

병원 외부로부터 반코마이신내성 장알균의 꾸준한 유입

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Steady Inflow of Vancomycin-Resistant Enterococci from Outside a Hospital

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Background: Cross-transmission within hospitals has been considered a major source of vancomycin-resistant enterococci (VRE) acquisition. Inflow of VRE from outside hospitals may also be an important factor in South Korea.

Methods: An active-point surveillance for VRE colonization was performed in one medical ward of a 767-bed hospital using single rectal swabs or stool samples. The proportion of VRE detected within 48 h of admission was sought. Risk factors for VRE acquisition were analyzed. To confirm the persistence of VRE inflow outside a single point, the degree of yearly VRE inflow was assessed by passive surveillance of clinical specimens over 2 years in the hospital, each one year before and after the active surveillance.

Results: The active-point surveillance of 9 days resulted in 28 (28/72, 38.9%) VRE-positive patients, of whom nine (9/72, 12.5%) were patients were estimated to originate from outside the hospital. The duration of hospitalization and the use of antibiotics were significant risk factors for VRE colonization after admission, and the number of days from admission to first VRE positivity was a median of 8.5 (interquartile range, 2.7-15.0). During the 2 years, 213 patients were identified to be VRE-positive per clinical specimens with 95.5% of concurrent stool VRE, and 12.6% (27/213) were estimated to have acquired the infection from outside the hospital. This confirmed that the VRE inflow was continuous, but not transient or resembling an outbreak on one point.

Conclusion: The inflow of VRE was steady in a tertiary hospital with an average infection control policy in South Korea and should be a further target for VRE control.

Keywords: Active surveillance, Infection control, Risk factor, Vancomycin-resistant enterococci (VRE)

Introduction

Received: June 17, 2017

Revised: July 9, 2017

Accepted: August 26, 2017

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The increase of vancomycin-resistant enterococci (VRE) colonization and invasive infection in medical facilities is a universal trend. According to National Healthcare Safety Network (NHSN) data from 2011-2014 in the United States, enterococci was ranked 3rd of healthcare-associated pathogens, and 30.0% of enterococci that caused healthcare-associated infections in 2014 were vancomycin-resistant [1]. Cross-transmission within hospital has been considered a major source of VRE infection, but several other factors have been associated with

out-of-hospital VRE [2]. Specific facilities are known as important reservoirs of VRE. In one study, 45% of long-term care facilities (LTCFs) residents who were admitted to acute care in hospitals were VRE carriers [3]. As the overall prevalence of VRE rises in hospitals, patients with ongoing medical care or recent hospitalization pose the risk of VRE influx into other hospitals.

The burden of VRE in medical facilities in South Korea seems to be high, but data regarding the epidemiology of VRE are limited. In one study, 7.2% of patients admitted to an intensive care unit between 2008 and 2010 were colonized with VRE [4]. In another study, 24.0% of patients who were admitted to neurosurgery wards with risk factors were positive for VRE [5]. The Korean Nosocomial Infections Surveillance System (KONIS) showed that enterococci including both *Enterococcus faecalis* and *Enterococcus faecium* ranked 2nd among nosocomial pathogens in 166 intensive care units of 94 hospitals in 2013-2014; 28.3% of all enterococci were VRE [6]. We have few data about the status of VRE inflow into hospitals from outside and its effect on nosocomial infections. As a pilot study, we tried to show the status of VRE inflow burden in a single hospital with standard infection control policy.

Materials and Methods

1. Study design

The study was performed in a 767-beds university-affiliated public hospital in South Korea. Primary purpose of this study was to estimate the burden of VRE inflow in one medical ward of a hospital with average infection control policy by an active point surveillance for VRE. Then, to confirm the persistence of VRE inflow excluding the possibility of an outbreak at the point surveillance, the degree of yearly VRE inflow was assessed during two years in the hospital, each one year before and after the point surveillance. The medical ward of a

