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Importance of the Risk Factors for Vancomycin Resistant Enterococcus Infection/Colonization –Development in Tertiary Intensive Care Units

Üçüncü Basamak Yoğun Bakım Ünitesinde Gelişen Vankomisin Dirençli Enterokok Enfeksiyon/Kolonizasyonu İçin Risk Faktörlerinin Önemi

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ABSTRACT

AIM: *Vancomycin Resistance Enterococci (VRE) infection and/or colonization is a serious problem in intensive care unit (ICU) patients. For this reason, in our study, we aimed to determine the potential underlying risk factors of VRE infection and/or colonization in ICU patients.*

METHODS: *The medical files of the patients that were hospitalized at least 48 hours in intensive care units between January 2012 – July 2013 were retrospectively analyzed. Patients' data on demographic values (age, sex, previous hospitalization, operation history), coexisting diseases (diabetes mellitus, coronary artery disease, malignancy, Alzheimer Disease) prior antibiotic use,the results of rectal swab culture and patient prognosis was collected from the hospital data. Patients were evaluated according to the Centers for Disease Control (CDC). First group was colonisation/ infection group that included the VRE infected and colonized patients according to rectal swab culture results in hospital. The second group was non-infected group that included negative culture results in terms of VRE infection. The risk factors for VRE infection were evaluated.*

RESULTS: *The prevalence of VRE colonization was %10.7 (53 patients of 496). In VRE colonized patients; prolonged hospitalization, malignancy, hemodialysis, Alzheimer Disease and antibiotic usage were assessed as risk factors.*

CONCLUSION: *For preventing the spread of VRE, we should take precaution considering the detected risk factors. Especially, the colonized patients should be isolated, hygiene rules must be exactly performed and the patients should be externed from ICUs as earlier as possible.*

Key words: *vancomycin resistant enterococcus; intensive care unit; rectal colonization*

ÖZET

AMAÇ: *Yoğun bakımda yatmakta olan hastalar için Vankomisin Dirençli Enterokok (VRE) enfeksiyonu ve/veya kolonizasyonu ciddi bir problemdir. Bu nedenle çalışmamızda yoğun bakıma yatmış hastalarda VRE enfeksiyon/kolonizasyonu için olası risklerinin belirlenmesi amaçlanmıştır.*

YÖNTEM: *Ocak 2012 – Temmuz 2013 yılında yoğun bakım ünitesinde enaz 48 saat yatmış olan hastaların dosyaları retrospektif olarak incelenmiştir. Hastaların dosyalarından demografik bilgileri (yaş, cinsiyet, daha önceki başvuru, yatış, ameliyat öyküsü) diabetus mellitus, koroner arter hastalığı, serebrovasküler hastalık, malignite, alzhemier gibi yandaş hastalıklar, daha önce kullandığı antibiyotikler,hastanın kültür sonuçlarına bakılarak VRE üremesi olup olmadığı ve prognozu gibi bilgiler toplanarak kayıt altına alınmıştır. Bu bilgilerden yararlanılarak Centers for Disease Control and Prevantion (CDC) kriterlerine göre VRE ile hastane enfeksiyonu tanısı konulan veya sadece rektal sürüntü örnekleri incelendiğinde kolonizasyon olarak kabul edilen hastalar enfeksiyon ve/veya/kolonizasyon grubunu oluştururken ve yoğun bakımda yattığı süre içinde hiçbir kültüründe VRE üremesi olmayan hastalarda VRE enfeksiyonu gelişmeyen grup olarak değerlendirmeye alınmıştır. VRE enfeksiyonu gelişmesi için risk faktörü olabilecek parametreler değerlendirilmiştir.*

BULGULAR: *Çalışmaya 496 hasta alınmıştır. Hastaların 53'ünde (%10,7) rektal sürüntü örneklerinde VRE üremesi saptanmıştır. Üremelerin hepsi kolonizasyon olarak değerlendirilmiştir. Hastalarda VRE enfeksiyonu ve/veya kolonizasyonu açısından risk faktörleri incelenmiştir. VRE ile enfekte ve/veya kolonize hastalarda uzun yatış, malignite, hemodiyaliz tedavisi ve altta yatan Alzheimer hastalığı varlığı ile antibiyotik (AB) kullanımı risk faktörleri olarak bulunmuştur ($p<0.05$).*

SONUÇ: *VRE gelişimini ve yayılımını önlemek için saptanan risk faktörleri göz önünde tutularak önlemler alınmalıdır. Özellikle kolonize hastalar izole edilmeli, hijyen kurallarına tam uyulmalı ve hastalar mümkün olan en kısa sürede yoğun bakımdan taburcu edilmelidirler.*

