Rectal culture screening for vancomycin-resistant enterococcus in chronic haemodialysis patients

: false-negative rates and duration of colonisation

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- Abstract –

Rectal culture screening for vancomycin-resistant enterococcus in chronic haemodialysis patients : false-negative rates and duration of colonisation

Infection or colonisation with vancomycin-resistant enterococci (VRE) is common in chronic haemodialysis(HD) patients. However, there is limited information on the duration of VRE colonisation or on the reliability of consecutive negative rectal cultures to determine the clearance of VRE in chronic HD patients. Chronic HD patients from whom VRE was isolated were examined retrospectively. Rectal cultures were collected more than 3 times, at least 1 week apart, between 1 June 2003 and 1 March 2010. The results of the sequential VRE cultures and patients' data were analyzed. Among 812 patients from whom VRE was isolated, 89 were chronic HD patients and 92 had three consecutive negative cultures. It took 60.7±183.9 and 111.4±155.4 days to collect three consecutive negative cultures in the 83 non-chronic haemodialysis patients and nine chronic haemodialysis patients, respectively (P= 0.011). The independent risk factors for more than three negative sequential rectal cultures were glycopeptide (odds ratio [OR], 2.155; P=0.003)and hospital day(OR, 1.009; P=0.001). After three consecutive negative rectal cultures, two of the six chronic HD patients, and 10 out of 36 patients were culture-positive again. In conclusion, a significant proportion of patients colonised with VRE cannot be detected even after three negative weekly rectal cultures, and the duration of VRE colonisation in chronic haemodialysis patients tends to be prolonged. These results may be contributing to the continued increase in the prevalence of VRE.

Keywords: vancomycin-resistant enterococci, haemodialysis, end-stage renal disease

TABLE OF CONTENTS

LIST OF FIGURE

LIST OF TABLES

I. INTRODUCTION

Hospital-acquired vancomycin-resistant enterococci (VRE) infections are increasingly common and difficult to treat.(Murray, 2000) Patients with VRE infections, as well as asymptomatically colonised patients, serve as a reservoir for the transmission of VRE to other patients.(Murray, 2000) Because dialysis-dependent patients have extensive contact with the healthcare system, they are often in close proximity to other VRE reservoirs. In addition, these patients often receive repeated, prolonged courses of antibiotics, including vancomycin, and frequently have multiple co-morbid conditions.(Axon et al., 2004) Therefore, patients with end-stage renal disease (ESRD) undergoing dialysis have an increased risk of acquiring VRE. A recent study reported that 17.8% of haemodialysis patients became colonised with VRE and had an incidence rate of one case per 9.8 patient–years of follow-up.(Atta et al., 2001) This high incidence of VRE suggests that practices within dialysis units may be a major driving force for the development and spread of VRE. Approximately 2%-10% of VRE-colonised patients will develop infections, even though this rate may be as high as 30% among chronic immunocompromised patients, such as liver transplant recipients.(Hayden, 2000; Atta et al., 2001) Since there is no effective antimicrobial therapy for VRE colonisation, strong efforts have been made to screen for VRE and isolate carriers when detected.(Murray, 2000) To prevent the spread of VRE, many guidelines recommend that health care providers use contact precautions during the care of colonised and infected patients until it can be demonstrated that they are no longer colonised.(Muto et al., 2003) However, little is known about the persistence of VRE colonisation in patients with ESRD on haemodialysis treatment. This study examined the duration of VRE colonisation and the adequacy of consecutive negative follow-up rectal swab(RS) cultures to determine the clearance in these patients.

