Eur J Pediatr (1998) 157: 20–27

INFECTIOUS DISEASES

C. Nourse · H. Murphy · C. Byrne · A. O'Meara · F. Breatnach · M. Kaufmann
A. Clarke · K. Butler

Control of a nosocomial outbreak of vancomycin resistant *Enterococcus faecium* in a paediatric oncology unit: risk factors for colonisation

Received: 18 February 1997 and in revised form: 6 May 1997 / Accepted: 13 May 1997

Abstract In order to determine the extent of vancomycin resistant enterococcus (VRE) colonisation within a paediatric oncology unit, the risk factors for the acquisition of the organism, the molecular epidemiology of the isolates and the impact of infection control measures, extensive patient and environmental surveillance was undertaken with identification, antibiotic susceptibility testing and pulsed-field gel electrophoresis (PFGE) of all VRE isolates. A matched case control study was carried out. Fourteen patients (19% of screened patients) with VRE colonisation were identified (12 with *Enterococcus faecium*). All isolates manifested the *Van A* phenotype. Extensive environmental contamination with VRE was present. PFGE of *E. faecium* isolates from 10 patients and from five of six environmental cultures revealed patterns suggesting genetic relatedness. Following comparison of the 14 cases with 41 controls matched for age (±4 years) and cohabitation on the oncology unit, risk factors for colonisation with VRE included duration of neutropenia, (OR, 3.72; 95% CI, 1.0–13.1), and antibiotic therapy, (OR, 4.07; 95% CI, 1.08–15.3), the number of antibiotic agents received, (OR, 8.4; 95% CI, 1.34–34.3) and the duration of therapy with amikacin, (OR, 10.7; 95% CI, 1.4–81.5), ceftazidime, (OR, 11.5; 95% CI, 2.2–59.9) or teicoplanin, (OR, 12.3; 95% CI, 2.25–67.4). Implementation of stringent infection control measures reduced environmental contamination from 25% of samples in week 1 to none in week 11. Two additional colonised patients were identified during the subsequent 6 months.

Conclusion Risk factors for VRE colonization in paediatric oncology patients included duration of neutropenia, duration of any antibiotic therapy, exposure to ceftazidime, amikacin or teicoplanin and the number of antibiotics used. The study suggests that environmental contamination played an important role in patient-to-patient transmission of VRE and interventions including implementation of infection control measures were associated with a decreased incidence of gastro-intestinal colonisation.

Key words *Enterococcus faecium* · Vancomycin resistance · Colonisation · Infection control

Abbreviations PFGE pulsed-field gel electrophoresis · VRE vancomycin resistant enterococcus

C. Nourse
Department of Paediatrics, University College Dublin

C. Nourse (✉) · H. Murphy · C. Byrne
A. O'Meara · F. Breatnach · K. Butler
Our Lady's Hospital for Sick Children, Crumlin,
Dublin 12, Republic of Ireland,
Tel.: 353-1-4558111, Fax: 353-1-4555307

M. Kaufmann
Clinical Scientist, Epidemiological Typing Unit,
Central Public Health Laboratory,
61, Colindale Avenue, London, United Kingdom

A. Clarke
Department of Public Health Medicine and Epidemiology,
University College 2, Republic of Ireland

Introduction

Traditionally regarded as avirulent gastro-intestinal tract commensals, over the past decade enterococci have become multiresistant pathogens, now the second leading cause of nosocomial infection in the U.S.A. [11, 40] and increasingly responsible for hospital acquired infection in Europe. In 1987 the Public Health Laboratory Service Communicable Disease Surveillance Centre (U.K.) reported that 17 hospitals in the U.K. had encountered vancomycin resistant enterococcus (VRE). By the end of 1995, VRE had been found in a total of 71 hospitals [1]. Invasive infection generally occurs in immunocompromised patient populations in intensive care, oncology, organ transplant and dialysis units [7, 15, 28, 37]. Of concern is the emergence of glycopeptide resistance in enterococci which, as it is commonly associated with resistance to all currently approved antimicrobials, leaves few therapeutic options. Systemic infection with VRE is associated with mortality rates of from 5%–100% [10, 13, 24, 41] and represents a significant threat to patients with altered host defence mechanisms.

In December 1995 catheter associated VRE bacteraemia was diagnosed in a paediatric oncology patient. Catheter removal resulted in clinical improvement and resolution of bacteraemia. In February 1996, a child undergoing intensive chemotherapy for B-cell lymphoma developed VRE peritonitis as part of his terminal illness. An investigation was initiated to determine the extent and epidemiology of VRE colonisation within the unit and infection control measures were instituted. A matched case control study was performed to define risk factors for acquisition of VRE in the unit.

Methods

Patient population and surveillance

The paediatric oncology unit in Our Lady's Hospital for Sick Children, Crumlin is the referral centre for paediatric oncology in the Republic of Ireland, servicing a total population of 3.5 million. Designed and staffed for 22 beds, it comprises a general ward with two single and seven double rooms; a high dependency unit with three single rooms, two laminar flow rooms and one isotope room and a day unit with a 6 bed capacity. There are a mean of 80 new admissions per year.

