ORIGINAL ARTICLE

Vancomycin resistance emerging in a clonal outbreak caused by ampicillin-resistant *Enterococcus faecium*

Stig Harthug[1], A. Digranes[2], O. Hope[3], B. E. Kristiansen[4], A. G. Allum[4] and N. Langeland[5]

[1]Department of Medicine and [2]Department for Microbiology and Immunology, The Gade Institute, Haukeland University Hospital, Bergen, [3]Institute of Medicine, Department of Medicine, Deaconess Hospital, Haraldsplass, Bergen, [4]Telelab, Skien, and [5]Centre for International Health, University of Bergen and Department of Medicine, Haukeland University Hospital, Bergen, Norway

Objective To describe the first nosocomial outbreak of ampicillin-resistant *Enterococcus faecium* (ARE) in Norway, where a few vancomycin-resistant strains have also been identified.

Methods All cases of ARE and vancomycin-resistant *Enterococcus faecium* (VRE) diagnosed by the medical microbiological laboratories in a region inhabited by approximately 1 million people were registered. Isolates obtained during the period 1 January 1995 to 31 December 1996 were characterized by pulsed field-gel electrophoresis and the clinical data were recorded.

Results One hundred and forty-nine patients (64 males, 85 females, mean age 70.5 years) were infected with ARE. Isolates from 115 cases were genomically related to the outbreak strain. Infections included bacteremia (14), wound infections (31), urinary tract infections (97) and other infections (seven). Most had a severe underlying disease and 93% of the patients had received antibiotics for a mean time of 23 days. Twenty-four patients (16.1%) died during hospitalization. Four infections were caused by a *vanB*-type VRE that was genomically related to the ARE outbreak strain. The prescription rate for vancomycin was low, but an increase in vancomycin use paralleled the appearance of VRE. The highest monthly incidence rate was 2.5 per 1000 patient admissions in July 1996 declining to 0.5 in December 1996.

Conclusions The first nosocomial outbreak caused by ARE was observed in 1995 in Norway and is still ongoing. One year after the onset, VRE occurred in wards which had a relatively high consumption of vancomycin.

Keywords Outbreak, vancomycin resistance, ampicillin-resistance, *Enterococcus faecium*, vanB

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INTRODUCTION

In recent years, enterococci have emerged as a significant cause of nosocomial infections [1,2], accounting for about 8% of hospital-acquired infections in the United States [3]. Urinary tract infections are most common, but enterococci are also frequently isolated from abdominal and surgical wound infections and are an important cause of bacteraemia and endocarditis [4–7]. The majority of clinical enterococcal infections are *Enterococcus faecalis*, but there is an increasing number of reports of infections caused by *Enterococcus faecium* [3]. The emergence of enterococci as significant pathogens is a matter for concern because these organisms are inherently resistant to a number of antimicrobial agents, including cephalosporins and aminoglycosides. Cell-wall-active drugs such as ampicillin and vancomycin are only bacteriostatic. Enterococci have acquired high-level resistance to aminoglycosides [8,9]. Later, ampicillin-resistant enterococci [10,11] and eventually vancomycin-resistant enterococci (VRE) emerged [12,13]. Multiple-drug resistant enterococci (MDRE) combine inherent resistance of *Enterococcus* spp. with resistance to ampicillin, high-level resistance to aminoglycosides and glycopeptide resistance [3]. Such strains seem to have a substantial potential for nosocomial spread.

Both the selection of various resistant strains and the clonal spread of ampicillin-resistant enterococci (ARE) have been

Corresponding author and reprint requests: Stig Harthug, Haukeland University Hospital, Department for Infection Control, N-5021 Bergen, Norway
Tel: + 47 55975000
Fax: + 47 55975813
E-mail: stig.harthug@haukeland.no

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reported [13,14]. Clonal outbreaks of infections caused by multiple-resistant *E. faecium* have been reported [15,16], and VRE outbreaks have been described from several countries [17–21]. It is also evident that the genetic determinants for glycopeptide resistance are transferable [16,22]. It is therefore important to study both mechanisms for the spread of multiple-drug-resistant enterococci and the spread of resistance factors independently. The purpose of this study was to describe a nosocomial outbreak of ampicillin-resistant *E. faecium* (ampicillin minimal inhibitory concentration $\geqslant 32$ mg/L) in which VRE emerged with clonally related strains.

