Gaziantep Tıp Derg 2011;17(2): 82-86
Gaziantep Med J 2011;17(2): 82-86

Gaziantep Tıp Dergisi
Gaziantep Medical Journal

Araştırma Makalesi
Original Research

Analysis of the molecular epidemiology and antibiotic sensitivity of vancomycin-resistant enterococci

Vankomisine dirençli enterokokların moleküler epidemiyolojisi ve antibiyotik duyarlılıklarının irdelenmesi

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Abstract
Vancomycin-resistant Enterococci (VRE) are important nosocomial infection agents which have become widespread in recent years. The legal obligation to establish hospital infection control committees and increase in monitoring studies in Turkey has generalized VRE notifications. The treatment options for VRE-induced infections are limited. This study was conducted to identify the molecular epidemiology of the VRE sources found in the study hospital, and to determine the resistance of these strains to various antibiotics.
The study was carried out on strains isolated in the microbiology laboratory of Şahinbey Research and Application Hospital, University of Gaziantep. Strains were identified at species level via conventional methods and a fully automated Vitek 2 (Biomerieux, France) identification system. Vancomycin sensitivity was tested via disc diffusion method and E-test (AB Biodisc) strips. Resistance genes of these strains were analyzed via PCR method using GeneOhm VanR (Becton Dickinson, Canada) moleculer tests. *In vitro* antibacterial efficiency of linezolid, dalfopristin, gentamicin, streptomycin and imipenem was analyzed via the disc diffusion method. All 81 strains included in the study were identified as *Enterococcus faecium*. VanA gene-type resistance was recorded in 76 (93.8%); vanB gene-type resistance in 2 (2.5%); and nonA-nonB type resistance in 3 (3.7%) of the study strains. No resistance was detected in any of the linezolid and dalfopristine strains. 75 VRE strains (92.6%) were found to be resistant to gentamicin, 28 strains (34.6%) to streptomycin and 79 strains (97.5%) to imipenem. Linezolid and dalfopristin were found to have complete *in vitro* efficiency against VRE strains, while these strains were found to be highly resistant to other antibiotics tested in the scope of the study. Since treatment of VRE-induced infections is relatively difficult, it is suggested that careful implementation of preventive measures is of great importance to patients in the fight against this agent.
Keywords: Antibacterial susceptibility; enterococci; resistance gene; vancomycin

Özet
Vankomisine dirençli enterokoklar (VRE), son yıllarda gittikçe yaygınlaşan önemli nozokomiyal infeksiyon etkenlerindendir. Ülkemizde hastane infeksiyon kontrol komitelerinin oluşturulmasının yasal zorunluluk haline gelmesi ve aktif sürveyans çalışmalarının yaygınlaşması VRE bildirimlerinin de yaygınlaşmasını sağlamıştır. VRE ile oluşan infeksiyonlarda tedavi seçenekleri oldukça kısıtlıdır. Bu çalışma hastanemizde saptanan VRE kökenlerinin moleküler epidemiyolojisinin belirlenmesi ve bu suşların çeşitli antibiyotiklere karşı direnç durumlarının saptanması amacı ile yapılmıştır. Gaziantep Üniversitesi Şahinbey Araştırma ve Uygulama Hastanesi mikrobiyoloji laboratuarında izole edilen VRE suşları çalışmaya dahil edilmiştir. Elde edilen suşlar konvansiyonel yöntemler ve Vitek 2 (Biomerieux, Fransa) tam otomatik identifikasyon sistemi kullanılarak tür düzeyinde tanımlanmıştır. Disk difüzyon yöntemi ve E test (AB Biodisk) stripleri kullanılarak vankomisin duyarlılığı test edilmiştir. Bu suşlara ait direnç genleri GeneOhm VanR (Becton Dickinson, Canada) moleküler testleri kullanılarak PCR yöntemi ile araştırılmıştır. Linezolid, dalfopristin, gentamisin, streptomisin ve imipenemin *in vitro* antibakteriyel etkinlikleri disk diffüzyon yöntemi ile araştırılmıştır. Çalışmaya alınan 81 suşun tümü *Enterococcus faecium* olarak tanımlanmıştır. Suşların 76'sında (%93.8) vanA geni, 2'sinde (%2.5) vanB geni, 3'ünde (%3.7) ise nonA-nonB türünde direnç tespit edilmiştir. Linezolid ve dalfopristine suşların hiçbirinde direnç saptanmamıştır. Yetmişbeş (%92.6) VRE suşunun gentamisine, 28 suşun (%34.6) streptomisine ve 79 suşun (%97.5) imipeneme dirençli oldukları bulunmuştur. Linezolid ve dalfopristinin *in vitro* etkinliğinin VRE suşlarına karşı tam olduğu, ancak bu suşların test edilen diğer antibiyotiklere karşı oldukça yüksek oranlarda dirençli oldukları görülmüştür. VRE ile gelişen infeksiyonlarda sağaltım oldukça zor olduğundan, bu etken ile mücadelede öncelikle infeksiyondan korunmaya yönelik önlemlerin dikkatli bir şekilde uygulanmasının hastanın yararına olacağını düşünmekteyiz.
Anahtar kelimeler: Antibakteriyel duyarlılık; enterokok; direnç geni; vankomisin

