs, Solna, Sweden). A susceptible strain of *E. faecalis* (ATCC 29212) was used as a control.

Isolates were compared for epidemiological relatedness by pulsed-field gel electrophoresis of *Sma*I chromosomal DNA digests as described previously [17].

Environmental screening was performed using premoistened swabs. These were steeped in nutrient broth incubated overnight and subcultured to selective Slanetz and Bartley agar plates as above.

RESULTS

Control of VRE colonization

Eleven months after the recognition of an outbreak (February 1996) and instigation of the control strategy three patients had died, one with VRE peritonitis and two due to unrelated causes while colonized. The remaining 13 colonized patients had reverted to a negative status for VRE. Median duration of colonization post identification was 16 (8·4–51) weeks. Between April 1997 (2 months after identification of the outbreak) and July 1998, no further colonized inpatients were identified and environmental screening failed to reveal VRE in the oncology unit (Table 1). Cephalosporin and glycopeptide consumption was compared for the 6-month period prior to the outbreak and 6 months following the outbreak. Antibiotic usage reduced as a result of the control strategy for all four antibiotics, specifically cefotaxime by 24%, ceftazidime by 15%, vancomycin by 55% and teicoplanin by 85%.

Screening of at-risk outpatients (conducted in July 1997 during a 6 week period)

Of 237 outpatients screened for VRE, 121 were male and 116 were female. Mean age was 8·7 years (range 8 months to 18 years). Four of 137 (2·9%) oncology patients, 5 of 65 (7·7%) CF patients and 1 of 12 (8·3%) patient with liver disease were colonized with

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Table 1. *Environmental screening of an oncology unit for vancomycin resistant enterococci*

Date	February 1996*	March 1996	April 1996	July 1996	July 1997	January 1998
No. of sites surveyed	120	141	46	116	175	97
No. positive for VRE	30	1	0	2†	0	0
Percentage	25	< 1	0	1·7†	0	

* Infection control measures introduced.
† Strain differed from the outbreak strain.

Table 2. *Screening of outpatients for VRE (July 1997)*

Patient category	No. of children identified for screening	No. of stool samples received (% uptake)	No. of children colonized with VRE (%)*
Oncology	191	137 (72%)	4 (2·9%)
Cystic fibrosis	120	65 (54%)	5 (7·7%)
HIV infection	25	23 (92%)	0
Liver disease	21	12 (57%)	1 (8·3%)
Total	357	237 (66%)	10 (4·2%)

* All VRE were Van A phenotype except for a strain of Van C phenotype from a CF patient.

VRE (Table 2). Nine isolates were identified as *E. faecium* and manifested high level resistance to vancomycin (MIC > 256 mg/l) and teicoplanin (MIC > 32 mg/l). One isolate was identified as *E. faecalis* and had a vancomycin MIC of 6–8 mg/l.

Molecular comparison of 9 isolates of *E. faecium* revealed that 2 were identical to the original outbreak strain (1 oncology and 1 CF patient). Three isolates represented a single strain that was not the outbreak strain (two oncology patients and a patient with liver disease). The remaining four isolates of *E. faecium* represented distinct strains.

Of the 10 colonized children, 2 had been hospitalized, 3 had received IV antibiotic therapy including pipericillin/tazobactam, amikacin, tobramycin, gentamicin and meropenem, and all had received oral antibiotic therapy, intermittently or continuously, in the preceding 3 months. Oral antibiotics included augmentin, penicillin, clarithromycin, azithromycin and flucloxacillin. There were no significant differences between colonized and non-colonized outpatient children with regard to age, sex, antibiotic use (oral or i.v.) or hospitalization in the preceding 3 months.

Subsequent stool screening in these children revealed loss of colonization within 2–12·6 (median 6) weeks. In 27 family members screened from 8 families, 2 adults were colonized with VRE. One mother harboured both *E. faecium* and *E. faecalis* (both Van A genotype) and one father had *E. faecium* (Van A genotype). PFGE band patterns for these strains differed from the respective index case.

