

Predictors of prolonged vancomycin-resistant enterococci colonization in acute stroke patients admitted to an intensive care unit

A retrospective cohort study

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Abstract

To investigate the factors affecting the duration of vancomycin-resistant enterococci (VRE) colonization in stroke patients.

A total of 52 stroke patients with VRE colonization were enrolled. We divided the groups into several factors and confirmed whether each factor affected VRE colonization. Independent *t* test, bivariate correlation analysis, and Cox proportional hazards model were used to confirm statistical significance.

Among 52 patients, 28 were ischemic stroke and 24 were hemorrhagic stroke. The mean duration of the VRE colonization was 39.08 ± 44.22 days. The mean duration of VRE colonization of the ischemic stroke patients was 25.57 ± 30.23 days and the hemorrhagic stroke patients was 54.83 ± 52.75 days. The mean intensive care unit (ICU) care period was 15.23 ± 21.98 days. Independent sample *t* test showed the hemorrhagic stroke ($P < .05$), use of antibiotics ($P < .01$), oral feeding ($P < .01$) were associated with duration of VRE colonization. Bivariate correlation analysis showed duration of ICU care ($P < .001$) was associated with duration of VRE colonization. Cox proportional hazard model showed oral feeding ($P = .001$), use of antibiotics ($P = .003$), and duration of ICU care ($P = .001$) as independent factors of duration of VRE colonization.

Careful attention should be given to oral feeding, duration of ICU care, and use of antibiotics in stroke patients, especially hemorrhagic stroke patients, for intensive rehabilitation at the appropriate time.

Abbreviations: ICU = intensive care unit, VRE = vancomycin-resistant enterococci.

Keywords: colonization, intensive care unit, stroke, vancomycin-resistant enterococci

1. Introduction

Enterococci is a normal intestinal flora and is one of the most important causes of nosocomial infection.^[1] Vancomycin-resistant enterococci (VRE) was first identified in Europe in 1986. Recently, the increasing use of antibiotics has increased the number of patients infected with VRE and has become a major

pathogen worldwide.^[2,3] Although the incidence of VRE colonization is uncertain, the results of a meta-analysis study on the incidence of VRE colonization in patients admitted to the intensive care unit (ICU) showed that the incidence rate was 5.3% in the ASIA population.^[4] Nationwide surveillance in Korea has also shown increasing resistance of *Enterococcus* to vancomycin, ranging from 2.9% in 1997 to 17%–21% in 2007.^[5,6] VRE colonization has been identified in most gastrointestinal tracts, but has also been identified in skin and genitourinary tracts.^[4] Health care workers' hands are now identified as the major source of transmission.^[7] Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.^[8] Brain damage due to lack of blood supply causes various disability.^[9] Stroke patients should undergo rehabilitation at the same time as acute care and should be focused on minimizing the sequelae of brain damage through more active rehabilitation after acute care.^[10–12] Stroke patients with VRE colonization are undergoing isolation and contact caution care to prevent infection.^[13] For this reason, VRE colonization is one of the important factors that makes active rehabilitation treatment difficult. Therefore, minimizing the duration of VRE colonization is an important factor to reduce patient disability. However, there is a lack of research on what factors currently affect VRE clearance in stroke patients. Previous studies have shown that antibiotic use, ICU care, affects VRE colonization.^[14–17] Dysphagia and gait disturbance are common in patients with

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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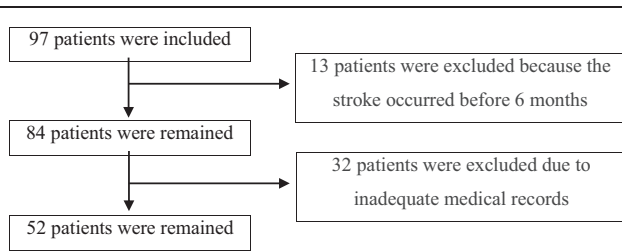


Figure 1. Number of patients in the study.

stroke. Therefore, in this study, we checked whether there was a change in the duration of VRE colonization according to feeding and ambulation, including the previously known antibiotic use and ICU care duration. In addition, duration differences of VRE colonization by underlying disease, comorbidity burden were also studied.