II. MATERIALS AND METHODS

1. Study design and population

Between 1 June 2003 and 1 March 2010 patients with VRE hospitalised at the 1,088-bed Ajou University Hospital in Suwon, South Korea were enrolled in this study. Ajou University Hospital has an average of 43,000 patient discharges per year. To follow the recommendations of the Center for Disease Control and Prevention (CDC) on VRE,(1995; Siegel et al., 2007) Ajou University Hospital uses private rooms, disposable gloves and gowns for the care of patients with VRE, and has executed follow-up rectal swab cultures at least a week apart. A follow-up rectal culture was obtained on the first day when patients were found to be culture-positive for VRE. The inclusion criteria for this study were as follows: patients with VRE infection or colonisation identified by culture; and patients with more than three follow-up rectal cultures collected at least a week apart. The demographics, VRE culture status, and antibiotic use were obtained from the medical records. Information on the cultures was collected from the date of the first known positive VRE culture through the date of the last available culture. Data on antibiotic use and cultured microorganisms within two weeks before the initial VRE-positive culture were obtained.

2. Microbiology methods

The faecal samples obtained with follow-up rectal cultures were streaked on phenylethanol agar and CHROMagar™ VRE plates (Becton Dickinson [BD], Sparks, MD, USA). The plates were incubated at 35°C in ambient air and examined for growth at 24 and 48 h. From each plate, up to three colonies with the distinctive morphology of enterococci were sub-cultured on bile esculin azide agar (BD). The organisms were identified from conventional biochemical reactions with the Vitek identification system (bioMérieux, Hazelwood, MO, USA), and the API Strep system (bioMérieux). Brain heart infusion agar containing 6 mg of vancomycin per ml was also inoculated, as described by the Clinical and Laboratory Standards Institute (CLSI) to enhance the detection of VRE. The minimal inhibitory concentrations of vancomycin and teicoplanin were determined using the E test (AB Biodisk North America, Inc., Culver City, CA, USA); vancomycin-susceptible *Enterococcus faecalis* ATCC 29212 and vancomycin-resistant *E. faecalis* ATCC 51299 were used for quality control.

3. Analysis

The categorical variables were analyzed using a χ^2 test or Fisher's exact test. Continuous variables were analyzed using a *t*-test or the Mann-Whitney test for the non-parametric distributions. Logistic regression was used to calculate the odds ratio of the independent risk factors for VRE colonisation. All statistical analyses were performed using SPSS software (version 12.0; Chicago, IL, USA).

III. RESULTS

During the study period (1 June 2003 to 1 March 2010), 812 out of 180,823 patients at Ajou University Hospital were VRE-positive. There was no VRE outbreak among the other hospital patients during this study period. Of the 812 patients, 453 had more than 3 follow-up rectal cultures one week apart. After two negative cultures, the next culture was negative in nine chronic haemodialysis patients and 83 non-chronic haemodialysis patients (Fig. 1). Table 1 lists the demographic and clinical data for the patients who had at least three additional cultures. Compared to the patients who were not on chronic haemodialysis, the chronic haemodialysis patients were older ($P = 0.008$), more likely to have diabetes mellitus ($P = 0.002$), more likely to have been treated with glycopeptides ($P < 0.001$), and less likely to have sensitivity to rectal cultures for the detection of VRE ($P = 0.001$). Table 2 shows that the chronic haemodialysis patients who were VRE-negative on more than three consecutive rectal cultures were more likely to have been treated with glycopeptide therapy ($P = 0.001$) and have a longer duration of glycopeptide therapy before becoming VRE-positive ($P = 0.001$). Chronic haemodialysis patients were also likely to have a longer interval between the initial VRE positive and three consecutive negative cultures ($P = 0.011$) with no significant difference in the number and length of time of the rectal cultures. Using logistic regression on all patients with more than three follow-up rectal cultures, glycopeptide therapy (OR, 2.16; $P = 0.003$) and hospital day (OR, 1.01; $P = 0.001$) were significantly associated with patients who were VRE-negative on more than three sequential cultures (Table 3). Table 4 lists the predictive value of a negative VRE culture. All cultures with at least one positive culture for VRE were identified followed by those with a minimum of three additional serial cultures, the first of which was negative. After three negative cultures, the fourth culture was negative in four out of six culture sets in chronic haemodialysis patients and 26 (72.2%) out of 36 culture sets in the other patients. Of the specimens processed for VRE from all the culture sets, the percentage of negative cultures after two, three and four consecutive negative cultures were 73.0%, 71.4% and 91.7%, respectively.

