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VANCOMYCIN-RESISTANT ENTEROCOCCUS FAECIUM INFECTIONS ON PEDIATRIC WARDS

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Nosocomial infections with vancomycin-resistant enterococci (VRE) have been reported with increasing frequency in recent years, and are associated with an increase in mortality. Isolates of VRE were first detected in our hospital between September 2006 and January 2007. In this study, we analyzed the phenotypic and genotypic characteristics underlying that resistance and clonal relationships amongst VRE isolated from six patients at pediatric wards. All isolates were identified as Enterococcus faecium and showed resistance to both vancomycin and teicoplanin by disk diffusion and E-test methods. The resistance patterns for other antimicrobials were similar, indicating that the isolates might belong to the same clone. The genes responsible for resistance were identified in the isolates by multiplex polymerase chain reaction (PCR). Four isolates from patients on the same pediatric ward showed the same random amplification of polymorphic DNA (RAPD) pattern, suggesting clonal dissemination of a single strain.

Descriptors: VANCOMYCIN RESISTANCE; ENTEROCOCCUS FAECIUM; RANDOM AMPLIFIED POLYMORPHIC DNA TECHNIQUE (RAPD); PEDIATRICS

INTRODUCTION

Enterococcus, which is part of the normal human gastrointestinal system flora, is increasingly common in nosocomial infections, and the strains are becoming increasingly resistant to antibiotics (1). Although more than a dozen species of enterococci exist, *Enterococcus (E.) faecalis* (80%-90%) and *E. faecium* (5%-15%) are responsible for the most infections in human (2, 3).

Glycopeptide resistance among enterococcal species is of great importance in medical practice because of the limited number of available therapeutic options and the spread of resistance to other species (2, 4). The first strains of vancomycin-resistant enterococci (VRE) were reported in 1988 in France and the United Kingdom. In subsequent years, this phenotype arose in other European countries and in the United States as a causative pathogen of nosocomial infection epidemics (1, 5). Ten years after the first isolate in the world has been announced, the first isolate in Turkey was recovered at Akdeniz University Hospital (6). In the United States, according to the National Nosocomial Infection Surveillance (NNIS) data collected between 1989 and 1993, the percentage of enterococcal isolates exhibiting vancomycin resistance increased from 0.3% to 7.9% in all infections, whilst the percentage of such infections in intensive care units (ICUs) increased from 0.4% to 13.6% (7). In the year 2000, the highest VRE ratio was reported to be 26.3% at an ICU in the United States (8). Although the rate of VRE has never been that high in Turkey, it is still a significant threat in hospital settings.

Six different glycopeptide resistance phenotypes (VanA, VanB, VanC, VanD, VanE and VanG) have been defined for enterococci. The most frequent phenotypes are VanA and VanB; VanA is described as inducible with a high level of resistance to both vancomycin and teicoplanin, whereas VanB exhibits moderate to high resistance to vancomycin with teicoplanin susceptibility (9, 10).

In this study, six strains of VRE isolated from six different pediatric patients between September 2006 and January 2007 were investigated for their phenotypic and genotypic resistance characteristics and clonal relationships amongst them.

MATERIALS AND METHODS

Bacterial strains and identification

This study was carried out between September 2006 and January 2007 at Şişli Etfal Training Hospital. Six strains of VRE isolated from pediatric ward patients were included (Table 1). Only one isolate *per* patient was taken into account even when the isolation site was different, as in

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Table 1. *Patient characteristics and antibiotic susceptibility of each isolate*
Tablica 1. *Karakteristike bolesnika i osjetljivost svakog izolata na antibiotik*