2. Methods

2.1. Subject

The study included patients admitted to the Kosin University Gospel Hospital from 2013 to 2017. This study was approved by our institutional review board, and the requirement for written consent was waived (IRB No. KUGH 2019-06-010). Patients were diagnosed with stroke and were admitted to the ICU and received a rectal swab at admission. The inclusion criteria were: patients with ischemic or hemorrhagic stroke, patients in whom VRE was cultured through a rectal swab, and patients who have finally confirmed VRE negative. All patients were assumed to be VRE-negative prior to admission. Patients with a stroke onset more than 6 months or patients with insufficient medical records were excluded. A total of 97 patients were included in the study and 13 patients were excluded after 6 months of stroke. Thirty-two patients were excluded because of the difficulty in confirming accurate records of ambulation and feeding type. A total of 52 patients were studied (Fig. 1).

2.2. Methods

The specimens were collected through a rectal swab. VRE colonization was confirmed by culturing the specimen in vancomycin-containing selective medium. When rectal culture was positive, the patient was treated with isolation and periodic rectal swabs were performed every week. After first identification of VRE-negative in the colonization test, 2 more tests were performed and the patient was released from the isolation if it was confirmed as 3 consecutive negative.

The test was performed periodically from the day VRE was confirmed. VRE clearance duration was set up to the first inspection date when the negative was confirmed in 3 consecutive times.

Age, sex, body mass index, stroke type, ICU care duration, feeding type, ambulation, underlying disease, comorbidity burden, and antibiotic usage were determined as factors affecting VRE colonization duration. The stroke type was divided into ischemic stroke and hemorrhagic type. Feeding type was divided into oral feeding and tubal feeding group. It was classified as oral feeding group if dietary intake was possible through oral cavity regardless of viscosity of solid, soft, etc. It was classified as tube

feeding group when nasogastric tube, percutaneous endoscopic gastrostomy, percutaneous radiologic gastrostomy. Ambulation was divided into walking group and immobile group. Patients were classified as walking groups if they were able to walk, regardless of whether they were using canes or walkers, and were classified as immobile group when riding a wheelchair or bed ridden state. Walking groups were classified as patients who could walk regardless of whether they were using cane or walker, and were classified as immobile group when wheelchair ambulation or bed ridden state. Patients who can walk but sometimes need a wheelchair were classified into the walking group. Diabetes mellitus and immune diseases were considered among the underlying diseases, and the groups were divided according to the history of diagnosis. Comorbidity burden was calculated using the Charlson comorbidity index, and groups were divided by scores from 0 to 5, and patients with scores of 6 or higher were assigned to the same group. The use of antibiotics was included only when used during the VRE colonization period. When antibiotics were used regardless of oral or intravascular administration, patients were classified into antibiotics administered group. ICU duration also included only those periods for which ICU care was given during the VRE colonization period.

2.3. Statistics

Continuous data were presented using mean and standard deviation, and independent *t* test was performed to statistically confirm the difference between the 2 groups. The log rank *P* value was calculated by the Kaplan-Meier method. In order to confirm the correlation between variables and VRE colonization, bivariate correlation analysis was performed and Pearson correlation coefficient was calculated to confirm the association. Factors affecting the duration of VRE colonization were calculated using competing risk analysis, with death considered as the competing risk.

3. Result

A total of 52 patients were included in this study. Among 52 patients, 23 were male and 29 were female. The mean age was 65.63 ± 13.45 years. There were 28 patients with ischemic stroke and 24 patients with hemorrhagic stroke. The mean body mass index was 23.17 ± 4.21 . The mean duration of the VRE colonization was 39.08 ± 44.22 days. The mean duration of VRE colonization of the ischemic stroke patients was 25.57 ± 30.23 days and the hemorrhagic stroke patients was 54.83 ± 52.75 days. The mean ICU care period was 15.23 ± 21.98 days (Table 1). On the day that VRE colonization was confirmed as negative, 27 patients were able to oral feed, and 12 patients were able to walk. During the VRE colonization, 36 patients were treated with antibiotics. Independent sample *t* test showed the hemorrhagic stroke ($P < .05$), use of antibiotics ($P < .01$), oral feeding ($P < .01$) were associated with duration of VRE colonization. Kaplan-Meier method showed that stroke type, feeding, and ambulation had a significant effect on VRE colonization period (Table 2). Sex and ambulation were not statistically significant. Bivariate correlation analysis showed duration of ICU care ($P < .01$) was associated with duration of VRE colonization (Table 3). Age and body mass index were not statistically significant. Competing risk analysis model showed oral feeding ($P < .01$), use of antibiotics ($P < .01$) and duration of

