Vancomycin-resistant enterococcus colonization and infection in children: six-year follow-up

Aslınur Özkaya-Parlakay, Ali Bülent Cengiz, Mehmet Ceyhan, Arzu Bağdat, Çağrı Barın-Kurtoğlu, Venhar Gürbüz, Ahmet Emre Aycan, Ateş Kara

Division of Pediatric Infectious Diseases, Department of Pediatrics, Hacettepe University Medical Faculty, Ankara, Turkey.
E-mail: aslinur.o@gmail.com
Received: 8 April 2014, Revised: 29 September 2014, Accepted: 14 October 2014

SUMMARY : Özkaya-Parlakay A, Cengiz AB, Ceyhan M, Bağdat A, Barın-Kurtoğlu C, Gürbüz V, Aycan AE, Kara A. Vancomycin-resistant enterococcus colonization and infection in children: six-year follow-up. Turk J Pediatr 2014; 56: 618-625.

Vancomycin-resistant enterococci (VRE) have become a major concern in medical practice. Asymptomatic VRE colonization of the gastrointestinal tract may lead to infection. In this study, which included patients who stayed in our hospital between 2006 and 2011, we looked at the cases of 342 patients with VRE colonization and 19 patients with VRE infection. Vancomycin and carbapenem exposure and intestinal disorders were significantly more common in patients with VRE infection than in those with VRE colonization (p=0.02/0.04/0.04 respectively). Secondary immune deficiency was significantly more common in VRE-colonized patients than in VRE-infected patients (p=0.03). VRE colonization time was significantly related with young age, presence of intravenous catheter, presence of mechanical ventilation, length of hospital stay, length of hospitalization before and after VRE isolation, length of ICU stay before and after VRE isolation, total ICU stay, antibiotic exposure within 3 months, hospitalization (in our hospital) within 3 months, and having a site of infection other than VRE (p=0.01/ 0.01/ 0.04/ <0.001/ 0.02/ <0.001/ 0.002/ 0.006/ 0.002/ 0.004/ 0.01/ 0.002, respectively). Overall mortality and sepsis was more common in the VRE-infected group than in the VRE-colonized group. Taking into consideration limiting antibiotic usage in potential cases and screening for patients at risk could be beneficial in terms of limiting VRE infection and colonization.

Key words: vancomycin resistant enterococcus, colonization, infection.

The first isolates of vancomycin-resistant enterococci (VRE) were reported from the United Kingdom at the end of the 1980s[1]. Infection with VRE is typically encountered after vancomycin-resistant enterococcal colonization, predominantly of the gastrointestinal tract. Colonization may last for a long time and may serve as a reservoir for the transmission of VRE to other patients[2]. Colonization is dependent on the patient's exposure to VRE and on his/her being a "susceptible" host. Risk factors are defined as receipt of vancomycin and some other antibiotics (i.e., cephalosporin, carbapenem[3]), long-term receipt of mechanical ventilation, immunosuppression and older age[4]; solid organ transplant recipients and hematology patients in particular are at increased risk for colonization with VRE. Healthcare workers and their household members are also at risk for VRE colonization.[5]

Enterococcal infections in hospitalized children are an important cause of morbidity and mortality. Enterococcal infections can be difficult to treat and may prolong the hospital stay [6]. Enterococci are the third most common type of nosocomial pathogen in the United States[7]. In Europe, the prevalance of VRE is lower than in the United States. VRE rates in Europe have ranged between <1% and 3% from 1995 to 1999[8-11]. The higher VRE rate of 8.7% that was reported in a multicenter study might be due to a disproportionately high

incidence of VRE in two centers in Portugal (59%)[12]. In that study, Turkey had a VRE prevalance of 6.7%.