All unit inpatients, patients who had been hospitalised in the unit within the preceding 3 months and all new admissions to the unit were identified for surveillance. Following informed consent from parents, three specimens (stool or rectal swab) were requested from each patient. These were obtained at admission, during outpatient attendance or from home. Surveillance continues with admission stool cultures from all inpatients and weekly stools in the case of colonised inpatients. Patients were categorised as: (1) VRE positive if the organism was isolated from two or more stool or rectal swab samples, (2) VRE negative if three consecutive stool or rectal swab cultures were negative; and (3) of indeterminate status if fewer than three negative samples were available for culture. In order to classify a previously colonised patient as VRE negative; at least three consecutive negative stool cultures at least a week apart were required. Urine samples and swabs from axillae and nares were taken on at least one occasion from all VRE colonised patients.

Infection control measures

Patient cohorting according to colonisation status was established. Colonised patients were placed in contact isolation; gloves and plastic aprons (single use) were used for entry to their rooms with gloves and gowns for patient contact. Gloves and plastic aprons were used for contact with indeterminate patients. Universal precautions were used for negative patients. Non critical equipment was dedicated to single patient use. Records of colonised patients were highlighted for ease of recognition.

Extensive environmental screening of the unit was performed using pre-moistened swabs directly inoculated into nutrient broth. Surveyed areas included a variety of surfaces and patient care devices in patient and parent rooms, sluice areas, kitchen, play and office areas. More stringent cleaning and disinfection (with 2% Stericol (Lever Industrial, Runcorn, UK)) of the unit was adopted. An intense educational programme about VRE, mode of spread and methods of prevention was commenced for all patients and parents, medical, nursing, portering and household staff. Because of the reported possible association of enterococcal colonisation and infection with the use of cephalosporins [29, 49] and the reported association of VRE colonisation and infection with the use of glycopeptides [4, 10, 19, 30, 32, 39, 41, 45], the unit empiric therapy for febrile neutropenia was modified. Prior to the outbreak, piperacillin and amikacin were used as first line therapy with substitution of ceftazidime at 48 h and the subsequent addition of teicoplanin if fever persisted. After the outbreak, use of ceftazidime and teicoplanin was restricted and piperacillin/tazobactam and amikacin constituted first line therapy. Vancomycin was very rarely given in the unit. Metronidazole was used for treatment of *Clostridium difficile* associated diarrhoea.

Microbiology

A modified Slanetz and Bartley agar (CM377, Oxoid, Basingstoke,UK) [42] was selected for detection of VRE. Modifications included the addition of vancomycin (6 g/ml), clindamycin (8 g/ml), colistin (50 g/ml) and amphotericin B (4 g/ml) to reduce the growth of other bowel flora. Media were stored in the dark at 40 °C and were used within 1 week. Stool and rectal swab samples and 24-h environmental broth cultures were inoculated onto this medium, streaked, incubated at 37 °C and examined for *Enterococcus* colonies at 24 and 48 h. Colonies from each plate were subcultured for identification and sensitivity testing. Isolates were identified by colony morphology, Gram stain, catalase reaction, group D antigen, PYR test (presence of pyrrolidonyl peptidase activity), growth in 4% and 6% salt broth and the API-20 S Streptococcus system (bioMerieux, Marcy L'Etoile, France) respectively. Initial sensitivity testing was performed on Isosensitest agar (Oxoid, Basingstoke, U.K.) using disk diffusion with ampicillin 10 g, vancomycin 5 g and 30 g, teicoplanin 30 g, gentamicin 100 g, chloramphenicol 10 g, erythromycin 5 g, cefotaxime 30 g and cefuroxime 30 g disks. The MIC of vancomycin was determined using E-test (Epsilometer) antibiotic strips (AB Biodiscs, Solna, Sweden) using a susceptible strain of *E. faecalis* (ATCC 29212) as a control. Enterococci with a vancomycin MIC between 2 and 8 g/ml were excluded from the study. All patient strains of VRE and a representative selection of environmental strains were referred to the Epidemiological Typing Unit, Laboratory of Hospital Infection, Colindale, U.K. for confirmation of identification by polymerase chain reaction (PCR) using primers described by Dutka-Malen et al. [9] and for molecular comparison using pulsed-field gel electrophoresis (PFGE).

Molecular comparison

Isolates were compared by PFGE by the method of Murray et al. [33], with modifications; cells were harvested from blood agar and suspended in SE buffer (75 mM NaCl, 25 mM EDTA pH 7.5) prior to mixing with low gelling agarose and the preparation of plugs. Following digestion with *Sma*I, plugs were loaded into wells of a 1.2% agarose gel and the fragments separated in a contour clamped homogeneous electric field of 6V/cm with pulse times increasing from 1 to 10 s over a 30 h period followed by 15 h with pulse times increasing from 10 to 30 s. Gels were stained for 1 h with ethidium bromide followed by at least 1 h destaining in distilled water. Banding patterns were photographed under UV transillumination and analysed with the aid of GelCompar software (Applied Maths, Kortrijk, Belgium). Pearsons correlation coefficient was applied and a dendrogram of percentage similarity produced by the unweighted pair group matching by arithmetic averages algorithm. Isolates clustering within 80% similarity were considered to represent the same strain.