Characteristics	Value
Age	65.63 ± 13.45
Sex	
Male	23
Female	29
Stroke type	
Ischemic stroke	28
Hemorrhagic stroke	24
Feeding type	
Oral feeding	27
Tube feeding	25
Ambulation	
Walking group	12
Immobile group	40
Underlying disease	
Diabetes mellitus	31
Immune disease	11
Charlson comorbidity index	
0	21
1	4
2	18
3	4
4	2
5	0
6	3
Use of antibiotics	
Administrated	36
Non-administrated	16

Values are presented as mean ± standard deviation or number.

ICU care ($P < .01$) as independent factors of duration of VRE colonization (Table 4).

4. Discussion

The incidence of VRE colonization is increasing.^[4] Despite the limitation of active rehabilitation treatment due to isolation, there is no study of which factors affect the duration of VRE colonization in stroke patients. Active rehabilitation for an appropriate period of time is crucial for stroke patients to return to society. Therefore, it is necessary to study the factors that reduce the duration of VRE colonization. In this study, duration of ICU care, oral feeding, and antibiotic use were found to affect duration of VRE.

Hemorrhagic stroke patients are generally more severe and have a higher mortality rate.^[18] Intracerebral hemorrhage is an independent predictor of poor neurologic outcome.^[19] Hemorrhagic stroke patients were found to have a longer duration of VRE colonization compared to patients with ischemic stroke in independent t test. However, it was not statistically significant in the Cox proportional hazards model. The patients with hemorrhagic stroke were severe and the general condition was bad, which induced prolonged ICU care duration, tubal feeding, and use of antibiotics. Perhaps these factors affected the prolonged VRE-colonization of hemorrhagic stroke patients.

Previous studies have shown that the use of antibiotics is a risk factor for VRE colonization.^[14,15] In this study, 36 patients were using antibiotics and antibiotic use was identified as an independent factor during VRE colonization ($P = .003$). This is thought to be the result of the use of antibiotics to alter the state of

	N	Duration of VRE colonization	P value	Log rank P value
Sex				
Male	23	46.52 ± 48.02	.284	.331
Female	29	33.17 ± 40.84		
Stroke type				
Ischemic	28	25.57 ± 30.23	<.05*	<.05*
Hemorrhagic	24	54.83 ± 52.75		
Feeding type				
Oral feeding	27	18.15 ± 24.39	<.01**	<.01**
Tube feeding	25	61.68 ± 49.86		
Ambulation				
Walking group	12	24.75 ± 34.52	.204	.080
Immobile group	40	43.38 ± 46.25		
Underlying disease				
With DM	31	38.52 ± 43.26	.311	.127
Without DM	21	41.97 ± 40.11		
With ID	11	40.06 ± 37.88	.216	.117
Without ID	41	27.32 ± 31.23		
Charlson comorbidity index				
0	21	31.37 ± 41.65	.341	.231
1	4	28.66 ± 36.51		
2	18	36.28 ± 43.97		
3	4	39.52 ± 37.04		
4	2	38.41 ± 40.23		
5	0			
6	3	39.41 ± 40.55		
Use of antibiotics				
Administrated	36	51.39 ± 48.22	<.01**	<.01**
Non-administrated	16	11.38 ± 6.40		

Values are presented as mean ± standard deviation.

DM = diabetes mellitus, ID = immune disease, VRE = vancomycin-resistant enterococci.

* $P < .05$.