Anahtar kelimeler: *vankomisin dirençli enterekok; yoğun bakım; rektal kolonizasyon*

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Introduction

Enterococcus spp. is one of the most common infectious agents. These are Gram-positive facultative anaerobic bacteria that live in the gastrointestinal microbiata of humans and animals[1,2]. Among the *Enterococcus* spp., *Enterococcus faecalis* and *Enterococcus faecium* are the most common species that cause infection and *E. faecalis* are the cause of the infection in 90% of cases. However, infections caused by *E. faecium* are increasing recently[3]. *Enterococus* spp., is generally colonized in microbiata of the gastrointestinal system, oral cavity, vagina, gall bladder and urethra as opportunistic pathogens, may sometimes cause urinary system, pelvic infections. They are less frequently localized in the bones, joints and meninges, causing infections[4,5].

Antimicrobial resistance differs among the starins and resistance can ocur in *Enterococcus* spp., by either intrinsic (natural) or extrinsic (acquired) ways. Enterococci are naturally resistant against cephalosporins, antistaphylococcal penicillins, clindamycin and aminoglycosides (low level)[6,7]. *Enterococcus* spp., is sensitive to vancomycin and has been safely used for the treatment of enterococcal infections until 1988. Vancomycin resistant enterococcus (VRE) case in the world has been reported first from United Kingdom, and then from France and United States of America. First VRE case in Turkey has been reported from Akdeniz University, in 1988[5,8]. Today, VRE colonization and infections are being encountered increasingly.

Enterococcus spp. have become one of the causative agents of nosocomial infections. They can transmitted directly from patient to patient as well as by the contaminated hospital equipment and environmental contact, causing nosocomial epidemics[9]. *Enteroccous* spp., have been detected as the causative agents of hospital acquired urinary tract and wound infections. According to SENTRY data of antimicrobial surveillance, blood stream infections have also been added to this rank[10].

In patients, first colonization occurs prior to infection, and in most of the times incidence of infection after the colonization is usually low. In general, the colonized patients are asymptomatic and *Enterococcus* spp., can be detected in stool or rectal swab cultures. The risk factors for VRE infections have been defined as long term stay in hospital or intensive care units, advanced age, being nursing home patient, having intraabdominal or cardiothoracic surgery, organ transplantation, renal failure, persistence of hematologic malignancy, enteral nutrition, high APACHE II score, use of antibiotics especially vancomycin and third generation cephalosporins. Besides these risk factors, poor compliance to hand hygiene was also an important factor for colonization and/infection, as hands of health care personnel may harbor VRE up to 60 minutes after the contact[11–14].

The objective of this study was to investigate persistence and the risk factors of VRE colonization in the patients that were admitted to the intensive care unit in our hospital.

Materials and Methods

After approval by the ethics committee, files of patients who were hospitalized at least for 48 hours in the seven-bed tertiary care Anesthesia Intensive Care Unit of Ankara Numune Training and Research Hospital between January 2012 and July 2013 were retrospectively screened. Files of the patients lost in less than 48 hours after admission to the intensive care unit were not included.

Demographic features (age, gender, history of previous hospitalization, surgery), and data such as underlying diseases (diabetes mellitus, coronary artery disease, cerebrovascular disease, malignancy, Alzhemier disease), previous antibiotic use, presence of VRE growth in the clinical samples and prognosis were recorded on the data collection forms. Based on this information; patients were grouped as infected and/or colonized or controls. Patients who had developed hospital infection with VRE and those have only VRE colonization were accepted to be colonized composed the infection and/or colonization group, while the patients who have not colonized with VRE in any swab culture during study period were considered as the control group.

As a part of our hospital policy active surveillance cultures such as rectal swab cultures have been performed to all the patients at admission to the ICU. Furthermore, rectal swab cultures have been repeated monthly as long as the patients stay in the intensive care unit. If gastrointestinal colonization was detected at admission to the intensive care unit or during their stay, rectal swab sampling had been continued weekly until negative outcome was obtained in successive three samples. Patients with VRE detected in the rectal swabs were isolated and strict isolation measures have been taken.

For the culture of the rectal swabs, Bile Aesculin Azide Agar (Oxoid, England) was prepared in line with the recommendations of the manufacturer, vancomycin 6 μg/mL and ceftriaxone 160 μg/ml were added and

the mixture was put on the sterile plates. Rectal swab samples were directly cultuvated in these plates and incubated for maximal 48 hours at 37°C in the aerobic environment. After gram staining and catalase tests applied on the colonies which were proliferated, forming black color in Bile Aesculin Azide Agar, definition of the colonies at species level and determination of antibiotic sensitivity were carried out using VITEK-2 automated system (bioMérieux-France).