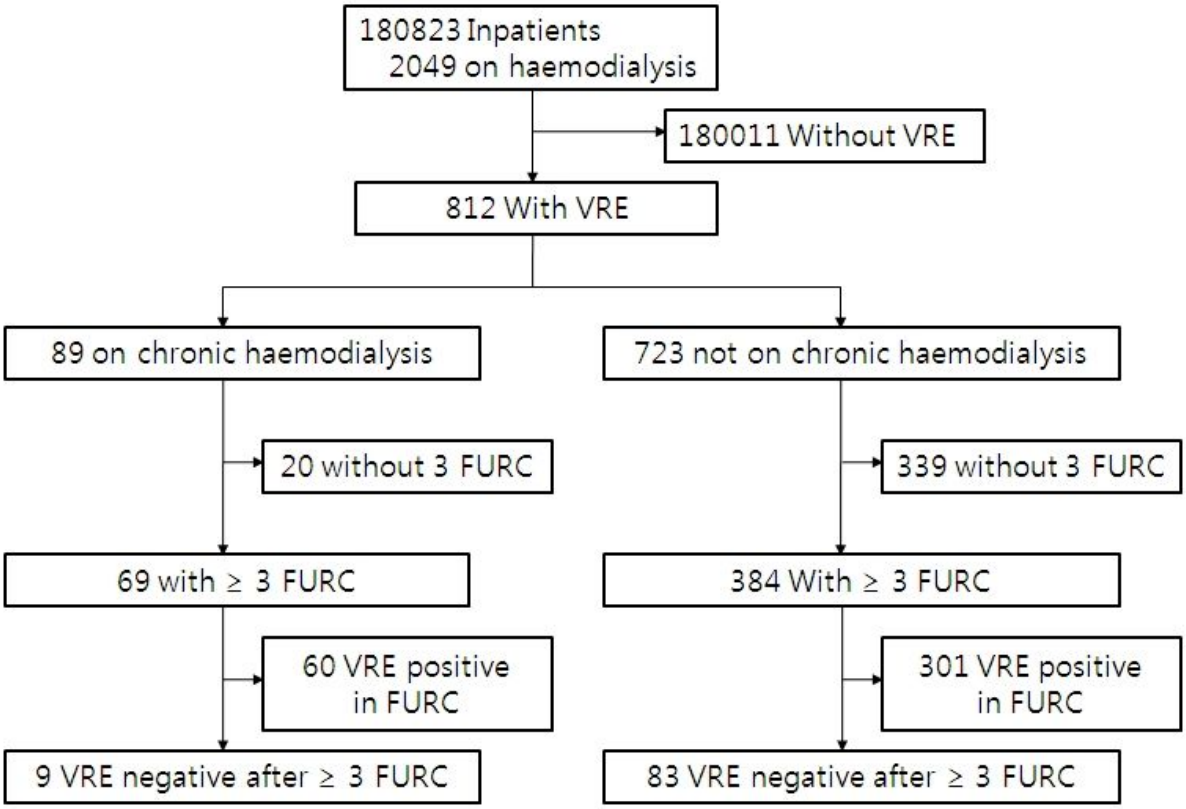

Fig. 1 Number of patients in the study.

VRE, vancomycin-resistant enterococci; FURC, follow-up rectal culture

Table 1. Characteristics of the patients with vancomycin-resistant enterococci (VRE) followed by more than 3 consecutive rectal cultures