Case control study

A case was defined as a patient who had VRE infection or colonisation confirmed during the 3-month period following identification of the index case i.e. 25 December 1995 to 31 March 1996. Each case was matched with three controls (except for one case for which only two controls were available). A control was a patient who was VRE negative at the time the case was positive and subsequently had three negative stool or rectal swab cultures at least 1 week apart. Controls were of similar age (within 4 years) and had an overlapping admission time of at least 3 days in the 3 months prior to the identification of the VRE colonised case. Case and control patient records were reviewed for the 3 months preceding the first positive culture in the case and the following was abstracted: (1) primary diagnosis (categorised as haematological or other); (2) ambulatory status; (3) bone marrow transplantation prior to the end of the study period; (4) preceding surgery (excluding minor procedures); (5) total number of inpatient days prior to VRE colonisation; and (6) total days of neutropenia. Antibiotic exposure was assessed by duration of antibiotic therapy (defined as total number of days of intravenous administration), number given, total antibiotic days (defined as the summation of days of each antibiotic administered) and number of days that individual antiinfectives were administered, including ceftazidime, amikacin, piperacillin, vancomycin, teicoplanin, acyclovir, amphotericin and metronidazole. In the case of patients who attended regional hospitals for part of their care, these hospitals were contacted and details of admissions in the relevant 3-month period including information about antibiotic use were obtained.

Statistical analysis

Statistical analyses were performed using the software program Epi Info (version 6.01, CDC, Atlanta, GA). Univariate analysis of categorical variables was performed using the Mantel-Haenszel x^2 test and odds ratios for matched data. A 5% level of significance were taken. For continuous variables median cut points for the odds ratio analyses were used. In order to assess for independent significance of variables, SAS statistics package was used to perform conditional logistic regression for matched data.

Results

VRE was first isolated from the blood culture of a child on 25 December 1995 and the second case occurred on 2 February 1996 (a former room-mate of the first child). During this interval, the patient census (28) exceeded the normal census (22). This was achieved by nightly occupation of the day unit and by the placement of two patients in single rooms.

Patient surveillance

We identified 131 patients for surveillance screening. By the end of March, 59 patients had been classified as VRE negative, 14 as positive (including the two infected patients) and 58 as indeterminate.

VRE was first recovered from the stools of the index patient 3 weeks after recovering the organism from blood culture through his broviac catheter. VRE was present in the stools of the second infected patient at the time of his VRE peritonitis. The remaining 12 colonised patients were identified within 2 weeks of initiation of the surveillance cultures. Regular stool cultures were obtained from the 13 surviving colonised patients. As of 1 August 1996, 6 patients have remained colonised either to time of death ($n = 1$) or to the present time ($n = 5$). Seven patients have reverted to a negative status (Fig. 1). Subsequent to the initial surveillance, two additional colonised patients have been identified. Of the total number of colonised patients (16), 2 patients died of unrelated causes while colonised and of the remaining 14, the median duration of colonisation after the first positive culture was identified was 16 weeks (Fig. 1). Of urine, axillary and nasal swab samples taken from each colonised patient, all were VRE negative except for one urine sample which was thought to be faecally contaminated. Subsequent urine samples were clear and the child was not treated for a urinary tract infection.

The median age of the 14 colonised patients enrolled in the case control study was 7.5 years (range 1.7–16.8). Thirteen were ambulatory. Three had undergone significant surgical procedures and no patient had undergone a bone marrow transplant. Median serum creatinine level was 55.0 mmol/l (range 38–119.5). The most frequent underlying malignancy in this group was haematological ($n = 8$). The median number of days hospitalised, receiving IV antibiotics and neutropenia in the 3 months prior to VRE colonisation are summarised in Table 1.

Environmental screening

Environmental surveillance cultures were first obtained on 6 February 1996. VRE was recovered from 25% (30 of 120) of sites sampled. Areas sampled included patient and parent rooms, sluice, kitchen and play areas. Bed rails, chairs, blood pressure cuff, sluice handle, toilet seat, bedpan washer and other sites throughout the unit were contaminated. More extensive contamination was found in VRE colonised patients' rooms. With continued implementation of stringent infection control measures, repeat environmental screening for the subsequent

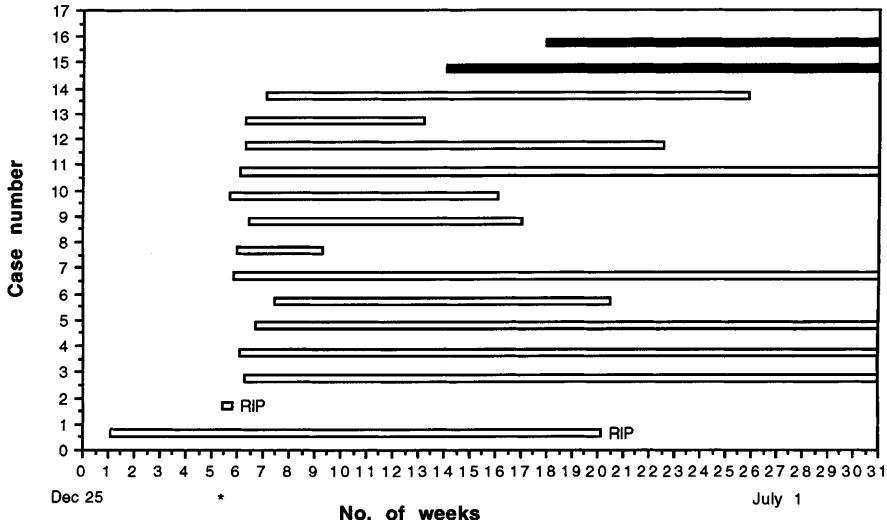

Fig. 1 Duration of patient colonisation with VRE * Institution of patient surveillance and infection control measures
□ Cases in case-control study
■ Cases identified post cut-off for entry to case-control study

