Prevalence and risk factors associated with vancomycin-resistant enterococci colonization

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Abstract
Enterococci have been recognized as clinically important pathogen in high-risk population of hospitalized patients. The aims of this study were to detect the prevalence of intestinal vancomycin-resistant enterococci (VRE) colonization among patients in the high-risk departments and the risk factors related to resistance in hospitalized patients in where VRE had been rarely isolated previously in Tepecik Educational and Research Hospital, Izmir, Turkey. Following the first isolation of VRE in two patient in intensive care unit (ICU) and neonatal ICU in the same day, we carried out a point prevalence culture survey. Rectal swabs were obtained from patients. For comparison, 30 control patients hospitalized in internal medicine service were also analyzed. Ninety-three patients were investigated. Eighteen patients (19.3%) were found to be VRE carriers, whereas none of the control group patients had VRE. Thirteen strains were identified as Enterococcus faecium, four were Enterococcus gallinorum, and one was Enterococcus casseliflavus. Nine of E. faecium strains were resistant to vancomycin; the remainders were intermediate resistance to vancomycin and all of them sensitive to teicoplanin. Lengths of hospital stay, age and low birth weight for newborn were significantly associated with VRE colonization. A high prevalence of colonization by VRE was found at our ICUs, emphazing the importance of length stay in the ICU and low birth weight for newborn as a risk factor for colonization. VRE colonization must be monitored and risk factors should be determined, because of establish prevention and control measures.

Keywords*: Vancomycin-resistant enterococci (VRE) – Prevalence – Intestinal colonization.*

INTRODUCTION

Although enterococci are normal inhabitants of the gastrointestinal tract, at present leading cause of significant nosocomial infections. Enterococci are formidable pathogens because of their resistance to antimicrobial agents. This resistance can be intrinsic (low-level resistance to penicillin, cephalosporins, low-level resistant to aminoglycosides, clindamycin, trimethoprim-sulfamethoxazole) or acquired (glycopeptides, high concentration of aminoglycosides, tetracycline, chloramphenicol). Vancomycin-resistant enterococci (VRE) were first isolated in 1986 in Europe[1] *and in 1987 in USA*[2]*, since then, it has increasingly been detected throughout the world. According to data from*

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National Infections Surveillance System, enterococci are fourth-leading cause of nosocomial infections, third among bacteremia and second among urinary tract infections in the USA[3]. In the United States, The Centers for Disease Control and Prevention (CDC) recorded a 20-fold increase in the incidence of VRE associated with nosocomial infection in intensive care units between 1989 and 1993[4]. Enterococci are the first bacteria to acquire vancomycin resistance. Increasing of VRE poses several challenges, including firstly and the greatest threat posed by vancomycin-resistant enterococci is the potential to transfer their resistance genes to more pathogenic Gram-positive bacteria, such as methicillin resistant Staphylococcus aureus, which could produce truly frightening pathogens. Since the VanA and VanB vancomycin-resistant determinants are transferable, glycopeptides resistance might be passed on to other pathogens[5,6]. Secondly, treatments options for infections with VRE are limited and rely on the use of older agents or new drugs that have not been evaluated. In addition, the high cost of treatment of VRE is an important issue when healthcare resources are scare[7].

The main source of these infections is usually fecal carriage of the microorganism. Although colonization of VRE is the first step toward infection, a low infection rate was observed. VRE colonization leads to infection depend on the health status of patient. Whereas immunocompetent patients colonized with VRE are at low risk for infection, weakened hosts (patient with haematologic disorders, transplant recipients, or severely ill patients) or prolonged hospitalization have an increased likelihood of developing infection following colonization[5]. CDC to publish guidelines for control of this pathogen in hospital environments; methods were suggested for the surveillance of colonization in the gastrointestinal tract, a major site of initial colonization[8].