	Chronic HD (n= 69)	Non-chronic HD (n= 384)	*P*-value
Age (years)	59.8±15.7	53.6±21.9	0.008
Male gender (%)	33 (53.2)	182 (47.4)	0.39
Diabetes (%)	20 (32.3)	57 (14.8)	0.002
Malignancy (%)	11 (17.7)	104 (27.1)	0.16
Glycopeptide (%)	48 (77.4)	183 (47.7)	< 0.001
3rd generation cephalosporin (%)	26 (41.9)	181 (47.1)	0.49
Imipenem (%)	8 (12.9)	62 (16.1)	0.58
Metronidazolde (%)	7(11.3)	58 (15.1)	0.56
MRSA (%)	29(46.8)	199 (51.8)	0.50
Hospital day (days)	53.2±43.8	49.0±48.9	0.53
The number of rectal cultures	12.9±16.6	9.9±8.4	0.19
The length of time of rectal cultures (days)	109.9±183.2	95.0±169.0	0.56
VRE-positive on the first follow up rectal culture (%)	44 (71.0)	339 (88.3)	0.001

HD, haemodialysis; MRSA, methicillin-resistant *Staphylococcus aureus*

Tabel 2. Characteristics of the vancomycin-resistant enterococci (VRE)-negative patients on more than 3 consecutive rectal cultures

	Chronic HD (n= 9)	Non-chronic HD (n= 83)	*P*-value
Age (years)	59.3±16.6	48.5±22.9	0.18
Male gender (%)	6 (66.7)	41 (49.4)	0.33
Diabetes (%)	1 (11.1)	10 (12.5)	0.93
Malignancy (%)	1 (11.1)	26 (31.3)	0.21
Glycopeptide (%)	8 (88.9)	26 (31.3)	0.001
Duration of glycopeptides use (days)	12.7 ± 8.3	4.5 ± 8.2	0.001
3rd generation cephalosporin (%)	5(55.6)	41(49.4)	0.73
Duration of cephalosporin (days)	9.3±10.4	7.0±9.6	0.60
Hospital day (days)	54.8.±33.2	68.7±73.3	0.97
The number of rectal cultures	26.6±29.0	11.0±10.3	0.18
The length of time of rectal cultures (days)	273.9±390.3	137.2±260.9	0.23
Interval between initial VRE positive and 3 consecutive negative cultures (days)	111.4±155.4	60.7±183.9	0.011

HD, haemodialysis

Table 3. Binary logistic regression analysis for vancomycin-resistant enterococci negative in more than 3 consecutive rectal culture

Variable	Odds ratio	95% CI	*P*-value
Male gender	1.438	0.88 - 2.37	0.15
Age	0.989	0.98 – 1.00	0.048
Chronic haemodialysis	1.183	0.53 - 2.64	0.68
3rd generation cephalosporin	0.874	0.53 - 1.44	0.60
Diabetes	1.452	0.70 - 2.99	0.31
Malignancy	0.711	0.41 - 1.22	0.22
Glycopeptide	2.155	1.30 - 3.58	0.003
Length of hospital stay	1.009	1.004 - 1.015	0.001

CI, confidence interval

Table 4. Predictive value of negative vancomycin-resistant enterococci rectal cultures

Number of consecutive negative cultures following a positive culture	Chronic HD		Non-chronic HD		Total	
	Number of culture	% with next culture negative	Number. of culture	% with next culture negative	Number of culture	% with next culture negative
2	14	64.3	112	74.1	126	73.0
3	6	66.7	36	72.2	42	71.4
4	2	100	10	90.0	12	91.7