Patient no./ Bolesnik	Age/ Dob	Underlying disease(s)/ Osnovne bolesti	Previous antibiotic (within 3 months)/ Uzimani antibiotici (u zadnja 3 mjeseca)	Ward/ Odjel	Isolate/ Izolat	Date of isolation (dd/mm/yyyy)/ Datum izolacije (dd/mm/gggg)	Source/ Izvor	Antimicrobial susceptibility Antimikrobna osjetljivost									
								Amp	P	E	Te	Lev	Cl	Lzd	Rif	G120[a]	S300[a]
1	3 months/ mjeseca	Posterior urinary valve/ Stražnja urinarna valvula Kidney insufficiency/ Zatajenje bubrega	AMX, AMP, TEC	Pediatric Infectious Diseases/ Dječje zarazne bolesti	1	04.09.2006.	Wound/ Rana	R	R	R	S	R	S	S	R	R	S
2	14 months/ mjeseci	Hydrocephalus/ Hidrocefalus Shunt infection/ Infekcija šanta	CRO, TEC, CAZ, MEM, Amphotericin B	Pediatric Infectious Diseases/ Dječje zarazne bolesti	1	17.10.2006.	CSF/ CSL	R	R	R	S	S	S	S	R	S	R
3	6 months/ mjeseci	Meningomyelocele/ Meningomielokela Shunt infection/ Infekcija šanta	VA, CRO, SCF, MEM,	Pediatric Infectious Diseases/ Dječje zarazne bolesti	1	18.12.2006.	CSF/ CSL	R	R	R	S	S	S	S	R	S	R
4	6 months/ mjeseci	Hydrocephalus/ Hidrocefalus Shunt infection/ Infekcija šanta	IMP,TEC, MEM, Cl, CIP	Pediatric Infectious Diseases/ Dječje zarazne bolesti	1	22.12.2006.	CSF/ CSL	R	R	R	S	S	S	S	R	S	R
					2	26.12.2006.	CSF/ CSL	R	R	R	S	S	S	S	R	S	R
5	4 months/ mjeseca	Varicella	CRO, Acyclovir	Pediatric Infectious Diseases/ Dječje zarazne bolesti	1	29.12.2006.	Urine/ Urin	R	R	R	S	S	S	S	R	S	R
6	15 days/ dana	Hypoglycemia/ Hipoglikemija Intestinal perforation/ Perforacija crijeva	AMP, MEM NET, AK, ODZ	Pediatric Surgery/ Dječja kirurgija	1	08.01.2007.	Wound/ Rana	R	R	R	S	S	S	S	R	R	R
					2	09.01.2007.	PF/ Pentonejska tekućina	R	R	R	S	S	S	S	R	R	R

S, Susceptible; *R*, Resistant; *AMX*, Amoxicillin; *AMP*, Ampicillin; *TEC*, Teicoplanin; *CRO*, Ceftriaxone; *CAZ*, Ceftazidime; *MEM*, Meropenem; *VA*, Vancomycin; *SCF*, Cefoperazone-sulbactam; I*MP*, Imipenem; *CIP*, Ciprofloxacin; *Cl*, Chloramphenicol; *NET*, Netilmicin; *AK*, Amikacin; *ODZ*, Ornidazole; *P*, Penicillin; *E*, Erythromycin; *T*, Tetracycline; *Lev*, Levofloxacin; *LZD*, Linezolid; *Rif*, Rifampin; *G120*, Gentamicin; *S300*, Streptomycin; *CSF*, Cerebrospinal Fluid; *PF*, Peritoneal Fluid; [a], High-Level Aminoglycoside

patient #6, in whom VRE were isolated simultaneously from a wound and peritoneal fluid samples. The specimen distribution of strains from the other five patients was as follows: one wound, three cerebrospinal fluid (CSF) samples and one urine sample. All patients were staying at the pediatric ward of infectious diseases, except for patient #6, who was at the pediatric surgery ward.

Identification at the genus level was achieved through conventional methods: Gram staining, testing for catalase production and hemolysis on sheep blood agar, testing for the presence of esculine hydrolysis and pyrolidonyl arylamidase (PYR), and testing for the ability to grow on 6.5% NaCl agar. The BD BBL Crystal Gram Positive ID System (Becton Dickinson and Co., Franklin Lakes, NJ, USA) was used for identification at the species level.

Antimicrobial susceptibility testing and MIC determination

In vitro activity against various antimicrobials was measured by the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) criteria for vancomycin (30 μg), teicoplanin (30 μg), penicillin (10 U), ampicillin (10 μg), erythromycin (15 μg), chloramphenicol (30 μg), tetracycline (30 μg), rifampin (5 μg), linezolid (30 μg), streptomycin (300 μg) and gentamicin (120 μg) (Oxoid Ltd., Hampshire, UK) (11).

The minimum inhibitory concentrations (MIC) for vancomycin and teicoplanin were determined by the E-test method (AB Biodisk, Solna, Sweden). Bacterial suspension with a turbidity level

equivalent to McFarland standard #2 was spread over the brain heart infusion agar. E-test strips were then placed onto the inoculated plates, which were incubated at 35°C for 24 h before evaluation according to CLSI MIC values (11). The *E. faecalis* ATCC 29212 and ATCC 51299 strains were used as controls.

Beta lactamase production by the enterococcal strains was monitored by the BBL DrySlide Nitrocefin test (Becton Dickinson and Co.).