Although VRE isolates have been reported previously in Turkey hospitals, there had been very rare isolates identified from our hospital[9-13]. Following the first isolation of VRE in two patient in surgical intensive care unit (ICU) and neonatal ICU in the same day, we carried out a point prevalence culture survey for investigate the prevalence of fecal carriage of VRE among patients in the high-risk departments. We also recorded epidemiological data in order to determine which patients are at high risk for VRE colonization.

MATERIAL AND METHODS

Patients

Tepecik Education and Research Hospital is a 1000-bed teaching hospital in Izmir. The clinical and epidemiological features of two patients who were VRE were isolated in blood and urine cultures in the same day were recorded (Table 1). The first patient was a 75-year-old man who had cerebrovascular disease and epidural hematoma. He was hospitalized to surgical ward. After his condition got worse because of hematoma, he was transferred to surgical ICU. VRE was identified from his urine in his last week in the ICU. Urinary tract infection was decided and he was treated by linezolid. Nevertheless, he died because of respiratory arrest. The second patient was a five-days-old baby admitted to hospital due to jaundice. His serum bilirubin level was found elevated and exchange transfusion was planned. After umbilical catheterization for exchange transfusion, blood culture was obtained from catheter. VRE was identified from catheter-blood culture before exchange whereas peripheral blood culture was negative at same time. His condition was good. Blood culture was also negative after exchange transfusion. All septic screen test was found normal. The existence of VRE in his initial blood culture was explained as skin contamination. The patient was discharged in healthy condition. Also, all the two patients had rectal colonization with VRE.

The prevalence studies on intestinal colonization with VRE among patients in the high risk departments (defined as areas where critically ill patients were treated and invasive procedures were performed) were sampled. Thirty-four patients from neonatal intensive care unit (NICU), 49 patients from intensive care unit (surgical and medicine intensive care), five patients from pediatric intensive care (P-ICU), and five patients from pediatric oncology service were examined. Ninety-three patients hospitalized for at least two days were enrolled in this investigation. For comparison, 30 control patients hospitalized in internal medicine

Table 1. *Demographic characteristics of patients who were VRE were isolated from cultures.*

Patient	Sex	Age	Unit	Site of infections	Species	VRE type	Outcome
1	M	75 year	ICU	Urine	E.faecium	VanB	Died
2	M	5 day	NICU	Blood	E.faecium	VanB	Discharged

Table 2. *Properties of 18 vancomycin-resistant enterococci strains.*

Strain	Species	Ward[1]	Vancomycin MIC (μg/mL)	S/I/R	Teicoplanin MIC (μg/mL)	S/I/R	Linezolid MIC (μg/mL)	S/I/R	HLGR	HLSR	Phenotype
1	E.faecium	NICU	32	R	0.5	S	0.75	S	<500	<500	VanB
3	E.faecium	NICU	48	R	1	S	0.50	S	>1000	>2000	VanB
4	E.faecium	NICU	16	I	1	S	1	S	>1000	>2000	VanB
5	E.gallinorum	NICU	8	I	1	S	1	S	>1000	>2000	VanC
12	E.faecium	NICU	64	R	1	S	1	S	>1000	>2000	VanB
18	E.faecium	NICU	32	R	0.5	S	0.50	S	>1000	>2000	VanB
21	E.faecium	NICU	16	I	0.75	S	0.25	S	>1000	>2000	VanB
33	E.gallinorum	NICU	8	I	0.38	S	1	S	<500	<500	VanC
37	E.faecium	ICU	48	R	0.75	S	1	S	>1000	>2000	VanB
39	E.gallinorum	ICU	8	I	0.75	S	1	S	<500	<500	VanC
49	E.faecium	ICU	64	R	0.38	S	2	S	>1000	>2000	VanB
50	E.faecium	ICU	96	R	0.75	S	0.75	S	>1000	>2000	VanB
54	E.faecium	ICU	48	R	0.38	S	0.50	S	>1000	>2000	VanB
62	E.faecium	ICU	64	R	0.25	S	1.25	S	<500	<500	VanB
64	E.faecium	ICU	8	I	0.5	S	0.50	S	>1000	>2000	VanB
82	E.gallinorum	ICU	8	I	0.38	S	0.75	S	>1000	>2000	VanC
85	E.faecium	P-ICU	16	I	0.5	S	0.50	S	>1000	>2000	VanB
86	E.casseliflavus	P-ICU	8	I	1	S	0.25	S	<500	>2000	VanC