MATERIALS AND METHODS

Setting

Haukeland University Hospital is a fully specialized 1100-bed hospital serving a population of 1 million as a referral hospital and 300 000 as an emergency hospital. Deaconess Hospital Haraldsplass is a 175 bed emergency hospital located nearby serving the same population. Patients that have been hospitalized in one of the hospitals will often be readmitted to the other. The Department of Microbiology and Immunology at Haukeland University Hospital serves these two hospitals and also the three other emergency hospitals located in Hordaland County. It is also the main service for outpatients in Hordaland County (431 000 inhabitants). The number of bacteriological specimen examined each year exceeds 80 000, some 50 000 of which are from outpatients. There are also two collaborating microbiological laboratories in the nearest two counties which serve the rest of the hospitals and outpatients in the region. With the exception of one clinical ARE and VRE case, these two laboratories did not report any other ARE or VRE cases during 1995 and 1996.

Patient inclusion

All patients with a clinical isolate of ARE detected between 1 January 1995 and 31 December 1996 at the Department for Microbiology and Immunology were prospectively included. One or more of the authors, who are specialists in infectious diseases, recorded the clinical data of the patients. Unclear cases were always discussed by at least two of the authors. The data-set included diagnosis, length of hospital stay, antibiotics prescribed, all wards visited, use of central venous catheters, surgical procedures, use of urinary catheters and outcome. The clinical diagnosis of infection was classified according to the CDC definitions [23] and intra-hospital death registered as attributable to enterococcal infection when active enterococcal infection was clearly recognized as the major cause of the fatal outcome [24]. Previous hospitalization with discharge within the last month was added to the length of the actual hospital stay. Statistical patient data concerning the number of patients admitted, average length of hospital stay and consumption of antibiotics for each of the hospital units were recorded from the annual hospital reports.

Identification of isolates

All isolates were identified by standard biochemical methods [25]. At least one isolate of each pulsed field type (see below) was verified as *E. faecium* by using a polymerase chain reaction (PCR) method [26].

Antimicrobial susceptibility testing

The susceptibility of the isolates to different antimicrobial agents (ampicillin, netilmicin, gentamicin, vancomycin and teicoplanin) was examined by an agar diffusion method [27] using paper discs and PDM Antibiotic Sensitivity Medium (AB Biodisk, Solna, Sweden). Urine isolates were also tested against ciprofloxacin, cotrimoxazole and nitrofurantoin using the same method. The susceptibilities were categorized in three groups (sensitive, intermediate, resistant) according to recommendations given by The Norwegian Working Group on Antibiotics [28]. All isolates classified as resistant to aminoglycosides were examined for high-level gentamicin resistance by a special E-test (AB Biodisk). The minimal inhibitory concentrations (MICs) of ampicillin, vancomycin and teicoplanin were determined for the majority of ARE isolates during the outbreak by E-test (AB Biodisk).

Pulsed-field gel electrophoresis

One hundred and forty-two isolates were available for pulsed-field gel electrophoresis (PFGE) as performed on *Sma1* (Promega Corp, Madison, WI, USA) digested genomic DNA as previously described [29] using the Rothapor type V electrophoresis unit (Biometra GmbH, Germany). DNA digests were loaded on 1% agarose gels with 2–15 s pulses at 180 V and 22°C for 20 h. The resulting patterns were interpreted as described [30].