Table 1 Summary of cases of VRE colonisation

Case no.	Age (years)	Sex	Diagnosis	Days of			Systemic Infection	Organis
				Hospitalisation	Neutropenia	Antibiotic therapy		
1	2.7	M	ALL	49	34	24	Y	*E. faecium*
2	11.0	M	Lymphoma	36	5	23	Y	*E. faecium*
3	15.6	F	ALL	24	15	27	N	*E. faecium*
4	16.8	M	Ewings sarcoma	59	19	39	N	*E. faecium* and *E. avium*
5	8.7	M	Rhabdomyo sarcoma	46	15	14	N	*E. faecium*
6	13.6	F	ALL	38	43	29	N	*E. casseli flavus*
7	15.9	M	ALL	34	20	13	N	*E. avium*
8	10.7	F	Lymphoma	11	0	6	N	*E. faecium*
9	5	F	ALL	26	26	6	N	*E. faecium*
10	6.4	M	ALL	19	14	19	N	*E. faecium*
11	4	F	Lymphoma	49	10	23	N	*E. faecium*
12	4	M	Nephro-blastoma	48	5	15	N	*E. faecium*
13	5.2	M	ALL	26	11	9	N	*E. faecium*
14	1.7	M	ALL	39	28	17	N	*E. faecium*
median	7.5			35	15	18		

2 months yielded on average a 5% positive swab rate with VRE detected both in patient rooms and in general areas of the unit. On 18 April 1996 all environmental swabs were negative for VRE. On 25 July 1996, two non-outbreak strains were detected in the environment.

Six environmental strains were studied by PCR and PFGE. These represented samples from different areas of the unit and included swabs from a washing machine used by patients, a sluice room fan and the window ledge, door handle, thermometer (axillary use) and infusomat pole from different patient rooms.

Species identification

Of the 14 VRE colonised patients, 11 harboured *E. faecium* alone, one had *E. faecium* and *Enterococcus avium,* one *E. avium* and one *Enterococcus casseliflavus*. All isolates of *E. faecium* were resistant to ampicillin, erythromycin, cephalosporins and chloramphenicol. High level gentamicin resistance (MIC > 2000 mg/l) was detected for one strain of *E. faecium*. This patient also harboured a glycopeptide dependent strain of *E. faecium*. The strain grew only in the presence of vancomycin (at concentrations of 3 to >256 mg/l) or teicoplanin (concentrations of 0.2 to 64 mg/l). Growth did not occur at teicoplanin concentrations >64 mg/l. All isolates manifested high level resistance to vancomycin (E test MIC > 256 mg/l) and teicoplanin (E test MIC > 32 mg/l) thus compatible with the *Van A* resistance phenotype. Of the 6 environmental isolates, 5 were identified as *E. faecium* and 1 as *E. casseliflavus*; each had the *VanA* resistance phenotype.

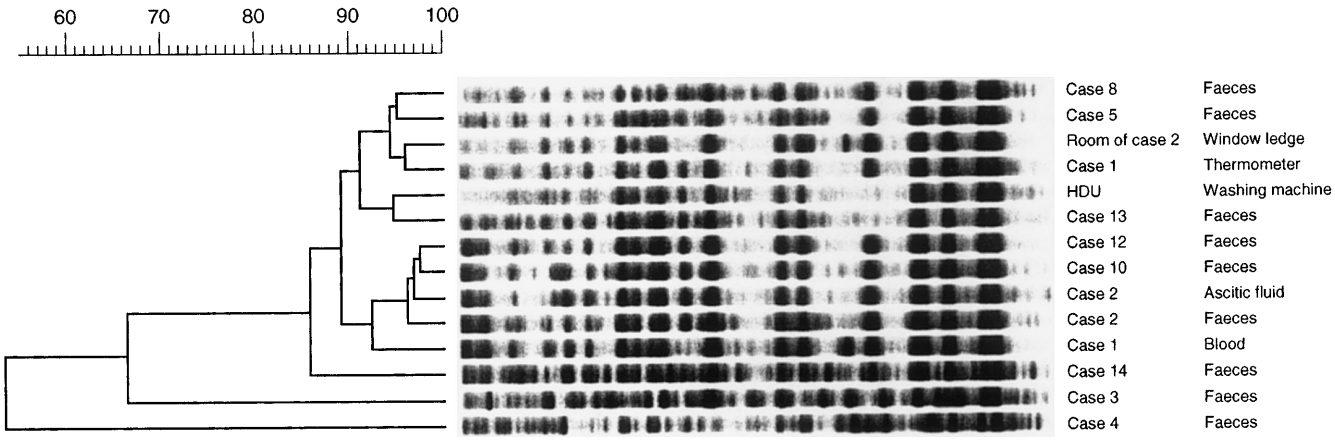

Fig. 2 PFGE pattern and dendogram of percentage similarity for patient and environmental isolates of *E. Faecium*. Cases 3 and 4 harboured molecularly dissimilar strains