study subject had 61 beds, consisting of one single room and twelve 5-bed rooms. All patients who were already staying or newly admitted in the ward during the study period were enrolled. The surveillance was performed for 9 days (29 December 2015 to 6 January 2016). Rectal swabs or stool were submitted for VRE culture. The screening culture was performed only one time for all patients. All in-patients in the ward were subjected to the surveillance in a single day to rule out the possibility of on-going cross-transmission. For newly admitted patients, the screening was done within 24 h after admission. Inter-ward transfer of in-patients was not permitted during the study period. To estimate the initial entry burden of VRE into the hospital from outside, patients having hospital stay less than 48 hours were grouped as new admission. To assess risk factors for VRE acquisition, clinical variables including demographic characteristics, comorbidities, use of antibiotics, length of stay, and route of admission were analyzed. The degree of yearly VRE inflow during two years was assessed retrospectively by passive surveillance of clinical specimens. The assumption was that the VRE inflow would be persistent during two years and the level of inflow would be comparable to the result of active single point surveillance, though the scale of magnitude was not same due to the difference of active versus passive surveillance methods.

2. Identification of VRE

Rectal swabs or stool were inoculated in VRE selection media (ETC Broth[®], Hanil Komed, Seongnam, South Korea) containing 6 μ g/mL of vancomycin and were incubated at 37°C for 24 h. Subcultures were performed on chromogenic agar (ChromID VRE) and enterococci were identified using the Vitek-2 System (bioMérieux, Marcy-l'Etoile, France).

3. Institutional infection control policy for VRE

Infection control policy for VRE in the study

hospital includes passive surveillance for VRE. Patients are incidentally found to have VRE in urine, wounds or sterile body sites as simple carriers or invasive infection in routine clinical practices. VRE carriers are isolated in a single room or in cohorts. Contact isolation continues until 3 consecutive negative cultures of VRE are obtained at 3-7 days interval. Medical items such as stethoscopes, thermometers, blood pressure cuffs and tourniquets are solely dedicated to individual patient with VRE. Environmental disinfection is performed routinely. Patients who were VRE carriers in the past 3 months but were not documented to meet the negative conversion criteria are isolated at their re-admission until they are confirmed to be negative for VRE. Audits for the proper implementation of contact precautions occur weekly, and feedback to healthcare workers is provided. Monitoring for hand hygiene using the World Health Organization hand hygiene guide is performed weekly.

4. Statistical analysis

Categorical variables were analyzed using Fisher's exact tests or chi square tests, and continuous variables were analyzed using t-tests. Univariate analyses were used to determine the risk factors for VRE colonization. Backward stepwise multiple logistic regression analysis including the variables with $P < 0.100$ in the univariate analyses was performed. All

statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant (SPSS 22.0; SPSS Inc., Chicago, IL, USA).

5. Ethics statement

This study was approved by the Institutional Review Board of Boramae Medical Center (26-2017-8). Collection of informed consent was waived because this study was conducted as part of institutional policies to improve internal infection control and the retrospective nature of the study. This research was in compliance with the Helsinki Declaration.

Results

1. VRE colonization

During 9 days of active point surveillance, 72 patients were screened for stool or rectal VRE colonization by culture. The hospital stay until the screening test for VRE was median 3.5 (interquartile range [IQR] 2.0-7.7) days. Twenty-eight (28/72, 38.9%) patients were VRE-positive. VRE was detected in 11 patients out of the twelve 5-bed rooms that had 1 to 4 VRE-positive patients in each 5-bed room. The duration from admission to first VRE positivity was median 8.5 (IQR, 2.7-15.0) days. All VRE isolates were *E. faecium*. There was no concurrent invasive VRE infection. Among the positive VRE, 12.5% (9/72) were from patients within 48 h