In a study in Turkey, the vancomycin-resistance rate among *Enterococcus* spp. was reported to have increased from 0% in 2004 to 12.5% in 2010[13]. In Turkey, VRE bacteremia in a child was first detected in 2003[14]. The intent of this study was to evaluate the clinical characteristics of patients staying in our hospital between 2006 and 2011 who had VRE colonization and infection.

Material and Methods

A retrospective review was conducted of the laboratory results and medical records of the VRE cohort, composed of individuals in Hacettepe University İhsan Doğramacı Children's Hospital during the period January 1, 2006, through December 31, 2011, who had VRE in any clinical specimens as either colonization or infection. Our hospital has 240 beds and was accredited by the Joint Commission International in 2011. Active VRE surveillance is routinely carried out in our hospital, with stool cultures if possible, and otherwise with rectal swabs, by screening all risk groups (patients hospitalized longer than a month, patients admitted from centers known to have high VRE rates, and periodic screening of patients in the intensive care, hematology and oncology units). Active surveillance swabs are done as part of the hospital's quality program. Additionally, patients who have VRE isolated in bacterial cultures done due to their complaints are screened for intestinal carriage; among such patients, those found to be colonized with VRE were also included in the follow-up program. Patients hospitalized within the previous year in hospitals known to have a high incidence of VRE are routinely screened for VRE colonization at the time of admission.

Identification of *Enterococcus* was performed using conventional techniques[15,16]. During the study period, the contact isolation precautions for patients with VRE in any clinical specimens were followed. In all cases in which VRE was cultured in a clinical specimen, a stool culture for VRE detection was repeated every week for all patients for whom continuous follow-up was possible. The policy regarding VRE specifies that patients with three consecutive negative stool cultures obtained at least 1 week apart are considered to be decolonized[17]. Data collection included age, sex, culture site, microorganism, underlying immune and intestinal disease if present, length of hospital stay (LOS) in the last 3 months and surgical procedures in last 6 months if present, infection type, length of hospital and intensive care unit (ICU) stay, invasive procedures if present, antibiotic exposure within 3 months, clinical state at the time of VRE isolation, date of colonization, VRE infection if present and outcomes of patients with VRE colonization and infection. Colonization of VRE was defined as a positive culture for VRE from any site, without any symptoms or signs of infection; VRE infection was defined as cultivation of VRE from any site other than stool with accompanying clinical and laboratory findings of infection. Statistical analysis was performed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as mean±standard deviation and categorical variables as frequencies and percents. Differences between groups were determined by the Mann-Whitney U test or the Kruskal-Wallis test, depending on the number of groups. The relations between categorical variables were evaluated by the chi-square test or Fisher's exact test. The Spearman correlation coefficient was used to investigate the relations between continuous variables. The significance value was set at $p<0.05$.

Results

During the study period, a total of 7356 patients were screened for VRE colonization with at least one stool culture; 361 had a positive culture and 19 developed a VRE infection (the 361 patients included the 19 VRE-infected patients). None of our patients had accompanying MRSA colonization or infection. The 361 patients—172 female (47.6%) and 189 male—from whose specimens VRE was cultivated were between 3 days and 18 years of age (median 0.96 years). For those 361 patients, VRE was in 342 cases (94.7%) isolated from stool, in 4 cases (1.1%) from blood, in 4 from urine, in 4 from both blood and stool, in 2 from pus and in 1 case each, from blood and tracheal aspiration fluid, from blood and pus, from pericardial fluid and stool, from tracheal aspiration fluid and from urine and stool. The