Table 2 Comparison of cases and matched controls in a case-control study of VRE colonisation

Variable[a]	Cases (n = 14)	Controls (n = 41)	Odds ratio[b] (95% CI)	P value[c] (univariate analysis)
Sex (no. males)	9	20	2.0 (0.51–8.22)	0.51
Haematological diagnosis	8	12	3.83 (0.86–17.2)	0.09
Ambulatory	13	35	2.0 (0.26–15.3)	0.79
Days hospitalised	35	26	1.3 (0.43–3.93)	0.04
Days neutropaenic[#]	15	6	3.72 (1.05–13.1)	0.03
No. antibiotics[#]	5	2	6.78 (1.34–34.3)	0.02
Days on IV antibiotics[#]	18	7	4.07 (1.08–15.3)	0.048
Total antibiotic days[#]	44.5	12	4.07 (1.08–15.3)	0.048
Days on ceftazidime[#]	5	0	11.5 (2.2–59.9)	0.002
Days on amikacin[#]	17	5	10.7 (1.4–81.5)	0.01
Days on teicoplanin[#]	5	0	12.3 (2.25–67.5)	0.002

[a] Median values given for all continuous variables
[b] Using the median value for cases and controls combined as the cut point
[c] Mantel-Haenszel $\times 2$ test
[#] Statistically significant variables

Molecular comparison of VRE

PFGE revealed that 10 of the 12 *E. faecium* patient isolates represented a single strain. This same pattern was found for isolates from the blood, urine and stool of the first index case, the peritoneal fluid and stool of the second infected patient, the stool samples of 8 colonised patients, and 5 environmental isolates. (Fig. 2). Two of the 12 patients harbouring *E. faecium* had patterns distinct both from each other and from the outbreak strain.

Case control study

Data from the 14 cases were compared to those for the 41 matched controls (Table 2). A slightly greater percentage of cases than controls were male (65% vs 49%). Significant risk factors for the development of VRE colonisation included duration of neutropenia and antibiotic therapy, number of antibiotics received and total antibiotic days (Table 2). Individual antibiotics were assessed as potential risk factors for the development of colonisation. Significant differences between cases and controls were found in the case of amikacin, ceftazidime and teicoplanin (Table 2). These, as well as piperacillin, were the most frequently used antibiotics in the unit. No child (case or control) received oral or IV vancomycin in the 3-month period assessed. Because of the large correlation between the variables, none were found to be independently significant having adjusted for all others.

Of all patients, only 5 (all controls) had had a bone marrow transplant and only 5 had had significant surgery during the study period. Underlying diagnosis categorised as haematological or other was not a significant factor for the acquisition of colonisation. The mean serum creatinine level in the two groups was within a normal range and did not differ between groups.

Discussion

Since the first identification of VRE in 1987 [25, 44], many outbreaks of infection and colonisation have been reported [3–6, 10, 18, 19, 22–24, 27, 30–32, 35, 46] oc-

curring predominantly among immunocompromised adults in large tertiary referral hospitals [5]. Few outbreaks in paediatric units have been reported [2, 16, 20, 39] and the extent of colonisation in hospitalised children, mode of nosocomial transmission, factors associated with colonisation and infection and optimal infection control strategies are unknown.

The outbreak we describe occurred in a characteristically susceptible population; paediatric oncology patients, in a tertiary referral hospital in which VRE had not previously been isolated. Our investigation revealed that as of March 31st 19% of children were colonised with VRE. A recent report from the U.K. found VRE in the stools of 15% of renal patients, 5% of other hospital patients and 2% of patients based in the community [22]. In Belgium, colonisation rates of 3.5% (point prevalence study of patients in an 800 bed hospital without previous isolation of VRE [14]) and 28% (of healthy community-based volunteers [45]) have recently been reported. Reports from the US have not detected VRE colonisation in healthy community volunteers [46] but colonisation rates in susceptible hospital populations vary from 6% to 20% [18, 19, 24, 30–32] with one report from a liver transplant unit finding a colonisation rate of 63% [16].

In our population, the median duration of colonisation after the first positive culture was identified was 16 weeks. It has been demonstrated that colonisation with the same strain of VRE may persist for at least a year [20, 30, 35] and that there is a significant association between gastro-intestinal colonisation and the subsequent development of invasive infection [6, 10, 20, 30–32]. Colonisation rates appear to be ten times more prevalent than infection rates [16, 20, 30].

Twelve of 14 isolates were identified as *E. faecium*. Although *Enterococcus faecalis* is the most prevalent species causing invasive enterococcal infection, *E. faecium* has been reported as the species accounting for most glycopeptide resistant infection, in particular *E. faecium* strains with the *Van A* resistance phenotype [10, 14, 19, 20, 27, 30, 35].