Detection of van-genes

All isolates with vancomycin MIC > 2 mg/L were analysed for the presence of *vanA, vanB* and *vanC* resistance genes by PCR. Preparation of DNA and PCR amplification was performed as described elsewhere [31]. The primers used for detection of the *vanB1* gene were those described by Clark et al. [32]. For *vanB2* the following primers were used: Forward: 5′ CAA AGC TCC GCA GCT TGC ATG 3′ (nucleotide positions 5340–5360). Reverse: 5′ TGC ATC CAA GCA CCC GAT ATA C 3′ (nucleotide position 5823–5802).

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Statistical data

Numbers of patients admitted and numbers of days in hospital for different units of Haukeland University Hospital were collected from the official administrative database used in the hospital. The data for consumption of antimicrobial agents were provided from the database of the hospital pharmacy as net delivered amount of individual drugs counted as defined daily dosages (DDD).

Statistical methods

Statistical analyses were performed by the Statistical Program for Social Sciences (SPSS-PC + version 7.0 SPSS inc., Chicago, IL). The Pearson correlation coefficient was calculated for correlation between the ARE incidence and antibiotic consumption and *P*-values were calculated for two-tailed distribution.

RESULTS

Clinical findings

A total of 149 patients (64 males and 85 females, mean age 70.5 years) had an ARE isolated from a clinical specimen. The basic characteristics for these patients are shown in Table 1. One hundred and twenty-three patients were hospitalized at Haukeland University Hospital, seven were outpatients there, 17 patients were hospitalized at Deaconess Hospital Haraldsplass and two patients had not visited these hospitals at all. The mean hospital stay was 43.2 days, compared with 6.5 days for all patients in the two hospitals. One hundred and four patients had the infection detected during hospitalization, 19 within 1 month after discharge, and 17 within 6 months of hospitalization. Seven patients had visited the outpatient clinic only during the last 6 months. Of the two patients who had not visited either of the two hospitals, one had been hospitalized at another hospital, which had previously had a patient with ARE transferred from our hospital. The other patient without hospital contact was a nursing home patient with an *E. faecium* unrelated to the outbreak strain. The dominating ARE infection type was urinary tract infection, but more severe infections occurred (Table 2). Long hospital stay was a reflection of the severe underlying disease. Malignancy was the most frequent underlying disease, followed by infections and cardiovascular disease (Table 1). The case fatality rate during the hospital stay was 16.1% and 4.7% was attributable to ARE as active enterococcal infection was clearly recognized as the major cause of the fatal outcome.

Data on antibiotic consumption was available for the 140 ARE patients admitted to the two hospitals (94% of all the patients) (Table 2). The rest were omitted because of incomplete data (seven outpatients and two admitted to another hospital). Of these 140 patients, 121 (86%) had received antimicrobial agents within the last month prior to the enterococcal infection. This figure also includes drugs prescribed before hospitalization. The mean duration of treatment for patients receiving antibiotics was 22.3 days. The most frequently used agents were cephalosporins, followed by penicillins, aminoglycosides and quinolones. Glycopeptides were

Table 1 Demographic characteristics and underlying diseases for 149 patients infected with ampicillin-resistant *Enterococcus faecium*

No. of patients included	149	
Female, no. (%)	85	(57)
Age, mean (range)	70.5	(1–95)
No. of patients with different underlying diseases (%) $n = 143$		
malignant	43	(30.0)
infection	30	(21.0)
cardiovascular	24	(16.8)
gastrointestinal	16	(11.2)
urogenital	9	(6.3)
immunological	6	(4.2)
bone and joint	5	(3.5)
other diseases	10	(7.0)

Table 2 Patient characteristics for 149 patients with clinical infection caused by ampicillin-resistant *Enterococcus faecium* (ARE)