HD, haemodialysis,

IV. DISCUSSION

Enterococci have been known for more than a century for their role as a common cause of endocarditis, a disease that is fatal without effective antimicrobial therapy. (Maccallum and Hastings, 1899) The reasons for the ongoing increase in the rates of VRE are multifactorial. They include poor compliance with contact precautions, antibiotic exposure, a long reservoir of patients who continue to disseminate VRE to other patients, and patients with unrecognised VRE colonisation. The enterococci are Gram-positive, facultatively anaerobic oval cocci that form chains of various lengths; they are sturdy and versatile, with a particular ability to survive under harsh conditions and at a wide range of temperatures (from 10° C to > 45° C).(Arias and Murray, 2012) They can survive for long periods on environmental surfaces, including medical equipment, bed rails and doorknobs.(Bradley and Fraise, 1996) Enterococci are also tolerant to heat, chlorine and some alcohol preparations, which may help explain why these organisms are widely disseminated in the hospital setting. Enterococci are common inhabitants of the gastrointestinal(GI) tract of humans and other animals as well as that of insects and nematodes. Although these species normally constitute a small proportion of the gut microbiota, an important first step towards nosocomial enterococcal infection seems to be increased density of colonization of the GI tract. (Eckburg et al., 2005; Arias and Murray, 2012) The exposure of hospitalized patients to antibiotics (for example, cephalosporins and some penicillins-that is, piperacillin-tazobactam-with activity against Gram-negative bacteria and Gram-positive species excluding *E.faecium*) results in substantial changes in the gut microbiota that facilitate colonization of the GI tract by VRE. (Donskey et al., 2000; Ubeda et al., 2010) Transmission can be amplified depending on how many patients have contact with the 'vector' and correlates with the density of VRE in patient stools. (Austin et al., 1999) This concept highlights the importance of curtailing the chain of transmission through active surveillance and contact precautions for infected and colonized individuals, through implementation of strict hand hygiene practices for health care workers, through judicious use of antimicrobials and through aggressive environmental cleaning methods. (Muto et al., 2003; Sydnor and Perl, 2011) This study demonstrated that chronic haemodialysis patients have a longer interval between the initial VRE isolate and three consecutive negative cultures than non chronic haemodialysis patients, and rectal culture method fails to detect a large proportion of patients with gastrointestinal VRE.

Colonisation with VRE can be prolonged, so the current recommendation by the Hospital Infection Control Practice Advisory Committee (HICPAC)(1995; Siegel et al., 2007) is that isolation precautions should be maintained until VRE-negative results are documented with at least three consecutive negative cultures collected a minimum of a week apart. However, there are few reports on the adequacy of consecutive negative follow-up rectal cultures to determine the clearance in chronic haemodialysis patients. In the current study, although the number of culture sets was small, four out of six cultures remained negative after three sequential negative rectal cultures. The negative predictive value of the third negative VRE culture in non-chronic haemodialysis patients was higher than that in chronic haemodialysis patients. Dialysis patients are predisposed to colonisation with VRE as a result of co-morbid conditions, frequent antibiotic exposure, and numerous hospitalisations.(Handwerger et al., 1993; Humphreys et al., 2004; Grabsch et al., 2006) Because of these unique factors in chronic haemodialysis patients, the considerable possibility of conversion to a positive status should be considered, even for patients deemed "cleared" of VRE based on three negative cultures. Although Byers *et al*.(Byers et al., 2002) reported that 35 (95%) out of 37 patients remained negative after three sequential cultures, in the current study, only 30 (71.4%) out of 42 culture sets were negative after three additional negative cultures. These results demonstrate that a significant proportion of patients colonised with VRE would not be detected, even after three negative weekly cultures. The considerable false-negative rate is associated with the rectal culture method in patients with low VRE stool densities. The overall sensitivity of follow-up rectal cultures for the detection of VRE colonisation was 58%, but this varied directly with the VRE density in stool specimens from 100% at high densities (≥ 7.5 logs per gram) to 0% at low densities (≤ 4.5 logs per gram) in one report.(D'Agata et al., 2002) Therefore, colonisation may go unrecognised until the faecal levels of VRE carriage become detectable (e.g., after antibiotic exposure).(Green et al., 1991) Furthermore, variations in sampling technique and sampling error might contribute to false-negative results in follow-up rectal cultures. The high rate of false-negatives of follow-up rectal cultures may contribute to the continued increase in the prevalence of VRE. Therefore, future studies will need to quantify the risk of VRE dissemination from patients with low VRE stool densities and determine if their contribution to the spread of VRE justifies the widespread use of more sensitive screening tests.