Vancomycin dependant strains of enterococci have been previously reported [8, 12, 17] in patients who have received therapy with oral or IV vancomycin. In this report the patient harbouring a glycopeptide dependant strain had received 22 days of teicoplanin and no vancomycin in the 3 months prior to a positive culture.

Previously thought to have an endogenous source, recent reports of VRE outbreaks using molecular analysis reveal identical clones isolated from multiple patients suggesting nosocomial transmission [3, 6, 10, 19, 20, 27, 39]. Many of these studies, however, have been based on plasmid analysis and it is possible that non-identical strains may exchange identical plasmid genomes. Other investigations report outbreaks with non- identical strains; Bingen et al. [2] reported an outbreak in a French paediatric hospital and Morris et al. [32] conducted point prevalence surveys in a university medical centre. In both studies patients were from different wards. In a report by Plessis et al. [38] of patients from a single haematological unit, genetic unrelatedness of strains was confirmed by PFGE. In our study, PFGE revealed that 10 of 12 *E. faecium* patient isolates and all 5 *E. faecium* environmental isolates had an identical molecular pattern, supporting nosocomial transmission of VRE from a common source. There was also evidence for simultaneous non-clonal VRE colonisation. All non-clonal strains were different suggesting a low background prevalence of VRE in this population.

It appears that our unit environment may have been a significant factor in the transmission of VRE among the unit patients; 25% of environmental swabs taken at initial screening were positive for VRE. At the time of the outbreak, there was significant overcrowding and understaffing in the unit; factors which must have contributed to the breakdown of optimal infection control practices. In this study, the index case was an active, sociable toddler with frequent diarrhoea who may have contributed significantly to the environmental contamination and patient to patient transmission. It has been reported [3] that diarrhoea in a colonised patient greatly increases the environmental yield from that patient's room. Inanimate objects such as rectal thermometers [27] and air-fluidized microsphere beds [36] have been implicated in the nosocomial transmission of VRE. Livornese et al. [27] found rectal thermometers to be the likely vehicle for transmission. Other studies have found evidence of VRE on many environmental surfaces eg. tables, floors, doors, intravenous pumps, blood pressure cuffs and other sources [3, 10, 46, 48].

The infection control measures implemented to control the outbreak closely resembled those recommended by the Hospital Infection Control Practices Advisory Committee (HICPAC) and Centres for Disease Control (CDC) [21]. Unit antibiotic policy was altered to restrict the use of both ceftazidime and teicoplanin. These measures appear to have contained the outbreak. In the 6 months following their instigation, only two further cases of VRE colonisation have been identified (one of which harboured the outbreak strain). Previous reports have shown varying success in reducing the incidence of VRE carriers following the introduction of infection control measures [3, 6, 20, 30, 39, 47].

It has been established that VRE colonisation and infection occur predominantly in patients with severe underlying disease. The most frequently identified factors for the acquisition of VRE colonisation or infection among these patient populations are length of hospital stay and duration of prior antibiotic therapy (in particular with vancomycin) [4, 10, 14, 19, 31, 39, 41]. A recent report by Van de Auwera et al. [45] has shown that following the use of oral glycopeptides, highly glycopeptide-resistant enterococci can be selected for and can reach high numbers (up to 106–108 cfu/g) in faeces. Other risk factors reported include severity of underlying illness [32, 41], prior administration of anaerobically active antibiotics [10], prior intra-abdominal surgery [19], haematological malignancy [41], proximity

to other affected patients and exposure to a nurse who cares for other affected patients [3]. The only other case control study in a paediatric population by Rubin et al. [39] found that colonisation with VRE was associated with prior administration of antibiotics (in particular vancomycin) and length of hospitalisation. In this study, length of neutropenia and prior antibiotic use were significant factors for the acquisition of VRE colonisation, findings similar to those found in adult populations [4, 10, 14, 19, 31, 39, 41]. This outbreak of VRE colonisation occurred in the absence of prior vancomycin usage. It is likely that teicoplanin exerts a similar selective pressure for the development of VRE colonisation.

Patient location on the ward was not assessed as a potential risk factor as due to overcrowding patients could change location (bed or room) up to twice a day. It is worth noting however, that no patient who was nursed exclusively in the high dependency unit acquired VRE colonisation despite the prolonged stays and extensive use of antibiotics. This underscores the importance of infection control measures, in particular those of case isolation and barrier precautions in preventing the spread of this organism.

Glycopeptide resistant enterococci are of increasing concern to hospital practitioners particularly as there is currently no proven treatment for VRE infection although a number of drugs are undergoing experimental trials [43]. Another major concern is the risk of transfer of resistance characteristics from VRE to other more common and pathogenic organisms such as the staphylococci which to date has only been demonstrated in the laboratory [34]. Resistance to vancomycin has been transferred from enterococci to other species by plasmid or transposon mediated mechanisms both in vitro and in clinical situations [26, 34]. Preventative measures are crucial to limiting the future impact of this organism on both hospital and community populations. It appears from this study that the most effective measures for control of VRE colonisation and infection in susceptible paediatric populations may be a high level of awareness and surveillance for the organism, recognition of VRE colonised/infected patients, the restriction of broad spectrum antibiotic use and the strict adherence to infection control policies in particular health care worker handwashing and environmental cleaning.