Note: NICU= Neonatal intensive care unit; ICU= medical and surgical intensive care unit; P-ICU= Pediatric intensive care unit; S/I/R= sensitive/ intermediate sensitive/ resistant; HLGR= high-level gentamicin resistant; HLSR= high-level streptomycin resistant.

service for hypertension or diabetes mellitus were also analyzed. A rectal swab (LabService, Italy) was taken from all patients and was transported to the microbiology laboratory.

Identification and antimicrobial susceptibility tests

All of the samples were inoculated onto brain-heart infusion agars containing 6 μg/ml vancomycin (Becton Dickinson, BBL Sparks, USA) and incubated aerobically at 35°C for 48 h. One or more colonies growing on agar with a dark brown halo and resembling enterococci morphologically were identified initially by Gram's stain, catalase test, growth in 6.5% NaCl broth, and bile esculine hydrolysis. All isolates were also identified for species level by the VITEK 2 (bioMérieux, Marcy, I'Etoile, France) automated system. Vancomycin, teicoplanin and linezolid resistance were tested by Etest (AB Biodisk, Sweden) according to the instructions of the manufacturer with Enterococcus faecalis ATCC 29212 as reference strains. High-level resistance to aminoglycosides was determined by growth of isolates on four Muller-Hinton agars containing 500 and 2000 μg of streptomycin per ml and 500 and 1000 μg of gentamicin per mL, respectively. The results were interpreted according to the standards of the Clinical and Laboratory Standards Institute[14]. For vancomycin, resistance was an MIC of ≥32 μg/mL, and susceptibility was an MIC of ≤4; for teicoplanin resistance was an MIC of ≥32 μg/mL, susceptibility was an MIC of ≤8 μg/mL; for linezolid resistance was an MIC of ≥8 μg/mL, susceptibility was an MIC of ≤2.

Epidemiological investigation

For each patient's sex, age, hospital ward, days of hospitalization, antibiotic treatments, surgical operation, length of hospitalization, catheterization (central venous, bladder), underlying disease (diabetes mellitus, heart disease, hypertension, malignity, and neurological disorders) were enrolled. Statistical analysis was performed using the SPSS software (Version 10.0; SPSS Inc., Chicago). Continuous data was analyzed using the Student's t test. Categorical data was assessed using Pearson's χ^2 test. The standard significance level, $p<0.05$, was used, and all tests of statistical significance were two-tailed.

RESULTS

Enterococcus spp. was identified in 29 (31.1%) patients. Eighteen (19.3%) of them were VRE: Eight patients (8.6%) in NICU, eight patients (8.6%) in ICU and two patients (2.1%) in P-ICU. No VRE strain was isolated in pediatric oncology service. None of the patients was presented with infection. Thirteen of 18 strains were identified as E. faecium (72.2%), four were identified as E. gallinorum (22.2%), and one was identified as E. casseliflavus (5.5%). None of the control group patients had VRE on rectal swab culture. VRE was significantly more common in the high-risk patients than in the control group patients ($p<0.05$).