Table I . Clinical Characteristics of VRE-Infected and -Colonized Patients

	VRE-infected group	VRE-colonized group	P
Age* (years)	4.21±5.34 (0.02-16)	3.04±4.64 (0.01-18)	0.42
Gender (female)	9 (47)	163 (47)	1.0
E. faecalis	1 (5)	12 (4)	0.77
E. faecium	17 (90)	321 (94)	0.77
HD before VRE isolation*	32.3±38.3 (0-142)	18.5±28.1 (0-193)	0.12
HD after VRE isolation*	16.5±25.4 (0-177)	21.1±46.1 (0-525)	0.51
LOS*	48.8±54.9 (0-167)	39.5±62.4 (0-611)	0.61
ICU stay before VRE isolation* (days)	2.7±5.1 (0-18)	3.9±10.5 (0-97)	0.52
ICU stay after VRE isolation* (days)	0.5±1.2 (0-5)	3.9±24.2 (0-375)	0.89
Total ICU stay* (days)	3.2±6.2 (0-23)	7.9±27.8 (0-383)	0.85
HD within 3 months*	18.4±30.5 (0-90)	12.8±25 (0-90)	0.40
History of surgery within 6 months	3 (16)	60 (18)	1
Invasive procedure	14 (74)	197 (58)	0.25
-Intravenous catheter	10 (53)	111 (33)	0.12
-Central venous catheter	1 (5)	16 (5)	0.61
-Mechanical ventilation	5 (26)	70 (20)	0.56
-Surgery	4 (21)	67 (20)	0.77
-Bronchoscopy	0	4 (1)	1
-Angiography	0	18 (5)	0.61
-Chest tube	0	7 (2)	1
Secondary immune deficiency	3 (15)	88 (25)	0.03
Intestinal disorder	3 (16)	12 (3)	0.04
Antibiotic exposure w/in 3 mos	16 (84)	245 (72)	0.35
Vancomycin exposure w/in 3 mos	11 (58)	101 (30)	0.02
Carbapenem exposure w/in 3 mos	11 (58)	111 (33)	0.04
Aminoglycoside exposure w/in 3 mos	11 (58)	185 (54)	0.93
Cephalosporin exposure w/in 3 mos	8 (42)	108 (32)	0.48
Sepsis	4 (21)	3 (1)	<0.001
Mortality	8 (42)	30 (9)	<0.001

Data are expressed as means or numbers (percent). HD: hospitalization days
*: mean; values in parentheses express minimum and maximum values

mean ages of the patients infected or colonized with VRE were 4.21±5.34 years and 3.04±4.64 years, respectively. The clinical charecteristics of the VRE-infected and -colonized groups are reviewed in Table I. Out of 19 VRE-infected patients, 10 had bacteremia, 5 had urinary tract infections (UTI), 2 had soft tissue infections and 1 had pericarditis. As one patient diagnosed with pneumonia had VRE isolated from tracheal aspiration fluid, the causative microorganism was interpreted as VRE. Six (1.8%) of the VRE colonizations ended with VRE infection

(the 19 VRE-infected patients included these 6 patients). Time between VRE colonization and infection ranged from 7 to 377 days (median, 54.5 days). The VRE from specimens other than stool collected from the remaining 13 VRE-infected patients was isolated during the study of these patients due to their complaints; they had not been screened, so their previous colonization status was unknown. In the cases in which VRE was isolated from more than one specimen, the same *Enterococcus* species was isolated. None of the VRE isolated from specimens other than stool was the result of colonization.

Enterococcus faecium (E. faecium) was cultivated from 338 specimens (93.6%) (321 in the VRE-colonized group, and 17 in the VRE-infected group). *Enterococcus faecalis (E. faecalis)* was isolated from 13 specimens (3.6%) (12 in the VRE-colonized group, and 1 in the VRE-infected group). Enterococcus spp. (could not be classified) were cultivated from 5 specimens (1.4%) (all from the VRE-colonized group). *Enterococcus avium (E. avium)* was cultivated from 2 specimens (0.6%) (all from the VRE-colonized group), *Enterococcus hirae (E. hirae)* from 2 specimens (0.6%) (all from the VRE-colonized group) and *Enterococcus solitarius (E. solitarius)* from 1 specimen (0.3%) (from the VRE-infected group),.