Acknowledgements The authors wish to thank Mr. Donald Morrison, clinical scientist, Colindale Public Health Laboratory and Dr. Carol J. Baker, Baylor College of Medicine for their critical review of the manuscript, Prof. Brendan Drumm and Dr. Marion Rowland for their helpful discussion and editorial advice, Ms. Margaret Byrne for laboratory expertise and Dr. Marguerite Clyne for her invaluable computer assistance.

References

1. Anonymous (1996) Vancomycin resistant enterococci in hospitals in the United Kingdom - 1995. CDR Weekly 6:267
2. Bingen EH, Denamur E, Lambert-Zechovsky MY, Elion J (1991) Evidence for the genetic unrelatedness of nosocomial vancomycin-resistant *Enterococcus faecium* strains in a pediatric hospital. J Clin Microbiol 29:1888–1892
3. Boyce JM, Opal SM, Chow JW, Zervos MJ, Potter-Bynoe G, Sherman CB, Romulo RLC, Fortna S, Medeiros AA (1994) Outbreak of multidrug-resistant *Enterococcus faecium* with transferable *vanB* class vancomycin resistance. J Clin Microbiol 32(5):1148–1153
4. Boyle JF, Soumakis SA, Rendo A, Herrington JA, Gianarkis DG, Thurberg BE, Painter BG (1993) Epidemiologic analysis and genotypic characterization of a nosocomial outbreak of vancomycin-resistant enterococci. J Clin Microbiol 31:1280–1285
5. Centers for Disease Control and Prevention (1993) Nosocomial enterococci resistant to vancomycin - United States 1989–1993. MMWR 42:597–599
6. Chadwick PR, Oppenheim BA, Fox A, Woodford N, Morgenstern GR, Scarffe JH (1996) Epidemiology of an outbreak due to glycopeptide-resistant *Enterococcus faecium* on a leukaemia unit. J Hosp Infect 34:171–182
7. Christie C, Hammond J, Reising S, Evans-Patterson J (1994) Clinical and molecular epidemiology of enterococcal bacteremia in a pediatric teaching hospital. J Pediatr 125:392–399
8. Dever LL, Smith SM, Handwerger S, Eng RH (1995) Vancomycin-dependent *Enterococcus faecium* isolated from stool following oral vancomycin therapy. J Clin Microbiol 33:2770–2773
9. Dutka-Malen S, Evers S, Courvalin P (1995) Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR. J Clin Microbiol 33(1):24–27
10. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, Wenzel RP (1995) Vancomycin-Resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis 20:1126–1133
11. Emori TG, Gaynes RP (1993) An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev 6:428–442
12. Fraimow HS, Jungkind DL, Lander DW, Delso DR, Dean JL (1994) Urinary tract infection with an *Enterococcus faecalis* isolate that requires vancomycin for growth. Ann Intern Med 121:22–26
13. Frieden TR, Munsiff SS, Low DE, Willey BM, Williams G, Faur Y, Eisner W, Warren S, Kreiswirth B (1993) Emergence of vancomycin-resistant enterococci in New York City. Lancet 342:76–79
14. Gordts B, Van Landuyt H, Ieven M, Vandamme P, Goossens H (1995) Vancomycin-resistant enterococci colonizing the intestinal tracts of hospitalized patients. J Clin Microbiol 33:2842–2846
15. Gray J, Marsh PJ, Stewart D, Pedler SJ (1994) Enterococcal bacteraemia: a prospective study of 125 episodes. J Hosp Infect 27:179–186
16. Green M, Barbadora K, Michaels M (1991) Recovery of vancomycin-resistant grampositive cocci from pediatric liver transplant recipients. J Clin Microbiol 29:2503–2506
17. Green M, Shlaes JH, Barbadora K, Shlaes DM (1995) Bacteremia due to vancomycin-dependent *Enterococcus faecium*. Clin Infect Dis 20:712–714
18. Guiot HFL, Peetermans WE, Sebens FW (1991) Isolation of vancomycin-resistant enterococci in haematologic patients. Eur J Clin Microbiol Infect Dis 10:32–34
19. Handwerger S, Raucher B, Altarac D, Monka J, Marchione S, Singh KV, Murray B, Wolff J, Walters B (1993) Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. Clin Infect Dis 16:750–755
20. Henning KJ, Delencastre H, Eagan J, Boone N, Brown A, Chung M, Wollner N, Armstrong D (1996) Vancomycin-resistant *Enterococcus faecium* on a pediatric oncology ward: duration of stool shedding and incidence of clinical infection. Pediatr Infect Dis J 15:848–854