Introduction

Enterococci are present in the gastrointestinal system as normal flora elements. Enterococci have gained gradual importance as nosocomial pathogens in the last two decades, as they have developed resistance to the majority of widely-used antibiotics (1,2). In the hospital environment, Enterococci are isolated from surfaces, the hands of hospital personnel and medical equipment (3).
Enterococci have intrinsic resistance to low-level penicillin and low-level aminoglycosides, trimethoprim-sulfamethaxazole, fluoroquinolone and lincosamide. They have also developed resistance to many other antibiotic groups via transmission of genetic material or via mutation (4,5). Among these resistances, the most clinically important one is the resistance developed against glycopeptides. Vancomycin resistance among Enterococci (VRE) was first notified in England in 1988, and similar notifications were subsequently made in European countries and the USA (6). CDC and the National Nosocomial Infections Surveillance declared that 30% of the Enterococci infections recorded in 2001 were caused by vancomycin-resistant strains (2). The widespread use of vancomycin and wide-spectrum cephalosporin contributed greatly to the rapid spread of VRE strains (7,8). In addition, avoparcin, which is a derivative of glycopeptides and is used as animal feed particularly in Europe, is believed to have an important

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Received: 09.03.2011 **Accepted:** 09.05.2011
Geliş Tarihi: 09.03.2011 **Kabul Tarihi:** 09.05.2011

DOI: 10.5455/GMJ-30-2011-36
www.gantep.edu.tr/~tipdergi
ISSN 1300-0888

role in the generalization of vancomycin resistance in Enterococci (9,10). Glycopeptide antibiotics affect Gram positive bacteria by damaging peptidogylcan synthesis and, in turn, cell wall synthesis (4). Five phenotypes have been identified as having resistance to this group of antibiotics: VanA, VanB, VanC, VanD and VanE phenotypes. Phenotypical naming is made on the basis of the resistance of the Enterococci strain to vancomycin and teicoplanin, the inductivity capacity of the resistance and the capacity of transferability of the resistance to other bacteria (4). VanA phenotype is the most common phenotype, and results in the development of high-level vancomycin and teicoplanin resistance. The most important characteristic of the resistance developed by VanA and VanB phenotypes is the inductivity and transferability (via plasmid) of the resistance (4,9). Molecular typing of VRE resistance genes is important in determination of microbial spread and use of infection control procedures. The present study was conducted to detect the molecular epidemiology of the isolated VRE strains and to analyze the *in vitro* efficiency of some antibiotics against these strains.

Material and Methods

This prospective study was conducted between January 2009 and August 2010 on Enterococci strains isolated from in-patients of the 800-bed capacity research hospital of the Faculty of Medicine, University of Gaziantep. Bacteria were isolated from samples sent to the laboratory for routine bacteriological examination, and from samples collected for monitoring.

Bacteriological Identification:

Bacteria were identified by using a fully-automated Vitek2 bacteria identification system. In addition conventional methods were used, if necessary (11). Blood culture samples were treated in fully-automated BacT ALERT 3D (Biomerieux, France) blood culture bottles.

Sensitivity Test:

Vancomycin resistance was analyzed using E test (AB Biodisc) strips, in compliance with the CLSI standards. The *in vitro* antibacterial efficiency of linezolid (30 µg, Oxoid), dalfopristin (15 µg, Oxoid) and imipenem (10 µg, Oxoid) was analyzed via the disc diffusion method, in compliance with the CLSI standards. 120 µg and 300 µg antibiotic discs were used to detect high-level resistance to gentamicin and streptomycin, respectively.