Distribution of infections, no. (%)		
urinary tract infection	97	(65.1)
wound or surgical site	31	(20.8)
bacteraemia	14	(9.4)
other	7	(4.7)
No. of hospital days, mean (range)	43.2	(1–285)
Antibiotics prior to MRE infection (data available for 140 patients)		
No. of patients receiving antibiotics (%)	121	(86.4)
Days on antibiotics, mean (range)	22.3	(1–134)
No. of antibiotics prescribed, mean (range)	2.7	(1–8)
No. of patients receiving specific antimicrobial agents ($n = 121$)		
penicillins	66	(50.0)
cephalosporins	81	(66.9)
fluoroquinolones	38	(31.4)
metronidazole	28	(23.1)
glycopeptides	10	(8.3)
trimethoprim-sulfamethoxazole	13	(10.7)
trimethoprim	4	(3.3)
clindamycin	13	(10.7)
aminoglycosides	40	(33.1)
carbapenems	21	(17.4)
Mortality, crude – no. of deaths (%)	24	(16.1)
Mortality, attributable – no. of deaths (%)*	7	(4.7)

*Active ARE-infection clearly recognized as the major cause of death.

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given to 8.3% of the patients receiving antimicrobial agents. None of the patients with vancomycin-resistant enterococci had received glycopeptide antibiotics, but they were admitted to wards with a high general consumption of vancomycin (Figure 1).

Case distribution

The epidemic started at the Haukeland University Hospital and spread to the nearby Deaconess Hospital Haraldsplass with a delay of about 6 months. The first case with ARE was detected in January 1995. Isolates from the first two patients were not genomically related to the outbreak strain. In 1994 two cases with infections due to *E. faecium* having reduced susceptibility to ampicillin (MIC: 8–16 mg/L) were observed, but no cases with ampicillin-resistant strains. The first few patients had been hospitalized in either the central intensive care unit, in a surgical ward or one of the medical wards that later had several ARE patients or they had been moved between these wards The epidemic curve for the ARE cases are shown in Figure 2. All the VRE cases appeared at the peak of the epidemic, between March and July 1996. Clinical and epidemiological characteristics for these patients are shown in Table 3.

The infection control program for the hospital was reinforced by elements from the recommendations given for VRE [33]. Special efforts were made to strengthen the general barrier precautions for patients admitted to the two wards with highest prevalence of ARE infection. All staff members were reminded about hand-washing, use of uniform and gloves and gowns when indicated. The wards were supervised intensively by infection-control nurses. All patients with VRE infection and patients with uncontrolled ARE infection were moved to isolation facilities. Several classes were held to educate the staff about the epidemic and the urgent need for their compliance. Updated guidelines for prescription of antimicrobial agents were distributed to all the physicians. The routines in the microbiologic laboratories were reinforced so that all cases of ARE and VRE were reported immediately to the wards and also registered by the infection-control team. These efforts were initiated during March and April 1996.

Within Haukeland University Hospital and its outpatient clinics, 70 cases were detected at the medical department, 24 at the surgical department, eight at the intensive care unit, eight at the orthopaedic department, five at the department for cardiac diseases and four or less at other departments. Within the medical department, three wards (out of six) had 53 of the 70 cases (76%). The paediatric department had one case at the outpatient clinic, the department for gynaecology one case, and the