** $P < .01$.

intestinal bacteria and cause overgrowth of VRE colonization.^[20] In patients with stroke, the incidence of all nosocomial infection was 30% and the most common infection was pneumonia.^[21] If any infection occurs, the duration of VRE colonization may be prolonged due to the administration of antibiotics. Therefore, it is necessary to pay attention to the infection in the stroke patient and to reduce unnecessary antibiotic use after completed infection treatment.

The mean ICU care period was 15.23 days and was confirmed to be independent of duration of VRE colonization ($P = .001$). Previous studies have shown that a longer ICU care period will increase the duration of VRE colonization because of the longer exposure to the pathogen.^[16,17] The duration of ICU care was increased by the severity or complication of the stroke, and the longer the ICU care duration, the longer the duration of VRE colonization. Therefore, attention should be paid to the occurrence of general condition deterioration and complication, which can lead to a longer ICU care duration. If the patient's condition is restored, transferring quickly from the ICU to the general ward will help reduce the duration of VRE colonization. The correlation between ICU care duration and VRE colonization duration was statistically significant. The single factor analysis Pearson correlation coefficient was 0.647, but the B value was low at 0.035 in the Cox hazard ratio. When ICU care period was prolonged, oral feeding was not performed in many cases, and complication such as infection occurred frequently and

Table 3**Correlation between variables and duration of VRE colonization (bivariate correlation analysis).**

Variables	B	HR (95% CI)	P value
Age	0.004	1.00 (1.00–1.00)	.199
Sex	0.003	1.00 (1.00–1.01)	.267
Duration of ICU care	−0.02	0.98 (0.97–0.99)	<.01**

CI=confidence interval, HR=hazard ratio, ICU=intensive care unit, VRE=vancomycin-resistant enterococci.

** $P < .01$.

antibiotics were used more frequently. These factors are thought to have affected the outcome.

Stroke patients who were unable to receive oral feeding had a consciousness degradation or swallowing difficulty due to their large lesions or general condition deterioration. However, feeding is a factor that affects the recovery of the condition and it is important to start oral feeding early. Tube feeding can increase the probability of infection with antibiotic-resistant bacteria and can be a source of infection.^[22] In this study, 27 patients were able to receive oral feeding, and oral feeding was found to be a factor in reducing the duration of VRE colonization ($P < .001$). Therefore, an active swallowing rehabilitation is important in order to start feeding early, and it is important to quickly identify the patient's dietary allowance through 3 spoon test, VFSS, etc, and to start a proper diet for swallowing disorder.

Ambulation was not statistically significant ($P = .204$). This result suggests that patients who receive ICU care may actually have ambulation, but most of them are immobilized for stability.

4.1. Strengthening

In this study, it was confirmed that it is important to pay attention to feeding, antibiotic use, and ICU care period to reduce VRE colonization duration of stroke patients. This is the first study of factors affecting the duration of VRE colonization in stroke patients. Previous studies have investigated the risk factors for VRE colonization. However, this study investigated the factors that influence the duration of colonization in patients who already have VRE. Therefore, it may help to reduce the duration of VRE colonization in patients.

Table 4**Factors associated with duration of VRE colonization (competing risk analysis model).**

Variables	HR (95% CI)	P value
Age	1.04 (0.96–1.07)	.279
Sex	1.07 (0.47–1.87)	.675
BMI	0.78 (0.64–1.05)	.346
Hemorrhagic stroke	0.56 (0.20–1.25)	.211
Oral feeding	4.09 (1.73–7.81)	<.01**
Ambulation	0.60 (0.28–1.83)	.310
Duration of ICU care	0.93 (0.89–0.97)	<.01**
Underlying disease - DM	0.41 (0.16–1.76)	.446
Underlying disease - ID	0.54 (0.11–1.44)	.511
Charlson comorbidity index	0.98 (0.43–1.66)	.133
Use of antibiotics	0.31 (0.10–0.62)	<.01**

BMI=body mass index, CI=confidence interval, DM=diabetes mellitus, HR=hazard ratio, ICU=intensive care unit, ID=immune disease, VRE=vancomycin-resistant enterococci.