Inpatient screening

Enterococci exhibiting moderate or high level resistance to vancomycin were not isolated from inpatients. Eight of 315 (2·5%) of children were colonized with enterococci manifesting low level resistance to vancomycin (Van C phenotype).

Screening of community-based children

Stool samples were received from 116 children of hospital staff members. There were 58 males and 58 females with ages from 1 month to 15·5 years (mean 6·2 years).

Twenty-one (18%) children had received oral antibiotics, two had been hospitalized and two had undergone surgery in the preceding 3 months. One child had Down's syndrome. The remainder were healthy and had not received antibiotics or been hospitalized in the preceding 3 months. No child was colonized with VRE.

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DISCUSSION

The control of VRE outbreaks in hospitals is not usually successful [4–13] because strict compliance with recommended guidelines [22] is difficult, and VRE is not readily eradicated particularly when a significant number of hospital inpatients or outpatients are colonized. Nosocomial transmission of VRE may be assisted in paediatric institutions by the close contact that occurs between children and the more frequent contamination of health-care workers' hands by childrens' faeces.

The spread of VRE in this paediatric oncology unit [17] was aided by overcrowding, short-staffing and sub-optimal implementation of infection control practices. Eleven of 16 (69%) strains of VRE isolated from unit inpatients were similar on PFGE analysis, supporting nosocomial transmission. Only 4 of 137 (2·9%) of oncology outpatients were colonized with VRE subsequent to the outbreak. The successful eradication of VRE was attributed to the prompt institution of infection control measures, which complied closely with currently recommended guidelines [22], coupled with a comprehensive educational programme and modification of antibiotic policy. Cephalosporin and glycopeptide usage dropped by 80 and 35% respectively following the introduction of control measures. The fact that the VRE were of a single clone and nosocomial spread was limited to the oncology unit combined with a relatively low underlying prevalence of VRE colonization in the oncology patient cohort probably contributed to successful resolution of the incident. Despite the potential adverse psychosocial consequences for children associated with prolonged use of strict gown-and-glove isolation, the increased morbidity, mortality and cost associated with these infections justified this intervention.

The absence of moderately or highly resistant VRE in our inpatient population is encouraging and underlines the need for continued attention to surveillance and control of the organism.

Between 3 and 8% of at-risk outpatients were colonized with different strains of VRE but the small numbers prevented risk factors for acquisition being reliably defined. Most of the children had neither been hospitalized nor received i.v. antibiotics in the preceding 3 months. These have been identified as potential risk factors for colonization [4, 17, 21, 28–34]. It is possible that VRE in these patients may be as a result of their high exposure to oral antibiotics as all had had at least one course in the previous 3 months. Alternatively, the diversity of strains and the lack of recognized risk factors in this group suggest that VRE may have been acquired from sources outside the hospital.

In Europe, colonization rates of between 2 and 28% have been reported in volunteers with no previous hospital or antibiotic exposure [35–37]. VRE have also been isolated from farm animals [38–42], household pets [43], sewage [42, 44] and animal foods consumed by humans [45–47]. The organism can therefore be part of the normal human flora for which the food chain can be a potential source.

We undertook to investigate the presence of VRE in a community-based paediatric population. Children of health-care workers might be expected to have a higher prevalence of VRE than children without hospital contact, as a result of intrafamilial transmission. The absence of VRE colonization in this group is indicative of a low prevalence in healthy children in this community.

This study demonstrates that even with a low background prevalence of VRE colonization in children attending a hospital, clinically significant problems with VRE can occur, given favourable circumstances of overcrowding, understaffing and relaxation of infection control. The prevention of spread of VRE is difficult once the organisms become endemic and therefore prevention of endemicity is of vital importance. Continued vigilance is necessary to detect and pre-empt the spread of this increasingly troublesome organism.

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