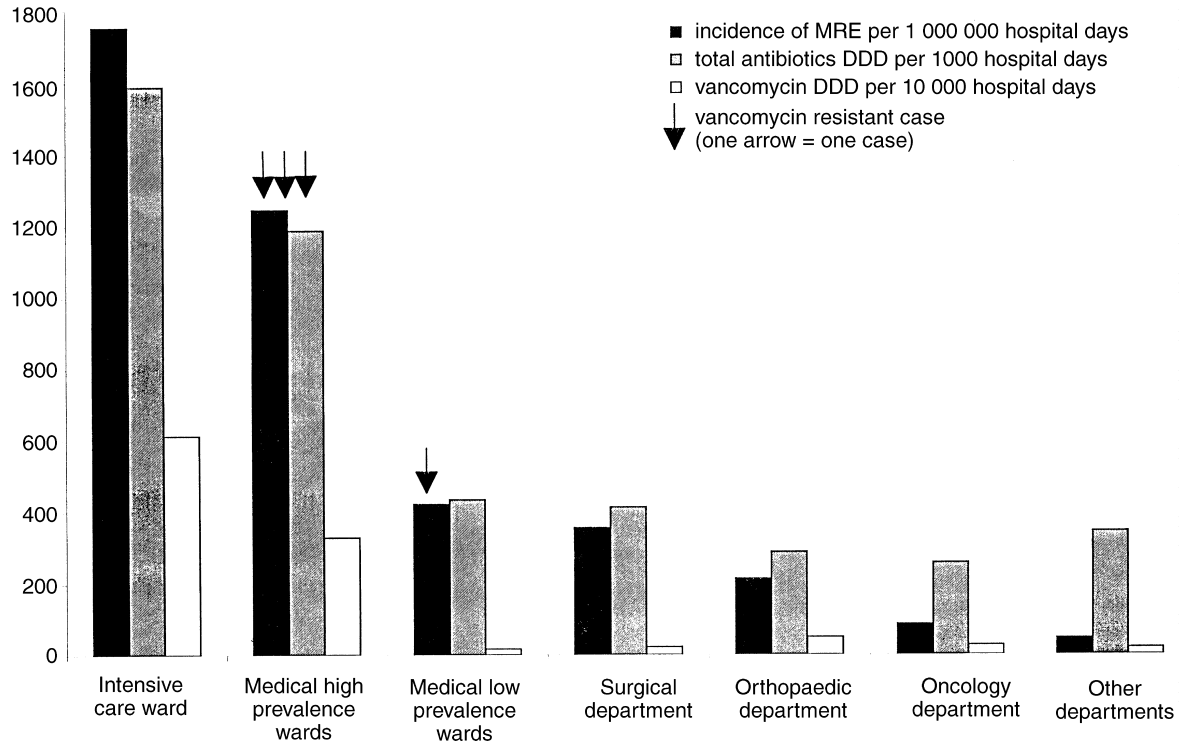

Figure 1 Mean incidence of infections caused by ampicillin-resistant *Enterococcus faecium* and prescription of antibiotics in selected departments during 1995 and 1996. Seventy-six per cent of the ARE-cases within the medical department were in three wards noted as high prevalence wards. The other three medical wards were noted as low prevalence wards.

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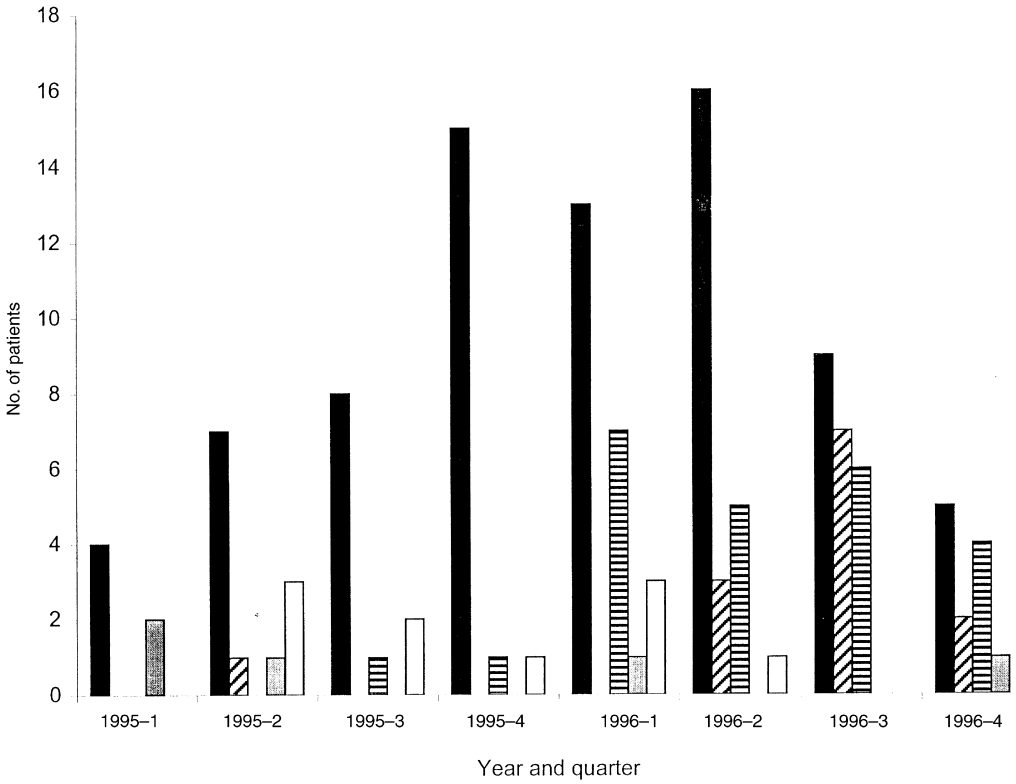