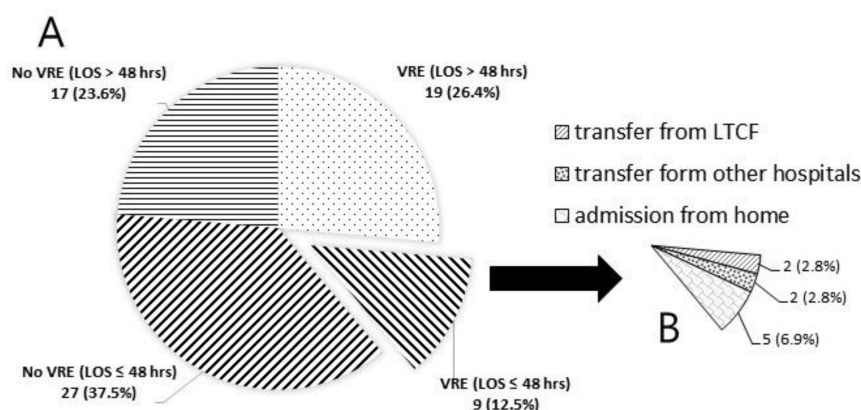


Fig. 1. (A) Results of active surveillance for vancomycin-resistant enterococci (VRE) by length of stay (LOS) and VRE-positivity. (B) Distributions of location before admission of the patients with VRE. LTCF, long-term care facility.

of admission (Fig. 1). Of these 9 patients, 5 patients were admitted directly from community, 2 patients from other acute care hospitals, and the other 2 patients from long-term care facilities. Thirty-six patients had stayed >48 h when the screening was performed. Their hospital stay until the VRE test was median 8.5 (IQR 5.0-13.2) days. Nineteen of these patients (19/36, 52.7%) were VRE-positive. The other 36 patients were newly admitted of whom 9 (9/36, 25.0%) were VRE-positive (Fig. 1). Of all subjects, 54.2% (39/72) were administered antibiotics during their current admission before the screening VRE tests.

2. Risk factors for VRE colonization

To determine risk factors for VRE colonization in the general ward, the 72 patients were divided into VRE-positive and VRE-negative groups. There were no significant gender or age differences between

two groups. There were various comorbidities, but the difference was not significant (Table 1). Risk factors for VRE in univariate analysis were hospitalization more than 48 h, use of antibiotics during hospitalization, and duration of antibiotic use (Table 1). Multivariate analysis showed that the duration of hospitalization was a significant risk factor for VRE colonization ($P=0.001$, 95% confidence interval 1.098-1.455).

3. Trend of VRE inflow into a hospital

During two-year period of before and after the point surveillance, 213 patients (104 patients in 'before period' and 109 patients in 'after' period) were identified to be VRE-positive in clinical specimens. Concurrent stool VRE positivity was 95.5% (173/181). The days from admission to first VRE positivity was median 18.0 (IQR, 8.0-34.0). VRE positivity within 48 h of admission was 12.6%

Table 1. Characteristics of patients in a point VRE surveillance in one medical ward (N=72)

Variable	VRE-negative (n=44)	VRE-positive (n=28)	P value
Gender, male, n (%)	26 (59.1)	17 (60.7)	0.545
Age, years (mean±SD)	65.4±16.4	64.7±11.9	0.847
Underlying diseases, n (%)			
Diabetes mellitus	21 (47.7)	10 (35.7)	0.224
Hypertension	32 (72.7)	17 (60.7)	0.209
Chronic kidney disease	14 (31.8)	7 (25.0)	0.365
Chronic liver disease	2 (4.5)	4 (14.3)	0.154
COPD	3 (6.8)	0 (0)	0.222
Solid tumor	4 (9.1)	5 (17.9)	0.230
Hematologic malignancy	0 (0)	1 (3.6)	0.389
Other*	13 (29.5)	12 (42.9)	0.183
No comorbidity	3 (6.8)	1 (3.6)	0.492
Duration of hospitalization, mean days (IQR)	3.3 (1.0-4.0)	13.7 (2.7-15.0)	0.022
≤48 h, n (%)	27 (61.4)	9 (32.1)	0.016
>48 h, n (%)	17 (38.6)	19 (67.9)	-
Route of admission, n (%)			
Transfer from LTCF	4 (9.1)	4 (14.3)	0.703
Transfer from other hospitals	3 (6.8)	3 (10.7)	0.672
Admission from community	37 (84.1)	21 (75.0)	0.197
New admission	3 (6.8)	6 (21.4)	0.140
In-hospital use of antibiotics	18 (40.9)	21 (75.0)	0.005
Duration, mean days (IQR)	1.2 (0-1.7)	8.6 (0.2-10.7)	0.008

*Other includes a small number of various comorbidities such as septic arthritis, extrapulmonary tuberculosis, lung abscess, and dermatomyositis.