309 of the VRE-colonized patients (90%) and 16 of the VRE-infected patients (84.2%) were staying in our hospital when VRE was isolated. 139 of the VRE-colonized patients (40.6%) had been hospitalized in other hospitals and 95 (27.8%) had been hospitalized in our hospital within the preceding 3 months (for a total of 68.4%); 108 (31.6%) had not been hospitalized in any healthcare facility. Hospitalization in our hospital within the preceding 3 months was significantly related to colonization time (p= 0.01). Of the VRE-infected patients, 7 (36.8%) had been hospitalized in other hospitals and 7 in our hospital, while 5 (26.3%) had not been hospitalized, which was not statistically significant. As noted, 68.4% of the patients in our study had experienced a hospital stay within the preceding 3 months.

Table II. Factors Evaluated for VRE Colonization Time

	P	Correlation coefficient
Gender	0.82	
Age	0.01	-0.14
Intravenous catheter	0.01	
Mechanical ventilation	0.04	
Length of hospital stay	<0.001	0.23
Hospitalization before VRE isolation	0.02	0.17
Hospitalization after VRE isolation	<0.001	0.21
Time of ICU stay before VRE colonization	0.002	0.17
Time of ICU stay after VRE colonization	0.006	0.15
Total ICU stay	0.002	0.17
Primary or secondary immune deficiency	0.35	
Intestinal disease and gastroenteritis	0.18	
History of surgery	0.33	
Antibiotic exposure w/in 3 mos	0.004	
Hospitalization (in our hospital) w/in 3 mos	0.01	
Having an infection site	0.002	

UTI: urinary tract infection, CNS: central nervous system.

Immune deficiency was present in 94 VRE-colonized patients (27.5%); 88 of them had secondary immune deficiency (due, for example, to malignancy, steroids or chemotherapy) and 6 (1.8%) had primary immune deficiency; 3 VRE-infected patients had secondary and 4 had primary immune deficiency. Secondary immune deficiency was thus more common in the VRE-colonized group than in the VRE-infected group (p=0.03) (Table I).

One patient (0.3%) had intestinal disease and 11 (3.2%) had gastroenteritis during the period of VRE colonization. Among the VRE-infected patients, 1 (5.3%) had intestinal disease and 2 (10.5%) had gastroenteritis (Table I). Intestinal disorders (both intestinal disease and gastroenteritis) were thus more common in VRE-infected patients than in VRE-colonized patients (p=0.04). Patients with intestinal disorders had a higher VRE infection rate (OR 5.2, p=0.18).

201 of the patients (58.8%) had infections other than VRE infection during VRE colonization. 56.7% of VRE-colonized patients with a history of surgery had infections and 72.3% of VRE-colonized patients with immune deficiency had infections. Among the VRE-colonized patients with immune deficiency, 39 had fever of unknown origin, 12 had pneumonia, 4 had central nervous system (CNS) infections, 3 had urinary tract infections (UTI), and 3 had intraabdominal infections. Immune deficiency increased infection risk in VRE-colonized patients (p=0.01); however, surgery did not have any effect on infection risk in our study.

Antibiotic exposure within the previous 3 months was significantly related to colonization time (p= 0.004). Vancomycin and carbapenem exposure was more common in the VRE-infected group than in the VRE-colonized group (p=0.02 for vancomycin, p=0.04 for carbapenem).

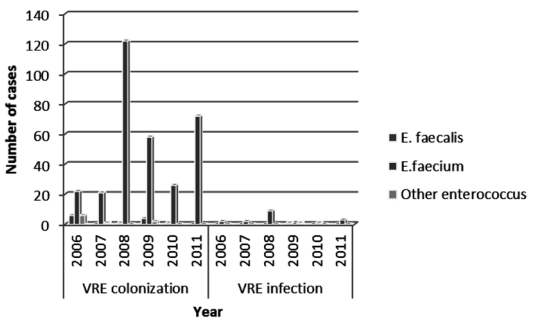

Fig. 1. Distribution of colonization and infection with VRE species by year.