Molecular:

Fresh cultures of bacteria found to be conventionally vancomycin-resistant were subjected to a BD GeneOhm VanR test in order to detect resistance genes. The kits used in these tests were the ready-to-use commercial kits designed to detect the vancomycin resistance of enterococci. Specific probes were used to detect VanA, VanB genes, which are responsible for vancomycin resistance. Other non-detected phenotypes are reported as nonA-non-B and, when there is no gene that develops vancomycin resistance, the sample is reported to be negative. After the sample lysis, vanA and vanB genetic regions (if any) were amplified and read using a SmartCyler PCR device.

Results

The present study was conducted on 81 stains, 44 of which were obtained from rectal swab samples collected for surveillance and 37 of which were from laboratory samples collected for routine identification. Distribution of the strains according to type and clinic is given in Table 1.

Table 1. Distribution of VRE strains according to type and clinic

	Clinic									
Sample Type	POH[1]	IICU[2]	Pediatrics	Infection	Hematology	Oncology	SICU[3]	Neonatal	Gastroenterology	**Total**
Blood culture	3	4	1	1	-	-	-	-	-	9
Rectal swab	22	13	7	-	-	1	1	-	-	44
Stool	6	-	3	-	-	2	-	-	1	12
Urine	1	4	3	-	2	-	1	-	-	11
Stomach swab	-	-	-	-	-	-	-	1	-	1
Tracheal swab	-	2	-	-	-	-	-	-	-	2
Style tip	-	2	-	-	-	-	-	-	-	2
Total	**32**	**25**	**14**	**1**	**2**	**3**	**2**	**1**	**1**	**81**

[1]POH: Pediatric oncology-hematology, [2]IICU: Intensive Care Unit of Internal Medicine Clinic, [3]SICU: Intensive Care Unit of Surgery Clinic

Thirty-two (39.5 %) of the VRE isolates samples were collected from Pediatric oncology-hematology (POH) clinic and 44 (54.3 %) of the isolates were isolated from rectal swab materials.

vanA gene-type resistance was recorded in 76 (93.8%) of the strains, vanB gene-type resistance in 2 (2.5%) and nonA-nonB type resistance gene in 3 (3.7%) of the strains. No resistance was detected in any of the linezolid and dalfopristine strains in antibiotic sensitivity tests. Seventy-five VRE strains (92.6%) were found to be resistant to gentamicin, 28 strains (34.6%) to streptomycin and 79 strains (97.5%) to imipenem (Table 3).

Table 2. Distribution of resistance genes of VRE isolates

Clinical	Resistance Gene			Total
	VanA	*VanB*	NonA-NonB	
POH	32	-	-	32
IICU	25	-	-	25
Pediatrics	12	1	1	14
Infection	-	-	1	1
Hematology	1	-	1	2
Oncology	3	-	-	3
SICU	1	1	-	2
Neonatal	1	-	-	1
Gastroenterology	1	-	-	1
Total	**76**	**2**	**3**	**81**

Each of the 81 strains included in the study was identified as *E. faecium*. Distribution of the resistance genes detected in these isolates is given in Table 2.

Table 3. Antibiotic resistance rates and clinical distrubition of VRE isolates

Clinic	Resistance strain number (%)				
	Linezolid	Dalfopristine	Gentamycin	Streptomycin	Imipenem
POH	0	0	32 (100)	10 (31.3)	32 (100)
IICU	0	0	25 (100)	8 (32)	25 (100)
Pediatrics	0	0	13 (92.9)	6 (42.9)	14 (100)
Infection	0	0	0	0	0
Hematology	0	0	1 (50)	1 (50)	2 (100)
Oncology	0	0	2 (66.7)	2 (66.7)	3 (100)
SICU	0	0	2 (100)	1 (50)	2 (100)
Neonatal	0	0	0	0	1 (100)
Gastroenterology	0	0	0	0	0
Total	0	0	75 (92.6)	28 (34.6)	79 (97.5)