Abbreviations: VRE, vancomycin-resistant enterococci; SD, standard deviation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LTCF, long-term care facility.

Table 2. VRE-positive patients in clinical specimens during two years, one year each ‘before’ and ‘after’ the point surveillance

Variables	Before, N=104 (2014.12-2015.11)	After, N=109 (2016.2-2017.1)	P value
Gender, female:male (%)	48:56 (53.8)	49:60 (55.0)	0.860
Age, years (mean±SD)	68.0±16.2	69.7±14.0	0.430
Admission to first VRE-positive (median days, IQR)	20.0 (10.0-36.0)	17.0 (8.0-34.0)	0.238
Route of admission, n (%)			0.564
LTCF	13 (12.5)	18 (16.5)	
Other hospitals	19 (18.3)	16 (14.7)	
Community (admission Hx ≤3 m)	23 (22.1)	30 (27.5)	
Community (no admission Hx ≤3 m)	49 (47.1)	45 (41.3)	
Organism: <i>Enterococcus faecium</i> , n (%)	98 (94.2)	108 (99.1)	0.061
Specimen-stool cultures concordance	85/88 (99.6)	88/93 (94.6)	0.721
VRE+ within 48 h of admission	13 (12.5)	14 (12.8)	0.940

Abbreviations: VRE, vancomycin resistant enterococci; SD, standard deviation; LTCF, long-term care facility; Hx, history.

(27/213). Patients who were transferred from other hospitals or long-term care facilities, and had recent hospitalization had higher risk of VRE at admission than patients who were admitted from the community without recent hospitalization (21/119 vs 6/94, $P=0.021$). When the ‘before’ and ‘after’ period were compared, the days from admission to first VRE positivity seemed to be longer in ‘before’ group (median 20.0, IQR 10.0-36.0) than in ‘after’ group (median 17.0, IQR 8.0-34.0), but the difference was not significant ($P=0.238$). Other variables like route of admission, proportion of *E. faecium*, concordance rate of VRE in clinical specimens and stool, and VRE positivity at admission were not significantly different between two groups (Table 2).

Discussion

Our study showed that considerable proportion of patients with VRE who would have easily been identified at admission by active screening might have been spreading VRE until incidentally found to be VRE-positive later during hospitalization. High concordance rate of clinical specimens and stool VRE positivity suggests that the burden of VRE in the patients was large and ready to be a source of cross-transmission when VRE was found in clinical specimens. In our study, 52.7% of in-pa-

tients staying for more than 48 h in one medical ward were stool VRE-positive by single screening, and the hospital stay prior to VRE detection was median 8.5 (IQR, 5.0-13.2) days. The length of hospitalization ($P=0.001$) and the use of antibiotics ($P=0.081$) were associated with the acquisition of VRE. These risk factors for VRE acquisition in this study are consistent with previous studies. However, the length of hospital stay before the detection of VRE colonization or infection in our study was shorter than those in previous reports which ranged from 16-39 days [7-10]. Twenty-five percent of new admissions were VRE-positive, and considering that the sensitivity of the first rectal VRE screening could be less than 50% [11], higher proportion of new patients might have been VRE carriers. Initial higher burden might have made the incubation period shorter. Antibiotics might have hastened the VRE acquisition, as previous studies indicated [12].

We analyzed VRE infected patients from passive VRE surveillance for two years. Due to the nature of retrospective and passive data collection, these data didn’t show the overall status of VRE in the hospital. Regardless of this limitation, there was definitely a steady number of VRE inflow from outside hospitals or community. In this context, the in-between active point surveillance data might suggest the proximation of real VRE occurrence. To

evaluate the exact magnitude of inter-hospital or inflow burden of VRE, multicenter active surveillance is needed.

The high endemicity of VRE in acute and long-term healthcare facilities in South Korea seems to be a source of VRE for other hospitals. So, we need to further focus on the inflow of VRE at admission. Active surveillance for VRE resulted in a reduction in VRE colonization, and was cost-effective [13,14]. Increasing trend of VRE infections and evidences of constant VRE inflow from outside as shown in our study make it clear that intensive surveillance and intervention at early phase of admission are critical for strict VRE control. According to the Management Guidelines for Healthcare Associated Infections released by the Korean Centers for Disease Control and Prevention (KCDC) [15], strict contact isolation is mandatory, and active surveillance for VRE is recommended for high-risk patients or patients from healthcare facilities and LTCFs.