Table 2 provides the results of in vitro susceptibility tests. Nine of E. faecium strains were resistant to vancomycin (MICs>32 μg/mL), the remainder were intermediate resistance to vancomycin (MICs from 8-16 μg/mL) and all of them sensitive to teicoplanin (MICs from 0.25 to 1 μg/mL, VanB phenotype). All E. gallinorum and E. casseliflavus strains intermediate resistance to vancomycin (MICs, 8 μg/mL) and sensitive to teicoplanin (MICs from 0.25 to 1 μg/mL, VanC

Table 3. *Risk factor analysis for intestinal colonization with and without vancomycin-resistant enterococci.*

Variable	*No (%) of VRE - positive (N: 18)*	*No (%) of VRE - negative (N: 75)*	*P value*
Mean age			
Newborn (day)	*8.6 ± 5.2*	*23.9 ± 20*	*0.04*
Adults (year)	*48.5 ± 25.6*	*47.7 ± 25.8*	*NS*
Sex			
Male	*10 (55.5)*	*42 (56)*	*NS*
Female	*8 (44.5)*	*33 (44)*	*NS*
Ward[1]			
NICU	*8 (44.4)*	*26 (34.6)*	*NS*
ICU	*8 (44.4)*	*41 (54.6)*	*NS*
P-ICU	*2 (11.1)*	*3 (4)*	*NS*
P-ONK	*0*	*5 (6.6)*	*NS*
Length of stay (days)	*28.7 ± 28.5*	*13.6 ± 18.9*	*0.007*
Antibiotic use	*14 (77.7)*	*43 (57.3)*	*NS*
Catheter			
Central venous	*13 (72.2)*	*50 (66.6)*	*NS*
Bladder	*7 (38.8)*	*34 (45.3)*	*NS*
Surgical operation	*5 (27.7)*	*13 (17.3)*	*NS*
Underlying disease	*6 (33.3)*	*23 (30.6)*	*NS*
*Low birth weight (n: 11)**	*7 (87.5)*	*4 (15.3)*	*0.03*

*Notes: NICU= Neonatal intensive care unit; ICU= Medical and surgical intensive care unit; P-ICU= Pediatrici ntensive care unit; P-ONK= Pediatric oncology; NS= Non-significant;*Thirty-four neonates were screened for VRE colonization. eight of 34 neonates were found VRE-positive; seven of eight VRE-positive and four of 26 VRE-negative neonates were found low birth weight.*

phenotype). Thirteen of 18 strains (72.2%) were high-level gentamicin resistant (HLGR), 14 of 18 strains (77.7%) were high-level streptomycin resistant (HLSR). Linezolid was found susceptible to all isolates.

Table 3 summarizes the epidemiological data and risk factors of patients with and without VRE. Length of hospital stay (28.7 days versus 13.6 days, p=0.007), age for newborn (8.6 days versus 23.9 days, p=0.04) and low birth weight (7 versus 4, p=0.03) were significantly associated with VRE colonization. Sex, ward, antibiotic use, catheterization, surgical operation, and underlying disease were not associated with an increasing risk of VRE colonization.

DISCUSSION

VRE are currently one of the principal pathogens that cause hospital infections, mostly due to their particular features; long-lasting colonization of the gastrointestinal tract, difficult decolonization, can survive in the environment for prolonged periods (>1 week), can be passed from one patient to another by health care workers, facilitating their spread in hospital[5,15]. Recently, VRE infected/colonized patients were starting reported and the incidence of VRE has continued to increase in our country[12,13]. This study documents the prevalence of intestinal colonization among patients from our hospital of high risk department. VRE colonization was found 19.3% of hospitalized patients. Although this high rate, some authors did not found VRE colonization in our country[10, 11, 16]. These rates are among the highest reported in Europe. Fecal colonization of VRE was found that 1.4% of hospitalized patients in The Netherlands[17], 3.5% in Belgium[18], 8% in Brazil[19]. The authors hypothesized that this was related to the limited use of glycopeptide antibiotics, the absence of cross-contamination, structured surveillance program. The prevalence rate was found in this study seems closest to the levels observed in an Israeli hospital that VRE colonization of gastrointestinal tract was revealed that 14.7%[20]. Cooper et al.[21], established 19.1% of VRE colonized patients in an Australian hospital by point-prevalence survey. In contrast, in several studies, the prevalence of VRE is high: 30.5% in Greece[22], 32.6% in Brazil.[15]

In this study, 13 (72.2%) and 14 of (77.7%) 18 VRE were found HLGR and HLSR, respectively. These high rates correlate with European prevalence study[23]. According to that study Turkey was the one of the countries with the highest prevalence of high-level gentamicin resistant enterococci. Commonly and also inappropriate usage can cause this high rate.