Figure 2 Distribution of patients infected by ampicillin-resistant *Enterococcus faecium* at the Haukeland University Hospital during 1995 and 1996.
■ outbreak-strain (PFGE-1); ▨ related cluster (PFGE-7); ▤ other related strains (11 different patterns); ▩ unrelated cluster (PFGE-8); □ other unrelated strains (11 different patterns).

oncology department had three cases. No case was found at the burns unit. The incidence of ARE disease was highest in the ICU with 1751 cases per 10^6 patient days, followed by the medical department with 828 cases and surgical department with 355 cases per 10^6 patient days (Figure 1). Fourteen of the 17 cases at Deaconess Hospital Haraldsplass were located in the medical department and three in the surgical department.

Microbiological characterization

One hundred and forty-five of the 149 patients (97%) were infected with *E. faecium* which were sensitive to glycopeptides, but resistant to all other antibiotics tested. The typical MIC of ampicillin was 64 mg/L, gentamicin 6 mg/L, vancomycin 1.5 mg/L, and teicoplanin 0.125 mg/L. Four of the isolates showed reduced susceptibility or resistance to vancomycin (MIC range 8–12 mg/L). The *vanB* gene was detected in all these isolates. All isolates were sensitive to teicoplanin. High-level gentamicin resistance was not detected and the outbreak strain showed a MIC of gentamicin of 6 mg/L. One hundred and forty-two isolates from 131 of the 149 patients were available for PFGE analysis (Table 4). Altogether 27 different PFGE patterns were detected, 14 related and 12 unrelated, whereof two patterns were found only in follow-up isolates. Repetitive isolates were available from 11 patients. In nine of these patients, only one pattern was detected. The distribution of PFGE patterns from primary isolates in different units is shown in Table 5. As isolates from 77 patients showed identical patterns of *Sma*1-digested DNA on PFGE, this was defined as the outbreak strain. Isolates from 38 patients had two to six band differences, and these were defined as being related to the outbreak strain according to the definitions of Tenover et al. [30]. Isolates from 16 patients showed more than seven bands different from the outbreak strain, and thus differed from the outbreak strain. Two of the four vancomycin-resistant isolates were indistinguishable from the outbreak strain, and the two others were closely related, with only two bands of difference.

Comparison of antibiotic consumption and ARE incidence at department and ward level

Since there were marked differences in incidence of ARE between departments (Figure 1) which we could not explain by the severity of disease, mean duration of hospital stay, rou-

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Table 3 Clinical and epidemiological characteristics of four patients developing nosocomial infections caused by ampicillin- and vancomycin-resistant *Enterococcus faecium* (VRE)