21. Hospital Infection Control Practices Advisory Committee (HICPAC) (1995) Recommendations for preventing the spread of vancomycin resistance. Infect Control Hosp Epidemiol 172:993–1000
22. Jordens JZ, Bates J, Griffiths DT (1994) Faecal carriage and nosocomial spread of vancomycin-resistant *Enterococcus faecium*. J Antimicrob Chemother 34:515–528
23. Karanfil LV, Murphy M, Josephson A, Gaynes R, Mandel L, Hill BC, Swenson JM (1992) A Cluster of vancomycin-resistant *Enterococcus faecium* in an intensive care unit. Infect Control Hosp Epidemiol 13:195–200
24. Lam S, Singer C, Tucci V, Morthland VH, Pfaller MA, Isenberg HD (1995) The challenge of vancomycin-resistant enterococci: a clinical and epidemiologic study. Am J Infect Control 23:170–180
25. Leclercq R, Derlot E, Duval J, Courvalin P (1988) Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 319(3):157–161
26. Leclerq R, Derlot E, Weber M, Duval J, Courvalin P (1989) Transferable vancomycin and teicoplanin resistance in *Enterococcus faecium*. Antimicrob Agents Chemother 33:10–15
27. Livornese LL, Dial S, Samel C, Romanowski B, Taylor S, May P, Pitsakis P, Woods G, Kaye D, Levison ME, Johnson CC (1992) Hospital-acquired Infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. Ann Intern Med 117:112–116
28. Luginbuhl LM, Rotbart HA, Facklam RR, Roe MH, Elliot SM, Elliot JA (1987) Neonatal enterococcal sepsis: case-control study and description of an outbreak. Pediatr Infect Dis J 6:1022–1030
29. Malone DA, Wagner RA, Myers JP, Watanakunakorn C (1986) Enterococcal bacteremia in two large community teaching hospitals. Am J Med 81:610
30. Montecalvo MA, de Lencastre H, Carraher M, Gedris C, Chung M, VanHorn K, Wormser GP (1995) Natural history of colonization with vancomycin-resistant *Enterococcus faecium*. Infect Control Hosp Epidemiol 16:680–685
31. Montecalvo MA, Horowitz H, Gedris C, Carbonaro C, Tenover FC, Issah A, Cook P, Wormser GP (1994) Outbreak of vancomycin-, ampicillin-, and aminoglycoside-resistant *Enterococcus faecium* bacteremia in an adult oncology unit. J Antimicrob Chemother 38(6):1363–1367
32. Morris JG, Shay DK, Hebden JN, McCarter RJ, Perdue BE, Jarvis W, Johnson JA, Dowling TC, Polish LB, Schwalbe RS (1995) Enterococci resistant to multiple antimicrobial agents including vancomycin: establishment of endemicity in a university medical center. Ann Intern Med 123:250–259
33. Murray BE, Singh KV, Heath JD, Sharma BR, Wienstock GM (1990) Comparison of genomic DNAs of different enterococcal isolates using restriction endonucleases with infrequent recognition sites. J Clin Microbiol 28(9):2059–2063
34. Noble WC, Virani Z, Cree RGA (1992) Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. FEMS Microbiol Lett 93:195–198
35. Nolkin GA, Cooper I, Peterson LR (1995) Vancomycin-resistant *Enterococcus faecium* sepsis following persistent colonization. Arch Intern Med 155:1445–1447
36. Orr KE, Gould FK, Perry JD, Ford M, Morgan S, Sisson PR, Morrison D (1994) Therapeutic beds: the Trojan horses of the 1990's? Lancet 344:65–66
37. Peng M-Y, Young T-G, Yang C-H, Chou M-Y (1994) Enterococcal bacteremia in a medical center. Chin Med J (Taipei) 54:306–311
38. Plessis P, Lamy T, Donnio PY, Autuly F, Grulois I, Le Prise PY, Avril JL (1995) Epidemiologic analysis of glycopeptide-resistant *Enterococcus* strains in neutropenic patients receiving prolonged vancomycin administration. Eur J Clin Microbiol Infect Dis 14:959–963
39. Rubin LG, Tucci V, Cercenado E, Eliopoulos G, Isenberg HD (1992) Vancomycin-resistant *Enterococcus faecium* in hospitalized children. Infect Control Hosp Epidemiol 13:700–705
40. Schaberg DR, Culver DH, Gaynes RP (1991) Major trends in the microbial aetiology of nosocomial infections. Am J Med 91(3B):72S–75S
41. Shay DK, Maloney SA, Montecalvo M, Banerjee S, Wormser GP, Arduino MJ, Bland LA, Jarvis WR (1995) Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis 172:993–1000
42. Slanetz LW, Bartley CH (1957) J Bact 74:591–595
43. Spera RV Jr, Farber BF (1994) Multidrug-resistant *Enterococcus faecium*: an untreatable nosocomial pathogen. Drugs 48:678–688
44. Uttley AH, Collins CH, Naedoo J, Heorge RC (1988) Vancomycin-resistant enterococci (letter). Lancet I: 57
45. Van der Auwera P, Pensart N, Korten V, Murray BE, Leclercq R (1996) Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. J Infect Dis 173:1129–1136
46. Wade JJ (1995) The emergence of *Enterococcus faecium* resistant to glycopeptides and other standard agents - a preliminary report. J Hosp Infect 30[Suppl]:483–495
47. Wells CL, Juni BA, Cameron SB, Mason KR, Dunn DL, Ferrieri P, Rhame FS (1995) Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. Clin Infect Dis 21:45–50
48. Yamaguchi E, Valena F, Smith SM, Simmons A, Eng RHK (1994) Colonization pattern of vancomycin-resistant *Enterococcus faecium*. Am J Infect Control 22:202–206
49. Yu V (1981) Enterococcal superinfection and colonization after therapy with moxalactam, a new broad-spectrum antibiotic. Ann Intern Med 94:784