At the time of VRE isolation, 7 of the patients (1.9%) had sepsis (4 of them VRE-infected patients who had sepsis due to VRE, the other 3 VRE-colonized patients whose sepsis was not due to VRE), 1 VRE-colonized patient required ICU transfer (0.3%) and 1 VRE-colonized patient needed mechanical ventilation. In 4 (1.1%) of the patients, VRE sepsis led to exitus. Patients having VRE infections were treated with linezolid. Sepsis was significantly more common in the VRE-infected group (p<0.001) (Table I).

As 3 patients died prior to the second specimen collection, repeated specimen collection was performed for 358 patients. Colonization time varied between 7 and 668 days, with a median of 29.5 days. 38 (10.5%) of the patients died. Mortality and VRE colonization time were not significantly related. Among the patients infected with VRE, 8 (42.1%) died, while 30 (8.8%) of the VRE colonized patients died. The rate of mortality was thus higher in the VRE-infected group (p<0.001) (Table I); VRE infection was related to higher mortality (OR 7.6, p<0.001).

On a year-by-year basis, there was no statistically significant difference in the number of patients infected and colonized with different VRE species (Fig. 1). Although the distribution of patients infected and colonized with different VRE species was not sufficient to be statistically significant, it nonetheless appears that in the VRE-colonized group, *E. faecium* was more common (n=122) in 2008, while colonization with *E . faecalis* was more common in 2006 than in other years.

Patients colonised with *E. faecium* were significantly younger than patients colonized with *E. faecalis* (p=0.01) or with other enterococcus species (species other than *E. faecium* and *E. faecalis*, p=0.006). But LOS and the frequency of surgery, invasive procedures and antibiotic exposure did not differ significantly in patients colonized with *E. faecalis*. Patients colonized with VR *E. faecalis* and VR *E. faecium* also did not have significantly different mortality rates.

Factors evaluated for their effect on VRE

colonization time and their correlations are summarized in Table II. The colonization time for patients with *E. faecalis* was not significantly different than that for patients with *E. faecium*.

Patients having an infection site had a higher mortality rate (OR= 3.9, p=0.007). Overall, mortality and having an infection site (other than VRE infection) were significantly related (p=0.008).

Discussion

VRE most frequently colonizes the gastrointestinal tract and the skin and is able to survive in the environment. The duration of colonization may be extremely prolonged, ranging between 7 weeks and 3 years[18,19]. In our study, VRE colonization time ranged between 7 and 668 days, with a median of 29.5 days, similar to what has been reported in the literature.

Bossaer et al.[20] reported the incidence of VRE infection developing from VRE colonization in high-risk febrile neutropenic patients as 38%. Zaas et al.[21] found the rate of VRE infection developing from VRE colonization in patients with cancer to be 13.4%. In our study, 6 (1.8%) of the VRE-colonized patients developed VRE infections. The higher rate reported by Bossaer et al.[20] might be due to the fact that their study looked at high-risk febrile neutropenic patients.

A prior study showed young age to be a risk factor for VRE colonization[22]; in our study, younger patients had a longer colonization time. Further studies should be conducted to investigate this issue .

Antibiotic exposure plays an important role in the transmission dynamic of VRE[5]. In our study, the proportion of VRE-colonized patients exposed to antibiotics within the previous 3 months was as high as 71.6%. In a study to investigate the association between antecedent intravenous antimicrobial exposure and isolation of VRE, exposures to imipenem (OR = 4.9) and ceftazidime (OR = 2.6) were significant predictors of VRE isolation[3]. In one study, ceftriaxone usage was also associated with a higher incidence of VRE bloodstream infection[23]. In our study, the percentage of VRE-colonized patients with a history of vancomycin exposure within the previous 3 months was 29.5%, while 32.5% had been exposed to carbapenem, 54.3% to aminoglycoside and 31.6% to cephalosporin. Similar to what has been reported in the literature[3,4], in our study vancomycin and carbapenem exposure was more common in the VRE-infected group than in the VRE-colonized group (p=0.02, 0.04, respectively). Up to now, various control measures aimed at reducing the incidence of VRE colonization and infection in hospitals have been implemented, yet despite this, VRE is still endemic in many hospitals[10]. Decreasing vancomycin and meropenem or imipenem usage to prevent VRE infection may have promise as a precautionary measure; nevertheless, it has been concluded that studies assessing the impact of restrictions on prescribing vancomycin with the aim of decreasing the prevalence of VRE-colonization have been heterogeneous, and thus the effectiveness of such interventions remains poorly defined[24].