Patient no.	Age and gender	Underlying diseases	Type of infection	Time of first VRE-isolate	PGFE-type	Medical service and ward	Invasive devices	Surgical procedures	Possible infectious links	Total no. of days in hospital	No. of days on antibiotics before VRE infection	Antimicrobial agents prescribed before VRE infection
1	87 female	staphylococcal endocarditis	urinary tract infection	06.03.1996	2	Internal medicine ward 5	none	none	hospitalized at ward 1 10 weeks before patient 2	61	53	cloxacillin, netilmicin and pivmecillinam
2	86 female	diabetes mellitus and renal failure	urinary tract infection	23.04.1996	2	Internal medicine ward 1	none	none		4	7	co-trimoxazole
3	81 male	paraplegia	deep wound infection and osteomyelitis	06.05.1996	1	Internal medicine ward 6	intermittent urinary catheterization	none	same ward as patient 4	47	28	ciprofloxacillin and cloxacillin
4	51 female	metastasing breast cancer	urinary tract infection	04.07.1996	1	Internal medicine ward 6	central venous catheter	none		30	24	cloxacillin, netilmicin, cefotaxime and metronidazole

PGFE, pulsed field gel electrophoresis.

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Table 4 Distribution of 131 ampicillin-resistant *Enterococcus faecium* isolates according to differences in pulsed field gel electrophoresis (PFGE) patterns

PFGE pattern	Genomic relation*	No. of patients
1	Outbreak strain	77
2	Related	2
6	Related	2
7	Related	13
14	Related	3
17	Related	2
18	Related	5
19	Related	6
20	Related	1
21	Related	1
23	Related	1
25	Related	1
26	Related	1
4	Unrelated	1
5	Unrelated	1
8	Unrelated	5
9	Unrelated	1
10	Unrelated	1
11	Unrelated	1
12	Unrelated	1
13	Unrelated	1
15	Unrelated	1
16	Unrelated	1
22	Unrelated	1
27	Unrelated	1

*The genomic relatedness is defined as identical, related and unrelated to the outbreak strain according to Tenover *et al.* [30].

tines to prevent spread of ARE, variation of antibiotic consumption was examined. There appeared to be a covariation between ARE incidence and total antibiotic consumption at department level with a Pearson correlation coefficient (R) of 0.83 (95% confidence interval 0.61–0.93 and $P < 0.0001$). There was no correlation between ampicillin consumption and incidence of ARE. The consumption of vancomycin was high at the intensive care unit (613 DDD per 10^4 hospital days) and the wards in the medical department with high ARE incidence (516–1232 DDD per 10^4 hospital days) compared with all other wards (31 DDD per 10^4 hospital days). The three medical wards with highest ARE incidence had also an increase in vancomycin consumption from 390 DDD in 1993 to 891 DDD in 1996, compared with 738 DDD (1993) and 821 DDD (1996) for all other wards at the hospital. Three out of the four VRE cases were in two of these three wards.

DISCUSSION

In Scandinavia there have been few reports of multiple-drug resistant enterococci, but an increasing rate of ampicillin resistance has been reported [34]. The first VRE case was observed in June 1995 [35], and minor outbreaks have been described in Denmark [18] and Sweden [31]. Only one clinical VRE case has previously been reported in Norway [36]. However, VRE carriers have been found among poultry workers. These strains have been *vanA* type and susceptible to ampicillin [37].

In our hospital *E. faecalis* has until recently been the dominating enterococcal species in blood cultures and virtually all enterococcal isolates have been fully susceptible to ampicillin

Table 5 Distribution of patients infected with ampicillin-resistant *Enterococcus faecium:* genomically identical, related and unrelated pulsed field gel electrophoresis (PFGE) patterns

Medical service (department)	PFGE-pattern Identical	Related	Not related	Not available for PFGE	All
Haukeland Hospital					
Internal medicine	41	15	8	6	70
Surgery	10	6	4	4	24
Intensive care unit	5	1	2		8
Orthopaedic	3	4		1	8
Cardiology	4		1		5
Dermatology	3			1	4
Neurology		2			2
Oncology	2				2
Other units*	2	3		2	7
Haraldsplass Hospital	7	7		3	17
Other hospital or not hospitalized			1	1	2
Totals	77	38	16	18	149

*None of these units had more than one patient with ARE-infection.

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[38]. The reason why multiple-drug-resistant enterococci and especially VRE, are uncommon in Scandinavia and their appearance has been delayed compared with other European countries may be the restrictive use of antibiotics [39].