Treatment options and effective antimicrobial agents for VRE are often limited. Linezolid is the most active compound against these multiresistant enterococci[24]. Although linezolid resistance became in the world, it is the most appropriate alternative today[25]. In this study, linezolid was found susceptible to all isolates.

There were many risk factors associated with colonization with VRE, including length of hospital stay, ICU stay, underlying disease such as renal failure, neutropenia, malignity, immunosuppression, prolonged use of antibiotics, in particular treatment with certain antibiotics (e.g., vancomycin, third-generation cephalosporin, metronidazole), proximity to colonized patients[15,18,19,22]. Enterococci have been recognized as clinically important pathogens in high-risk populations of hospitalized patients. Risk factors for VRE infections have varied across different studies. Furtada et al.[15], found only significant factor was length of hospital stay. Gordts et al.[18], showed hospitalization, duration of stay in the hematology department and prior vancomycin treatment were associated with VRE colonization. In this research, we found long-term hospitalization was significantly associated with VRE colonization. Enteococci can survive in the hospital environment long time and passed from patient to patient by hands easy. This may explain why the long-term hospitalization was a risk factor for VRE colonization. Also, patients were exposure to more equipment and antibiotic when they stay long time in hospital. Yuce et al.[26], showed that low birth weight and long term antibiotic therapy was associated with intestinal colonization. Nevertheless, Toledano et al.[20], was not found VRE colonization in NICU. The authors explain this finding may be physical isolation, intrinsic differences in the bowel milieu, and lack of exposure to food or other environmental sources. Prematurity and low birth weights are bringing many health problems. In this study, VRE colonization was found eight of the 34 patients (23.5%) in the NICU. Age and low birth

weight were found significantly associated with VRE colonization for newborns. The small number of VRE isolate limited our ability to evaluate risk factor of neonates in this study. Administration of vancomycin or other antibiotics such as cephalosporin is frequently reported as a risk factor for VRE infection or colonization[5,18,22]. However, in this study antibiotic administration did not appear to influence selection for VRE colonization. Furtada et al.[15] also failed to find antibiotic administration to be reliable cause of the presence of VRE strains in fecal flora.

E. faecalis and E. faecium are the predominant enteroccocal species identified in clinical microbiology laboratories. Historically, these laboratories report that 80 to 90% of enterococci are E. faecalis, whereas E. faecium accounts for 5 to 10% of enterococci[5,27].

More recently, the SENTRY Antimicrobial Resistance Surveillance Program reported that in 2003, E. faecium accounted for 91% of clinical enteroccocal infections in North America and Europe[25]. According to European prevalence study, most VanA and VanB VRE identified as E. faecium[23]. Treitman et al.[27], found that E. faecium has been a significant increase in the numbers of VRE over a 10 year period and nearly three-quarters of E. faecium were vancomycin-resistant at their medical center. These findings are of potential concern, as E. faecium is more commonly associated with vancomycin resistance than are the other enterococci. In this study, the majority of the clinical isolates were E. faecium (72.2%), while E. gallinorum accounted for 22.2% and E. casseliflavus accounted for 5.5% of the isolates. No E. faecalis strains were detected. E. gallinorum and E. casseliflavus are not always taken into account because their resistance to glycopeptides is intrinsic and their pathogenicities are very low[22]. Nevertheless recently, these isolates have been found to be associated with invasive infections[19].

Nosocomial spread of VRE is associated primarily with the increasing use of vancomycin, while community-acquired colonization with VRE in Europe may be related to the use of glycopeptides, particularly avoparcin, for growth promotion in livestock and might have selected VRE strains in animals. The presence of VRE in population might be caused by transmission from domestic and farm animals colonized because of using glycopeptides-containing feeds[28]. The European Union banned all use of avoparcin as feed additive in April 1997, and in December 1998, avilamycin, bacitracin, tylosin, and virginiamycin were banned. However, controversy still exists over the impact of these measures on the VRE prevalence in humans[17].