Polymerase chain reaction (PCR)

DNA was extracted using a High Pure PCR Template Preparation Kit (Roche, Mannheim, Germany). Amplification of the VanA, VanB and VanC resistance genes was achieved by multiplex PCR as described previously (12). Ten microliters of DNA were added to a master mix containing 64.5 µL of distilled water, 10 µL of 10× PCR buffer, 6 µL of 25 mM $MgCl_2$, 2 µL of 10 mM dNTP mixture (dATP, dCTP, dGTP and dTTP), 50 pmol of each primer and 0.5 U of Taq DNA polymerase. The amplification procedure was as follows: 94˚C for 5 min followed by 30 cycles of 94˚C for 30 s, 58˚C for 30 s and 72˚C for 30 s, with final extension at 72˚C for 10 min. The products were run on 1.8% agarose gels with 0.5× TBE (Sigma, St. Louis, MO, USA), then stained with ethidium bromide. The resulting bands were compared to those from a standard mix (Φ174 HaeIII) under UV light.

Random amplification of polymorphic DNA (RAPD)-PCR

Clonal relationships amongst the isolates were investigated by RAPD-PCR using ERIC-2 primers (13). Five microliters of DNA were added to a master mix containing 29.3 µL of distilled water, 5 µL of 10× PCR buffer, 5 µL of 25 mM $MgCl_2$, 5 µL of 2 mM dNTP mixture (dATP, dCTP, dGTP and dTTP), 50 pmol of primer, 1 U of Taq DNA polymerase and 0.2 µL of Triton X-100. The amplification procedure was as follows: 94˚C for 3 min followed by 40 cycles at 94˚C for 1 min, 55˚C for 1 min and 72˚C for 2 min, with final extension at 72˚C for 5 min. The products were run on 1% agarose gels with 0.5× TBE (Sigma), then stained with ethidium bromide. The resulting bands were compared to those from a standard mix (Φ174 HaeIII) under UV light.

RESULTS

The first strain was isolated from a wound at pediatric department of infectious diseases at our hospital. Additional strains of VRE were subsequently isolated from five other patients over a 3-month period. All isolates were identified as *E. faecium* by conventional methods and a Crystal GP ID System panel. The strains were found to be resistant to vancomycin and teicoplanin by disk diffusion testing, and the results were confirmed by E-test. The MIC values for vancomycin and teicoplanin in all cases exceeded 256 µg/mL, except for isolates #1 and #2, which had reduced MIC values for teicoplanin (128 and 64 µg/mL, respectively).

The characteristics of study patients, including age, underlying diseases, history of antibiotic therapy, specimen types and susceptibility patterns of the isolates for other antimicrobials are summarized in Table 1. All isolates were found to be resistant to ampicillin, penicillin, erythromycin and rifampin, and susceptible to linezolid and tetracycline.

Multiplex PCR analysis of the strains produced a 1030-bp product, which is concordant with the VanA genotype.

RAPD-PCR analysis of the strains showed three different banding patterns (Figure 1). Lines 3, 4, 6 and 7 represent the strains from four patients (# 2, 3, 4, 5) from pediatric ward of infectious diseases, showing the same banding pattern (pattern A). Therefore, these strains were interpreted as being clonally related to one another. The other two banding patterns were detected in isolates from patient #1 (line 5, pattern B) and #6 (line 8, pattern C), who were hospitalized on the pediatric ward of infectious diseases and pediatric surgery ward, respectively. Although patient #1 was hospitalized on the same ward with the patients who were infected with the same clone, the infecting strain was found to be clonally unrelated to the others.

DISCUSSION

The first vancomycin-resistant enterococcus was isolated in our hospital in 2006. In the 3 months following that isolation, five additional cases of infection involving VRE were identified, and all of the patients except for one were staying on the same ward. We characterized the glycopeptide resistance phenotype of each strain and clonal relationships amongst them.

Figure 1. *RAPD-PCR patterns of vancomycin-resistant enterococci. Line 1, molecular size marker (Φ174 HaeIII); line 2, negative control; lines 3-8, six strains of VRE. Lines 3, 4, 6 and 7 show pattern A; line 5 shows pattern B; line 8 shows pattern C.*
Slika 1. *RAPD-PCR obrasci enterokoka otpornih na vankomicin. Linija 1, marker molekularne veličine (Φ174 HaeIII) linija 2, negativna kontrola linije 3-8, šest sojeva VRE. Linije 3, 4, 6 i 7 pokazuju uzorak; linija 5 pokazuje uzorak B, linija 8 pokazuje uzorak C.*

Six different glycopeptide resistance phenotypes (VanA-D, VanF and VanG) have been described according to the presence of specific ligase enzymes, the inducibility of resistance and transferability to other bacteria (9). VanA is the most common phenotype encountered in infections (1, 3). In this study, all of the strains detected were *E. faecium* harboring the Van A gene. This result is compatible with those from other studies conducted in Turkey (1, 13-16).