It is evident that we need to concentrate on both the cross-transmission within hospital and the entry from outside for proper VRE control. In a practical aspect, however, considerable cost and resources are necessary for the strict infection control which have not properly been evaluated in South Korea. Strict contact precautions have resulted in negative effects on patients [16]. Isolated patients were twice as likely to experience adverse events, which may be detrimental to care, as a result of the decreased patient contact with healthcare workers [17,18]. VRE is not the only problem. Other MDROs and infectious organisms are increasingly becoming targets for intensive infection control [15]. In South Korea, the government which controls all essential medical practices and related costs has been under continuous pressure to invest in and improve the infection control, the allocation of resources is still limited. We need both to increase the size of investment and to utilize the limited resources in a balanced manner to combat the overflowing prob-

lem of MDROs including VRE. As the Australian experience of policy change in a VRE-endemic area suggested [19], universal infection control strategies that cover all MDROs as targets would deserve to be considered in managing MDROs infection than concentrating on the several specific organisms (vertical intervention) in gradually loosing combat to VRE.

Our study has some limitations. First, our findings are based on single hospital experience and the small number of subjects might not represent most hospitals in South Korea. Second, as we performed only single VRE surveillance for each patient, this might cause the underestimation of VRE prevalence and the bias for some variables like durations. Third, as we provided with limited number of passive surveillance data for the 2-years period instead of active surveillance data covering all the patients in the hospital, we couldn't estimate the proportion or denominators of variables. This limited our understanding of overall epidemiology in the hospital.

In summary, we showed from an active point surveillance plus passive surveillance for VRE during 2 years in one tertiary hospital in South Korea that there was steady inflow of VRE into a hospital, and this might be another important component of VRE burden in the medical facilities. Infection control strategy to focus on the inflow of VRE is needed. Further study is needed to clarify whether this inflow of VRE into hospitals would be an important source of aggravation in invasive infections by VRE.

Summary

배경: 병원내 교차전파는 반코마이신내성 장알균(VRE) 획득의 주요 원인으로 생각되었다. 그러나 국내에서는 병원 외부로부터의 유입도 중요한 원인이 될 수 있을 것이다.

방법: 한 대학병원의 내과계 병동 한 곳에서 전체 입원환자들의 VRE 보균여부를 확인하기 위해 직장도말 또는 대변 1회 검사를 이용하여 단

시점 능동감시를 시행하였다. 대상환자 중 입원 48시간 이내에 VRE 양성인 환자의 분율을 구하였고, VRE 양성의 위험인자를 분석하였다. 외부로부터의 VRE 유입의 지속성을 확인하기 위해 단시점 능동감시 전후로 각각 1년씩 총 2년 동안 대상 병원의 임상검체를 수동적 감시로 평가하여 연간 VRE 유입의 정도를 측정하였다.

결과: 9일간의 단시점 능동감시에서 28명(28/72, 38.9%)이 VRE 양성환자였고, 이 중 9명은 병원 외부에서 유래한 것으로 추정되었다. 입원기간과 항생제의 사용이 입원 후 VRE 보균의 유의한 위험인자였고, 입원부터 VRE 첫 양성까지의 기간은 중앙값 8.5 (사분위수 범위 2.7-15.0)일이었다. 능동감시 전후 총 2년 동안 환자 213명의 임상검체에서 VRE가 분리되었고, 95.5%는 동시에 대변에서 VRE 양성이었으며, 이 중 12.6% (27/213)는 병원 밖에서 유래한 것으로 추정되어 외부로부터 VRE 유입은 일시적이거나 단기의 유행에 의한 것이 아니라 지속적임을 확인할 수 있었다.

결론: 한국에서 평균적인 감염관리정책을 시행하고 있는 한 3차병원에서 VRE의 유입은 꾸준하였고, 이것은 VRE 관리의 추가적인 표적이 되어야 할 것이다.

Acknowledgements

The authors have no potential conflicts of interest to disclose.

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