VRE-colonized individuals may be at risk of developing severe infections when cancer, transplantation, surgery or advanced age suppresses normal host defenses[25,26]. In our study, 18% of the VRE-colonized patients had a history of surgery, and 27.5% had primary or secondary immune deficiencies. Among VRE-colonized patients with a history of surgery, 56.7% had infections; 72.3% of VRE-colonized patients with immune deficiencies had infections. Similar to what has been reported in the literature, immune deficiency increased infection risk in the VRE-colonized patients (p=0.01) in our study; however, surgery did not have any effect on infection risk in our patients.

In one study, it was concluded that hospitalized inflammatory bowel disease patients have increased susceptibility to VRE, which is associated with an increased economic burden[27]. Gastrointestinal disease has also been identified as a risk factor for acquiring VRE bacteremia[28]. Similarly, intestinal disorder was more common in VRE-infected patients than in the VRE-colonized group in our study.

In another study, previous isolation of methicillin-resistant *S. aureus* (MRSA), chronic hemodialysis, admission from another hospital, antibiotic exposure within 30 days, hospitalization within one year, and age >60 years were all independent risk factors for VRE recovery and were included in the risk scoring[10]. Furuno et al.[29] found that patient

self-reporting of previous hospital admission and of antibiotic exposure within 1 year of the current admission were the most sensitive variables in identifying patients colonized with MRSA or VRE, with a sensitivity of 76% and 69%, respectively. In our study, 68.4% of the patients had a hospital stay within the previous 3 months. Hospitalization in our hospital within the previous 3 months and antibiotic exposure within the previous 3 months were significantly related to colonization time (p= 0.01, 0.004, respectively).

In the study by Hakayawa et al., it was stated that patients with bacteremia due to VR *E. faecalis* had been more frequently exposed to cephalosporins, trimethoprim-sulfamethoxazole and vancomycin than had been patients with VR *E. faecium* bacteremia[30]. In our study, there were no significant differences between *E. faecalis* and *E. faecium* in terms of antibiotic exposure.

Although in previous studies bacteremia due to VR *E. faecalis* was independently associated with a twofold lower in-hospital mortality than bacteremia due to VR *E. faecium*[30], as colonization does not necessarily cause infection, in our study patients colonized with VR *E. faecalis* and *VR E. faecium* did not have significantly different mortality rates.

An ICU stay during the current hospitalization prior to VRE isolation was independently associated with bacteremia due to VR *E. faecium* in a previous study[31]. Similarly, ICU admission prior to VRE isolation was directly correlated with prolonged VRE colonization time in our study. In the study by Hakayawa et al., bacteremia due to VR *E. faecalis* was associated with a longer duration of hospitalization after VRE isolation, and a higher frequency of surgeries and invasive procedures in the 3 months following VRE isolation than was bacteremia due to VR *E. faecium*[30]. In our study, LOS and frequency of surgery and invasive procedures did not differ in patients colonized with *E. faecalis*.

In the literature, VRE infected patients have been reported to have mortality rates between 23% and 56.9%[4,32]. In our study, VRE-infected patients had a mortality rate within this range (42.1%). One study[33] reported the mortality rate in VRE-colonized patients to be 24.5%; in our study, this was lower (8.8%).