Enterococci are most frequently encountered in relation to urinary tract infections, but they can also cause bacteremia, endocarditis, and rarely meningitis. Although the Enterococcal meningitis ratio is about 0.3%-4% in bacterial meningitis cases, it is a severe infection associated with a high mortality rate (30%-33%) (17, 18). Anatomic defects in the central nervous system and a history of corrective neurosurgery are predisposing factors for enterococcal meningitis (17). Concordant with this information, three of the pediatric cases included in this study, two with hydrocephalus and one with meningomyelocele, had undergone shunt operations and the placed shunts had become infected with VRE.

Therapy with broad-spectrum cephalosporins, glycopeptides and antianaerobic antibiotics increases colonization and the risk of infection with VRE (2, 3, 19). It has been reported that when the usage of broad-spectrum cephalosporins was

limited to a single healthcare center, VRE colonization and the rate of infection decreased over time (20). Multivariate analysis, which was performed at the Hospital for Sick Children in Toronto, also identified cephalosporin use as a major risk factor for VRE colonization (21). In our study, all of the patients were treated with at least one of these antimicrobial agents; in addition, two of them were treated with drugs from all three antimicrobial classes.

In severe enteroccocal infections, combination therapy with penicillin/ampicillin or vancomycin and aminoglycoside is warranted; however, vancomycin is no longer an option in infections with VRE. Unfortunately, there are few therapeutic alternatives in cases of ampicillin and high-level aminoglycoside resistance (2). A multicenter study performed in Europe placed Turkey on the second place in terms of the prevalence of high-level gentamicin-resistant enterococci (48%) (22). In another Turkish study, the high-level gentamicin and streptomycin resistance rates were found to be 22% and 36%, respectively (4). Although the degree of high-level streptomycin resistance was more profound in our study, this could have been due to clonal dissemination of the same strain.

Linezolid is an oxazolidone used to treat VRE infections. It acts bacteriostatic against *Enterococcus* by inhibiting protein synthesis (3). Although it is a newly developed drug, strains of enterococci resistant to linezolid have been reported (23). Fortunately, none of the VRE in this study was found to be resistant to linezolid; in addition, no beta lactamase production was detected, in accordance with the results of other studies in Turkey (1, 4, 14).

Finally, clonal relationships amongst the strains was investigated by RAPD-PCR. Four of the isolates showed the same RAPD-PCR pattern and were therefore interpreted as being clonally related. These strains were isolated from patients hospitalized on the same ward. Enterococci are able to survive in hospital environment and on the hands of healthcare personnel for a long time. Although the dissemination route from one patient to another could not be elucidated, rapid control of infection was achieved by the early detection and application of strict infection control measures including isolation of the patients; education of the staff and patients about hygiene, especially hand-washing procedures; and cleaning of the ward environment (3, 16, 21). Since then, we have had a few sporadic cases, but we have not had a new outbreak of VRE. The prudent use of vancomycin, the education of hospital staff, the use of gloves and gowns, the early and true detection of VRE in the laboratory, as well as the implementation of isolation precautions for VRE-colonized patients are keys for dealing with hospital infections with VRE (24, 25).

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S a ž e t a k

INFEKCIJE NA PEDIJATRIJSKIM ODJELIMA UZROKOVANE ENTEROCOCCUSOM FAECIUMOM OTPORNIM NA VANKOMICIN

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U posljednjih nekoliko godina izvijestilo se povećanje bolničkih infekcija uzrokovanih vankomicin-rezistentnim enterokokima (VRE), što se povezuje s povećanjem smrtnosti. VRE izolati otkriveni su prvi put u našoj bolnici između rujna 2006. i siječnja 2007. godine. U ovoj studiji analizirali smo fenotipsku i genotipsku podlogu otpornosti izolata i klonski odnos između VRE izolata šestero bolesnika koji su ležali na pedijatrijskim odjelima. Svi izolati bili su identificirani kao Enterococcus faecium i metodama disk difuzije i E-testiranja pokazali su istodobnu otpornost na vankomicin i teikoplanin. Izolati su bili slični i u otpornosti na druge antibiotike, što je upućivalo na to da izolati možda pripadaju istom klonu. Geni odgovorni za otpornost na vankomicin identificirani su u izolatima putem multipleks PCR-a. Četiri izolata uzeta od bolesnika u istom pedijatrijskom odjelu pokazala su isti profil metodom slučajne amplifikacije uzoraka polimorfne DNA (RAPD), sugerirajući klonsko širenje jedne loze.

Deskriptori: NEOSJETLJIVOST NA VANCOMYCIN; ENTEROCOCCUS FAECIUM; RAPD-PCR; PEDIJATRIJA

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