Data obtained in this study were evaluated through licensed SPSS 18.0 package software. Chi-square test was used for two-group comparison as the result of normality tests. Statistical significant level was considered as 0.05 and $p<0.05$ values were accepted as statistically significant.

Results

A total of 515 patients were followed-up during the study period. Of these, 497 patients in whom rectal swab samples collected were enrolled into the study. Among the patients, 48.1% were male with a mean age of 65±19.12. Demographic and clinical features of the patients were shown in Table 1. Cardiovascular disease, cerebrovascular event and malignancy were detected in 50.3%, 31.0%, 18.7% of the patients, respectively. Patients were followed-up in the intensive care unit for average 8.08±11.6 days. Mortality rate was found as 43.9%.

VRE was detected in total 53 patients (10.7%). Patients were divided into two groups based on the presence of VRE colonization and risk factors were investigated between the groups. Although colonized patients were older than those of the non-colonized patients, the difference was not statistically significant ($p>0.05$) (Table 2). Same as mean age, history of previous hospitalization was more detected in the colonized patients compared to the non-colonized patients; the difference was not statistically significant ($p>0.05$). Length of stay in the intensive care unit was statistically significantly longer in the rectal colonization group ($p<0.05$). Among the risk factors defined; coexistence of malignancy, beeing on hemodialysis and Alzheimer disease as an underlying disease were found to be significant in the colonized patients ($p<0.05$) (Table 3).

Rate of the use any antibiotic was significantly higher in the rectal colonization group ($p<0.05$) (Table 3). Among the antibiotics considered as risk factor, use of third generation cephalosporins was found as 35.4% and glycopeptide as 22.5% in the colonized patients. None of the colonized patients developed VRE related infections.

Discussion

There are 16 species in enterococci genus with *E. faecalis* and *E. faecium* are the most common species, while *E.gallinarum* and *E.casseliflavus* less frequently cause infections[15]. Gastrointestinal system is the most common resource of enterococcal infections. First, colonization develops and than the infection occurs. In a study, 40.2% of the bacteria that colonize in the gastrointestinal system were found to be *E.gallinarum,* but no infection was observed due to these bacteria[16]. In our study, 53 of 497 patients developed colonization and the prevalence of VRE colonization in the intensive care unit was found as 10.7%. In their studies performed by Furtado et al. and Pan et al. This rate was found as 32.6% and 11.3%, respectively[17,18]. Whereas Byers et al. found this rate as 6%, Euihan et al. as 7.2% and Pan et al. as 21.9%[19–21]. *E.faecium* ve *E.faecalis*-related infections have been reported in the above mentioned studies, none of the VRE colonized patients developed infection in our study.

It is difficult to distinguish colonization from infection in the patient group with underlying disease. Mortality directly related to VRE is difficult to determine. In our study, we compared the mortality

Table 1. *Characteristics of the patients*

Feature	n	%
1. Age (years)	65±19.12	
2. Hospitalization days (mean)	8.08±11.6	
3. Gender		
Female	258	51.9
Male	239	48.1
4. Reason of hospitalization		
Internal	463	93.1
Surgical	34	6.8
5. Previous hospitalization		
Yes	237	47.7
No	260	52.3
6. Underlying disease		
CVD	250	50.3
CVE	154	31.0
DM	118	23.7
Malignancy	93	18.7
Alzheimer	43	8.7
7. History of antibiotic use		
No	334	67.2
Glycopeptide	12	2.4
Cephalosporin	54	10.8
8. Prognosis		
Discharge	279	56.1
Exitus	218	43.9

Table 2. *Comparison of the colonized and non-colonized patients*

		Colonization patients	Non-colonization patients	p
Age		69.75±17.3	65.4±19.3	>0.05
Gender	Female	28 (52.8%)	230 (51.8%)	>0.05
	Male	25 (47.2%)	214 (48.2%)	
Prognosis	Discharge	28 (52.8%)	251 (56.5%)	>0.05
	Exitus	25 (47.2%)	193 (43.5%)	
Reason of hospitalization	Internal	47 (88.7%)	415 (93.5%)	>0.05
	Surgical	6 (11.3%)	28 (6.3%)	
Previous hospitalization	Yes	30 (56.6%)	229 (51.7%)	>0.05
	No	23 (43.4%)	214 (48.3%)	