Discussion

Enterococci, which are included in the intestinal flora of humans and animals, frequently lead to in abdominal infections, urinary system infections, endocarditis and bacteriemia. Enterococci have also been observed as nosocomial infection agents since the 1970s. A limited number of treatment options are available for enterococci-induced infections. Most of the microorganisms either have intrinsic resistance or have the capacity to develop resistance to many antibiotics (12). Vancomycin is effective in the treatment of multi-resistant Enterococci infections; however, VRE notifications were first made in England and France in 1988, followed by increasingly common notifications of resistance globally (6,13). The first VRE notification in Turkey occurred in 1998 (14), since when the number of VRE notifications has rapidly increased (15). VRE, which had never been recorded in our hospital until recent years, was isolated from 81 patients during the study period. In addition, 57 of the study strains were

isolated from two clinics, with 32 (70.4%) isolated from pediatric oncology hematology and 25 from the intensive care unit of the internal diseases clinic. Thirty-five of the strains isolated from these two clinics were isolated from rectal swab samples collected for surveillance. With the increase in the vancomycin-resistance of Enterococci, the CDC's "Hospital Infection Control Practices Advisory Committee" (HICPAC) issued a "suggestions package" in 1995 about the possible measures to be taken to prevent nosocomial VRE dispersion (16). One of the suggestions was that, where a VRE case is detected, surveillance cultures should be collected from each patient in the same room and service as the infected person, in order to detect colonized patients and to ensure insulation. As is the case in many other health centers, VRE isolation has increased in the study hospital following the application of such measures. In many patients, VRE is detected only in colonized form. However, some centers which have reported a colonized/infected patient ratio of 10:1 (17,18).

E. faecalis is the most frequently isolated clinical Enterococci; however, *E. faecium* species develop high-level vancomycin resistance (19). The ratio of *E. faecalis* to *E. faecium* has recently decreased from 3.7:1 to 1.9:1, particularly in blood culture sources (19). All of the strains isolated in the scope of the present study were identified as *E. faecium*. Nearly 94% of the detected strains were found to have VanA-type glycopeptides resistance. Similar results have been produced by many studies conducted in Turkey (15,20-22). The present study differs from such studies in terms of the high number of Enterococci analyzed. Accordingly, the data obtained in this study were found to be epidemiologically meaningful, at least for the study hospital. Zer et al. (23) conducted a study at the present study hospital in 2002, followed by Ekşi (24) in 2008; neither of these previous studies detected vancomycin resistance in the Enterococci isolated in the scope of their studies. A study in 2007 by Menteş et al. (25) detected vancomycin resistance in 4 of 126 Enterococci strains and identified them as VanA genotype. A significant increase has been observed in the number of VRE detections in our hospital. This increase, as emphasized, may be related to the increased isolation rate due to infection prevention applications, and to the increased number of the patients monitored in our hospital. Resistance to glycopeptides has necessitated the use of other drug options in the treatment of Enterococci-induced infections. Linezolid is an oxazolidine-type antibiotic and is a ribosomal protein synthesis inhibitor in bacteria (26). Linezolid is granted a primary use permit for VRE infections (27). Linezolid is observed to be very effective against VRE strains. Most of the studies conducted on this drug have revealed no resistance (28-30); however, some resistant VRE strains have been reported (31,32). No linezoid resistance was recorded in the present study. Another antibiotic group suggested for the treatment of vancomycin-resistant Enterococci is quinopristin/dalphopristin. This antibiotic is a combination of quinopristin and dalphopristin at a ratio of 30:70 (33). This antibiotic is reported to be more effective than *E. faecalis* on *E. faecium* strains (34). Some studies have revealed nearly 90% sensitivity (34,35). No quinopristin/dalphopristin-resistant strain was detected in the present study. This may be due to the fact that this drug is not approved for sale in Turkey and has not yet been introduced into clinical use. High-level resistance to gentamicin and streptomycin -in the aminoglycoside group antibiotics tested in the study- was recorded as 92.6% and 34.6%, respectively. In a multi-centered study carried out in Turkey, a high-level aminoglycoside resistance (48.1%) was detected (36). Turkey has the second-highest level of aminoglycoside resistance in Europe. The rates recorded in the present study are found to be relatively high, particularly for gentamicin. This is thought to result from widespread and frequent use of gentamicin in Turkey for other infections, in addition to VRE. This finding may also have resulted from the fact that the present study was conducted on a resistant bacteria type.

The resistance of Enterococci to antibiotics is found to be at alarming levels; it is therefore concluded that it is easier to implement infection control measures than to treat the enterococci-induced infections.

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