A significant correlation was observed between the duration of glycopeptide use and VRE colonisation. Previous studies also reported an association between antibiotic exposure, particularly exposure to vancomycin, and the acquisition of VRE in chronic haemodialysis patients.(Siegel et al., 2007),(D'Agata et al., 2001) The judicious use of vancomycin is particularly relevant among chronic haemodialysis patients because these patients receive vancomycin substantially more often than other patients.(Green et al., 2000) Moreover, patients who need glycopeptides might tend to be more serious ill status. Therefore, they can have more frequent chances to contact contaminated care givers and medical divices. The present study showed that 228 patients (50.3%) with VRE had methicillin-resistant *Staphylococcus aureus* (MRSA). Of even greater concern is the potential for the vancomycin-resistance gene complex to transfer to MRSA, which would render the most important nosocomial pathogen resistant to virtually all antibiotics. Strains of *S. aureus* with reduced susceptibility to vancomycin have been reported.(Smith et al., 1999) Of the six patients from whom these strains were isolated, four had received chronic haemodialysis and one had undergone acute dialysis.(Fridkin, 2001) Because of the significant role of chronic haemodialysis patients in the epidemic of VRE, MRSA and vancomycin-intermediate and vancomycin-resistant *S. aureus*, physicians providing care for these patients have an important responsibility to use antimicrobials judiciously and carefully follow practice guidelines that could limit the further spread of these organisms.

This study had several limitations based on the retrospective design and single rectal culture. Increasing the number of rectal cultures or stool cultures obtained at each collection might have increased the VRE yield. However, this study was based on the standard practice of surveillance.

V. CONCLUSION

In summary, chronic haemodialysis patients may have prolonged VRE colonisation and the currently used culture techniques may fail to detect VRE.

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- 국문요약 -

만성 혈액투석 환자에서 반코마이신 내성 장구균 검출을 위한 직장 배양검사 : 위음성률과 집락형성의 지속 시기

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반코마이신 내성 장구균 (vancomycin-resistant enterococci, VRE)의 감염과 집락 형성은 만성 혈액투석환자에서 흔히 발견된다. 그러나, 이들 환자에서 VRE 집락 유지 기간이나 집락이 더 이상 없다고 하는 직장내 검체를 이용한 배양 검사 (이하 직장 배양 검사)의 유의성에 대해서는 잘 연구 되어 있지 않는 실정이다. 이 연구에서는 VRE가 검출된 만성 혈액 투석 환자들을 후향적으로 분석하여 집락 유지 기간과 직장 배양 검사의 유의성을 알아 보고자 하였다. 직장 배양 검사는 연속적으로 3회 이상 일주일 이상의 간격을 두고 실시한 경우로 2003년 6월 1일부터 2010년 3월 1일까지 시행된 결과를 대상으로 연구하였다. 연구 기간 동안 812명의 환자에서 VRE가 동정되었고 그 중 89명이 만성 혈액투석환자였으며, 92회의 3회 연속 직장 배양 음성 결과가 있었다. 3회 연속 직장 배양 음성 결과가 나오는 데 소요된 날은 비만성 혈액투석환자에서는 60.7±183.9 일 이었으며 만성 혈액 투석 환자에서는 111.4±155.4 일이었다 (P= 0.011). 3회 연속 직장 배양 검사

가 음성으로 나오는 데 관여하는 독립 위험 인자는 글라이코펩타이드계 항생제 사용 (odds ratio [OR], 2.155; *P*=0.003) 과 재원 기간(OR, 1.009; *P*=0.001)이었다. 3회 연속 직장 배양 검사 음성 후, 만성 혈액 투석 환자 6명중 2명을 포함해서, 전체 36명중 10명 에서는 다시 VRE 직장 배양 양성 결과가 나왔다. 결론적으로, 3회 연속 VRE 직장 배양 검사 결과가 음성이어도, 상당한 비율로 VRE 양성 환자일 수 있으며, VRE 집락 유지 기간은 만성 혈액 투석 환자에서 더 긴 경향이 있었다. 이 결과는 VRE의 유병률의 증가와 관련되어 있을 수 있다고 생각된다.

핵심어 : 반코마이신 내성 장구균, 혈액투석, 말기 신부전