Studies have shown that cross-contamination is the main mechanism of transmission of VRE in hospitals. Since this pathogen is introduced in the environment, the tendency is that it becomes endemic if effective measures for control are not taken[29]. The CDC recommends that hospitals develop a comprehensive plan to prevent and control infection and colonization of patients with VRE[13]. Following the isolation of these strains in our hospital, Hospital Infections Control Committee performed precautions required to control the spreading of VRE included; isolation precautions, cohorting of VRE-positive and negative patients and VRE-exposed patients with separate personnel and equipment for each group, use of gowns and gloves on room entry, and hand washing before and after each patient contact. In addition, rational use of antibiotics particularly vancomycin, cephalosporins education were given to personnel.

The present study indicates that at least 19.3% of hospitalized patients in high-risk groups are healthy VRE carriers; we conclude that the spread of nosocomial VRE epidemics probably cannot be prevented only infection control precautions. VRE surveillance is not routinely performed in our hospital. After detected this high rate, prompt attention for the detection of new cases of VRE colonization and disease, continuous surveillance of this pathogen, and employment of infection control policies are mandatory.

There are several limitations to this study. This study was a point-prevalance survey and number of VRE colonized patients were limited for evaluate the risk factors. Also, analysis of factors such as previous antimicrobial therapy or proximity to known patients with VRE were absent. Therefore, more studies are needed to clarify the epidemiology of VRE colonization.

In summary, we found high rate of VRE colonization at our hospital, emphasizing the importance of length stay in the hospital, low birth weight and age for newborn as a risk factor for gastrointestinal colonization. These data also highlights the importance of routinely screening for VRE in hospitalized patients, as possible as decrease to length of hospitalization, judicious use of antibiotics and recommends the institution of control measures to prevalent the further spread of VRE.

Prevalência e fatores de risco associados à colonização por enterococos resistente à vancomicina

Resumo

Os enterococos foram reconhecidos como patógenos clinicamente importantes na população de alto risco de pacientes hospitalizados. Os objetivos deste estudo foram detectar a prevalência da colonização por enterocos intestinais resistentes à vancomicina (VRE) no Hospital Tepecik, Izmir, Turquia, entre pacientes dos serviços de alto risco e os fatores de risco relacionados com a resistência em pacientes internados onde a VRE foi raramente isolada anteriormente. Após o primeiro isolamento de VRE em dois pacientes na unidade de terapia intensiva (UTI) e UTI neonatal, no mesmo dia, foi realizado um levantamento de prevalência utilizando swab retal. Para efeito de comparação, 30 amostras de pacientes-controle do serviço de controle de medicina interna também foram analisadas. Noventa e três pacientes foram investigados. Dezoito pacientes (19,3%) foram considerados portadores de VRE, apesar de nenhum dos pacientes do grupo controle tinham VRE. Treze cepas foram identificadas como *Enterococcus faecium*, quatro foram *Enterococcus gallinorum*, e um foi *Enterococcus casseliflavus*. Nove cepas de *E. faecium* foram resistentes à vancomicina, os restos eram de resistência intermediária à vancomicina e todos eles sensíveis à teicoplanina. O tempo de permanência hospitalar, idade e peso baixo ao nascer de recém-nascidos foram significativamente associados à colonização por VRE. A alta prevalência de colonização por VRE foi encontrado em nossas UTIs, enfatizando a importância do tempo de internação na UTI e baixo peso ao nascer de recém-nascidos como fator de risco para a colonização. A colonização por VRE deve ser monitorada e fatores de risco devem ser determinados, no intuito de estabelecer medidas de prevenção e controle.

Palavras-chave: Enterococos resistente à vancomicina (VRE) – Prevalência – Colonização intestinal.

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