The different modes by which antibiotic resistant enterococci are spread may not be discovered in an outbreak situation due to lack of knowledge of the epidemiological background [40]. Previous reports on nosocomial infections caused by multiple-drug-resistant enterococci have demonstrated both a selection and a spread of different antibiotic-resistant strains and the clonal spread of certain epidemic strains [19]. As gentamicin and glycopeptide resistance have emerged, reports have shown that both clonal [14,41] and nonclonal [2,42] spread occur. It is evident that some strains have a greater potential for spread than others. As the genes regulating antimicrobial resistance, especially glycopeptide resistance, can be independently transferred [16], the epidemiological pattern may be complex. The ARE described in the present paper belong mainly to the same clonal complex judged by PFGE indicating exogenous acquisition of ARE. The strain most probably has acquired resistance genes from the environment, thus becoming vancomycin resistant.

Our patients had been hospitalized for a long time prior to ARE-infection, had high consumption of antibiotics and a high proportion of the patients had severe underlying diseases. These findings are in accordance with those in other outbreaks [5,14,43]. Many cases of multiple-drug-resistant enterococcal infections have been described in debilitated patients with prolonged hospital stay [19,44,45] who have received multidrug regimens or antimicrobial agents for a long time [15,43–46]. Use of imipenem and metronidazole have been reported to facilitate ARE [24] and the use of vancomycin [20,41,44,46,47], third generation cephalosporins [43,45], or agents with activity against anaerobic bacteria [17], have been shown to facilitate VRE colonization or infection. Failure in hospital infection control practices has also been claimed to cause the spread of VRE in hospital environments [48].

Several factors have also been suggested as modifiers of the outcome of enterococcal infection, among them ampicillin resistance [5,24]. None of the fatal cases in this study was found in patients without underlying severe and life-threatening diseases. However, larger case-control studies are needed to address such questions.

Patients with ARE-infections had been admitted to many wards at Haukeland University Hospital during the observation period and many of them had also moved between wards and departments (data not shown) and so patients in nearly every department could have been exposed. However, the majority of ARE patients at this hospital was found in three medical wards. We therefore compared some characteristics of the different units. A strong correlation was found between the incidence of ARE-infection and antibiotic consumption. There was no correlation between the consumption of ampicillin and the incidence of ampicillin resistance. Others have reported such correlation [14]. Within the Department of Internal Medicine, there were no significant differences between the mean length of hospital stay or mean age for the patients at the high prevalence wards and other wards. As far as we were able to recognize, there were no great differences in carrying out the infection control program. However, when we strengthened the efforts to adhere to the program, we observed a significant reduction in the overall incidence of ARE, which was most clearly demonstrated in the high prevalence wards.

Even though the total consumption of vancomycin was low in our hospital, three of the VRE cases appeared in wards with a relatively high consumption. The fourth VRE-patient was hospitalized in a dialysis unit where a relatively high proportion of the patients receive low doses of vancomycin. The vancomycin exposure in this ward may therefore be higher than reflected by the total vancomycin consumption. None of the VRE-patients had received glycopeptides prior to the infection. As these isolates were clonally identical or nearly identical and appeared during a period of less than 3 months, it is likely that the patients have been cross-infected by a VRE-variant of the outbreak strain, and that this strain had acquired the *vanB* gene. However, VRE have not been found by faecal surveillance (data not shown). Since this variant disappeared, it probably had less potential for spread than the outbreak strain.

Half the vancomycin consumption of the hospital was within the three wards in the medical department with the highest incidence of ARE. The whole increase in vancomycin consumption at the hospital during the period 1993–96 was attributable to these wards. It seems that vancomycin consumption at the ward level, was an important reason for the emergence of VRE

In conclusion, the consumption of antibiotics appears to be an indicator for high incidence of ARE. The outbreak strain developed vancomycin resistance in those wards with the highest vancomycin consumption.

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