In the years since 1988, vancomycin-resistant enterococci has emerged as one of the most common and important causative pathogens of healthcare-associated infections. Although some new antimicrobial agents such as daptomycin, linezolid and tigecycline are clinically effective for the treatment of VRE infection, there is no drug appropriate for eradicating VRE colonization, and the use of daptomycin and tigecycline in the pediatric age group is controversial. Thus, active surveillance and strict contact precautions are still the best and most important methods for combatting VRE colonization and transmission[34].

According to data gathered from the literature, reduction in the transmission and colonization time of VRE would be beneficial. In order to achieve these goals, prospective comparative studies of infection control approaches would be useful. Our study supported the findings that previous hospitalization and antibiotic exposure were the most sensitive variables in identifying patients colonized with VRE, but also indicated that young age and previous ICU stay are other critical factors related to VRE colonization time. Intestinal disorders and vancomycin and carbapenem exposure was found to be more common in VRE-infected patients in our study. Thus, restriction of vancomycin and carbapenem usage, especially in patients with intestinal disorders, could be an important point to consider.

REFERENCES

1. Uttley AH, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci [letter]. Lancet 1988; 1: 57–58.
2. Zirakzadeh A, Patel R.Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. Mayo Clin Proc 2006; 81: 529–536.
3. Chavers LS, Moser SA, Funkhouser E, et al. Association between antecedent intravenous antimicrobial exposure and isolation of vancomycin-resistant enterococci. Microb Drug Resist 2003; 9: S69–S77.
4. Haas EJ, Zaoutis TE, Prasad P, Li M, Coffin SE. Risk factors and outcomes for vancomycin-resistant Enterococcus bloodstream infection in children. Infect Control Hosp Epidemiol 2010; 31: 1038–1042.
5. Murray BE. Vancomycin-resistant enterococcal infections. N Engl J Med 2000; 342: 710–721.
6. English BK, Shenep JL. Enterococcal and viridans streptococcal infections. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL (eds). Textbook of Pediatric Infectious Diseases (5th ed). Philadelphia, PA: WB Saunders; 2004: 1175–1203.

7. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol 2008; 29: 996 –1011.
8. Low DE, Keller N, Barth A, Jones RN. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 2001; 32: S133–S145.
9. Barisić Z, Punda-Polić V. Antibiotic resistance among enterococcal strains isolated from clinical specimens. Int J Antimicrob Agents 2000; 16, 65–68.
10. Ozkuyumcu C. Resistant enterococci: prevalence and factors associated with colonization in a Turkish university hospital. Acta Microbiol Pol 1999; 48: 203–207.
11. Reinert RR, Conrads G, Schlaeger JJ, et al. Survey of antibiotic resistance among enterococci in North Rhine-Westphalia, Germany. J Clin Microbiol 1999; 37: 1638–1641.
12. Bouchillon SK, Johnson BM, Hoban DJ, et al. Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant Enterococcus faecium and methicillin-resistant Staphylococcus aureus in 38 centres from 17 countries: the PEARLS study 2001–2002. Int J Antimicrob Agents 2004; 24: 119–124.
13. Inan A, Ozgultekin A, Akcay SS, et al. Alterations in bacterial spectrum and increasing resistance rates in isolated microorganisms from device-associated infections in an intensive care unit of a teaching hospital in Istanbul (2004-2010). Jpn J Infect Dis 2012; 65: 146–151.
14. Altun B, Cengiz AB, Kara A, et al. First vancomycin-resistant blood isolate of Enterococcus faecium in a children's hospital and molecular analysis of the mechanism of resistance. Turk J Pediatr 2008; 50: 554-558.
15. Domig KJ, Mayer HK, Kneifel W. Methods used for the isolation, enumeration, characterisation and identification of Enterococcus spp. 1. Media for isolation and enumeration. Int J Food Microbiol 2003; 88: 147–164.
16. Domig KJ, Mayer HK, Kneifel W. Methods used for the isolation, enumeration, characterisation and identification of Enterococcus spp. 2. Pheno- and genotypic criteria. Int J Food Microbiol 2003; 88: 165–188.
17. Lee WG, Park IJ, Jin HY, Park MH. Relapse and reacquisition of rectal colonization by vancomycin-resistant Enterococcus faecium after decolonization. Epidemiol Infect 2010; 138: 1449–1453.
18. Martone WJ. Spread of vancomycin-resistant enterococci: why did it happen in the United States? Infect Control Hosp Epidemiol 1998; 19: 539–545.
19. Byers KE, Anglim AM, Anneski CJ, Farr BM. Duration of colonization with vancomycin-resistant Enterococcus. Infect Control Hosp Epidemiol 2002; 23: 207–211.
20. Bossaer JB, Hall PD, Garrett-Mayer E. Incidence of vancomycin-resistant enterococci (VRE) infection in high-risk febrile neutropenic patients colonized with VRE. Support Care Cancer 2010; 19: 231–237.
21. Zaas AK, Song X, Tucker P, Perl TM. Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. Clin Infect Dis 2002; 35: 1139–1146.
22. Linden PK, Pasculle AW, Manez R, et al. Differences in outcomes for patients with bacteremia due to vancomycin-resistant Enterococcus faecium or vancomycin-susceptible E. faecium. Clin Infect Dis 1996; 22: 663–670.
23. McKinnell JA, Kunz DF, Chamot E, et al. Association between vancomycin-resistant Enterococci bacteremia and ceftriaxone usage. Infect Control Hosp Epidemiol 2012; 33: 718–724.
24. de Bruin MA, Riley LW. Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review. BMC Infect Dis 2007; 7: 24.
25. Montecalvo MA, Horowitz H, Gedris C, et al. Outbreak of vancomycin-, ampicillin-, and aminoglycoside-resistant Enterococcus faecium bacteremia in an adult oncology unit. Antimicrob Agents Chemother 1994; 38: 1363–1367.
26. Edmond MB, Ober JF, Weinbaum DL, et al. Vancomycin-resistant Enterococcus faecium bacteremia: risk factors for infection. Clin Infect Dis 1995; 20: 1126–1133.
27. Nguyen GC, Leung W, Weizman AV. Increased risk of vancomycin-resistant enterococcus (VRE) infection among patients hospitalized for inflammatory bowel disease in the United States. Inflamm Bowel Dis 2011; 17: 1338-1342.
28. Peel T, Cheng AC, Spelman T, Huysmans M, Spelman D. Differing risk factors for vancomycin-resistant and vancomycin-sensitive enterococcal bacteraemia. Clin Microbiol Infect 2012; 18: 388–394.
29. Furuno JP, McGregor JC, Harris AD, et al. Identifying groups at high risk for carriage of antibiotic-resistant bacteria. Arch Intern Med 2006; 166: 580–585.
30. Hayakawa K, Marchaim D, Martin ET, et al. Comparison of the clinical characteristics and outcomes associated with vancomycin-resistant Enterococcus faecalis and vancomycin-resistant E. faecium bacteremia. Antimicrob Agents Chemother 2012; 56: 2452–2458.
31. Han SH, Chin BS, Lee HS, et al. Vancomycin-resistant enterococci bacteremia: risk factors for mortality and influence of antimicrobial therapy on clinical outcome. J Infect 2009; 58: 182–190.
32. Sakka V, Tsiodras S, Galani L, et al. Risk-factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. Clin Microbiol Infect 2008; 14: 14–21.
33. Reduction of Nosocomial Vancomycin-Resistant Enterococci (VRE) Colonization and Infection by Active Surveillance and Intervention of Infection Control. http://clinicaltrials.gov/show/NCT01201031. Accessed in Jun 2013.