Table 3. *Risk factors for VRE colonization*

Risk factor		Colonized patients	Non-colonized patients	p
Hospitalization days		18.4±2.7	6.8±0.5	<0.001
CVD	Yes	33 (62.2%)	217 (48.9%)	>0.05
	No	20 (37.8%)	226 (51.1%)	
CVE	Yes	15 (28.3%)	139 (31.4%)	>0.05
	No	38 (71.7%)	304 (68.6%)	
Malignancy	Yes	3 (5.7%)	90 (20.3%)	<0.05
	No	50 (94.3%)	353 (79.7%)	
Dialysis	Yes	12 (22.6%)	42 (9.5%)	<0.05
	No	41 (77.4%)	401 (90.5%)	
Alzheimer	Yes	17 (32.1%)	26 (5.9%)	<0.05
	No	36 (67.9%)	417 (94.1%)	
Antibiotics	Yes	31 (58.5%)	132 (29.9%)	<0.05
	No	22 (41.5%)	312 (71.1%)	

rates between colonized and non-colonized patients and no statistically significant difference was found in terms of mortality.

Since enterococci are the elements of the normal flora of gastrointestinal system, infection due to these microorganisms may occur in case of impaired tissue integrity, perforation, immunosuppression and peritoneal dialysis. In a study performed by Ostrowski et al., prevalence of VRE colonization in surgical intensive care unit was found as 12% and organ transplantation was defined as a risk factor[18]. When reasons of the hospitalization were analyzed in our patient groups; number of the patients who were admitted to the intensive care unit with internal reasons was found to be higher than the other causes. Unlike the above-mentioned study no increase was observed in VRE colonization in the patients who admitted to ICUs after any kind of operation or trauma.

Several studies demonstrated that long hospitalization periods cause increased risk of colonization, higher rates of morbidity and mortality and cost[21–24]. In a study by Pan et al., long stay in the intensive care unit was found as a major risk factor for VRE colonization[22]. Likewise in our study, length of stay in the intensive care unit was found to be significantly longer in the colonization group.

Other risk factors for VRE colonization include underlying diseases such as chronic renal failure, diabetes mellitus, cardiovascular disease and dialysis[25]. Development of VRE colonization can lead to a life-threatening complication especially in the immunosuppressed patients[26]. Similarly to the other studies, in this study we found the risk factors for VRE colonization as the existence of malignancy, renal failure requiring dialysis and concomitant Alzheimer's disease. It was thought that one of the causes increase colonization in the patients having underlying Alzheimer's disease was the lack of self-care.

Antibiotic use seems to be an important risk factor for VRE colonizations and/or infections. Especially wide use of third generation cephalosporins and vancomycin increases the risk[17]. In their studies, Shorman et al. and Saka et al. reported that the use of vancomycin and cephalosporins as well as antimicrobial agents and antianaerobic effect have influence in the development of

VRE colonization[9,25]. In our study, use of antibiotic was found to be significantly higher in the rectal colonization group compared to the non-colonized group. The most common types of antibiotics used were found as glycopeptide and cephalosporins in our study, which was consistent with the literature.

In conclusion; as a result of this study significant risk factors for VRE colonization were found as long hospitalization period, malignancy, being on dialysis, concomitant Alzheimer's disease and excess the use of antibiotics. Since the patients having these risk factors are mainly followed-up and treated in intensive care units, determination of VRE colonization from the rectal swab sampling during the first admission to these unit is crucial. We believe that, rates of VRE colonization and infections would be decreased by the isolation of patients, performing strict infection control implementations and the use of proper antibiotics.

References

1. Schmidt S, Heimesaat MM, Fisher A, et al. Saponins increase susceptibility of vancomycin-resistant enterococci to antibiotic compounds. Eur J Microbiol Immunol 2014;4:204–12.
2. Sievert DM, Ricks P, Edwards JR, et al. National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities: Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemol 2013;34:1–4.
3. Dahlen G, Biomqvist S, Almstahl A, et al. Virulence factors and antibiotic suspectibility in enterococci isolated from oral mucozal and deep infections. J Oral Microbiol 2012;4:10855.
4. Oli AK, Raju S, Rajeshwari, et al. Biofilm formation by Multidrug resistant Enterococcus fecalis (MDEF) originated from clinical samples. J Microbiol Biotechnol Res 2012;2:284–8.
5. Uttley AH, Collins CH, Naidoo J, et al. Vancomycin-resistant enterococci. Lancet 1998;1:57–8.
6. Klare I, Witte W, Wendt C, et al. Vancomycin-resistant enterococci (VRE). Recent results and trends in development of antibiotic resistance. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1387–400.
7. Taşbakan MI. Vankomisine dirençli enterokok olguları. ANKEM Derg 2010;24:82–4.
8. Vural T, Şekercioğlu AO, Öğünç D ve ark. Vankomisine dirençli Enterococcus faecium suşu. ANKEM Derg 1999;13:1–4.
9. Atalay S, Ece G, Şamlıoğlu P ve ark. Evaluation of Vankomycin-Resistant Enterococcus Cases at a Tertiary Level Hospital in İzmir. Mikrobiyol Bul 2012;46(4):553–9.
10. Deshpande LM, Fritsche T, Moet G, et al. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: A report from the SENTRY antimicrobial surveillance program. Diagn Microbiol Infect Dis 2007;58:163–70.
11. Çetinkaya Şardan Y. Vankomisine dirençli enterokoklara bağlı hastane enfeksiyonlarının epidemiyolojisi ve kontrolü. Ulusoy S, Usluer G, Ünal S (editörler). Gram Pozitif Bakteri Enfeksiyonları 1. Baskı Ankara: Bilimsel Tıp Yayınevi, 2004:171–85.
12. Katırcıoğlu K, Özkalkanlı MY, Yurtsever S ve ark. Olgu Sunumu: Yoğun bakım ünitesinde vankomisin dirençli enterokok kolonizasyonu ve alınan önlemler. Türk Anest Der Dergisi 2009;37:249–53.
13. Hayden MK. Insights into the epidemiology and control of infection with vancomycin-resistant enterococci. Clin Infect Dis 2000;31:1058–65.
14. Yamazhan T, Ulusoy S. Vankomisine dirençli enterokoklar. Doğanay M, Ünal S, Çetinkaya Şardan Y (editörler). Hastane İnfeksiyonları Kitabı Ankara: Bilimsel Tıp Yayınevi; 2013:355–7.
15. Uttley AH, George RC, Naidoo J, Woodford N, Johnson AP, Collins CH, et al. High-level vancomycin-resistant enterococci causing hospital infections. Epidemiol Infect 1989;103:173–81.
16. Yamazhan T, Ulusoy S. Vankomisine dirençli enterokoklar. Doğanay M, Ünal S, Çetinkaya Şardan Y (editörler). Hastane İnfeksiyonları Kitabı Ankara: Bilimsel Tıp Yayınevi; 2013:251.
17. Furtado GHC, Martins ST, Coutinho AP, Wey SB, Medeiros EAS. Prevalence and factors associated with rectal vancomycin-resistant enterococci colonization in two intensive care units in Sao Paulo, Brazil. Braz J Infect Dis 2005;9:64–9.
18. Kara A, Devrim İ, Bayram N, Katipoğlu N, Kıran E, Oruç Y ve ark. Risk of vancomycin-resistant enterococci bloodsteram infection among patients colonized with vancomycin-resistant enterococci. Braz J Infect Dis 2015;19:58–61.
19. Byers KE, Anglim AM, Anneski CJ, Germanson TP, Gold HS, Durbin LJ, et al. The hospital epidemic of vancomycin-resistant Enterococcus: risk factors and control. Infect Control Hosp Epidemiol 2001;2:140–7.
20. Pan SC, Wang JT, Chen YC, Chang YY, Chen ML Chang SC. Incidence of and risk factors for infection or colonization of vancomycin-resistant in patients in the intensive care unit. PLoS One 2012;7: e47297.
21. Euihan J, Sookjin B, Hojin L, Sang YM, Hyuck L. American Journal of Infection Control, 2014;42:1062–6.
22. Çekin Y, Daloğlu AE, Öğünç D, Baysan BÖ, Dağlar D, İnan D ve ark. Evaluation of vancomycin resistance 3 multiplexed PCR assay for detection of vancomycin-resistant enterococci from rectal swaba. Ann Lab Med 2013;33:326–30.
23. Hayakawa K, Marchaim D, Palla M, Gudur UM, Pulluru H, Bathina P, et al. Epidemiology of vancomycin-resistant Enterococcus faecalis: a case-case-control study. Antimicrob Agents Chemother 2013 Jan; 57(1):49–55.
24. Shorman M, Al-Tawfiq JA. Risk factors associated with vancomycin-resistant enterococcus in intensive care unit setting in Saudi Arabia. Interdiscip Perspect Infect Disease 2013;2013:369674.
25. Whang DW, Miller LG, Partain NM, McKinnell JA. Sistematik review and meta-analysis of Linezolid and Daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. Antimicrob Agents Chemother 2013;57:5013–8.
26. Grabsch EA, Mahony AA, Cameron Dr, Martin RD, Heland M, Davey P, et al. Significant reduction in vancomycin-resistant enterococcus colonization and bacteraemia after introduction of a bleach-based cleaning-disinfection programme. J Hosp Infect 2012;82:234–42.