** $P < .01$.

4.2. Limitation

This study was limited in obtaining the necessary information as a retrospective study. Although the duration of VRE colonization may vary due to the complications of the underlying disease of the patients, the medical record lacks information on underlying diseases. In the case of oral feeding, dietary intake such as solid diet and soft diet is used. However, due to lack of records, we could not classify feeding type into subdivisions. In the case of using antibiotics, there were many cases in which various kinds of antibiotics were used at the same time or changed while using 1 antibiotic instead of using only 1 antibiotic. Therefore, it was difficult to consider the duration of antibiotic use. The duration of the VRE colonization may vary depending on the type of antibiotic, since the bacteria that can be eradicated depends on the type of antibiotic. Therefore, subdivision of the antibiotic class will be necessary in the next study. Also, time-varying covariance due to changes during repeated follow-up was not considered.^[23] And this study was not externally validated.

5. Conclusion

This study showed that stroke type, feeding type, duration of ICU care, and use of antibiotics affect the duration of VRE colonization in stroke patients. It is important that stroke patients be released from isolation and receive intensive rehabilitation treatment. Therefore, careful attention should be given to oral feeding, duration of ICU care, and use of antibiotics in stroke patients, especially hemorrhagic stroke patients, for intensive rehabilitation at the appropriate time.

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References

- [1] Humphreys H. Controlling the spread of vancomycin-resistant enterococci. Is active screening worthwhile? *J Hosp Infect* 2014;88:191–8.
- [2] Uttley AHC, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci. *Lancet* 1988;1:57–8.
- [3] Willems RJL, Top J, van Santen M, et al. Global spread of vancomycin-resistant *Enterococcus faecium* from distinct nosocomial genetic complex. *Emerg Infect Dis* 2005;11:821–8.
- [4] O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. *Infect Drug Resist* 2015;8:217–30.
- [5] Lee K, Lee MA, Lee CH, et al. Increase of ceftazidime- and fluoroquinolone-resistant *Klebsiella pneumoniae* and imipenem-resistant *Acinetobacter* spp. in Korea: analysis of KONSAR study data from 2005 and 2007. *Yonsei Med J* 2010;51:901–11.
- [6] Lee K, Jang SJ, Lee HJ, et al. Increasing prevalence of vancomycin-resistant *Enterococcus faecium*, expanded-spectrum cephalosporin-resistant *Klebsiella pneumoniae*, and imipenem-resistant *Pseudomonas*

- aeruginosa in Korea: KONSAR study in 2001. *J Korean Med Sci* 2004;19:8–14.
- [7] Noskin GA, Stosor V, Cooper I, Peterson LR. Recovery of vancomycin-resistant enterococci on fingertips and environmental surfaces. *Infect Control Hosp Epidemiol* 1995;16:577–81.
- [8] Duncan PW, Zorowitz R, Bates B, et al. Management of adult stroke rehabilitation care: a clinical practice guideline. *Stroke* 2005;36:e100–43.
- [9] Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064–89.
- [10] O'Mahony PG, Thomson RG, Dobson R, Rodgers H, James OFW. The prevalence of disability among adults. *J Public Health Med* 1999;21:166–71.
- [11] Adams HJ, Adams R, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the stroke council of the American Stroke Association. *Stroke* 2003;34:1056–83.
- [12] The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack. *Cerebrovasc Disc* 2008;25:457–507.
- [13] Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. *Mayo Clin Proc* 2006;81:529–36.
- [14] Sohn KM, Peck KR, Joo E-J, et al. Duration of colonization and risk factors for prolonged carriage of vancomycin-resistant enterococci after discharge from the hospital. *Int J Infect Dis* 2013;17:e240–6.
- [15] Banerjee T, Anupurba S, Filgona J, Singh DK. Vancomycin-resistance enterococcal colonization in hospitalized patients in relation to antibiotic usage in a tertiary care hospital of north India. *J Lab Physicians* 2015;7:108–11.
- [16] Pan S-C, Wang J-T, Chen Y-C, Chang Y-Y, Chen M-L, Chang S-C. Incidence of and risk factors for infection or colonization of vancomycin-resistant enterococci in patients in the intensive care unit. *PLoS One* 2012;7:e47297.
- [17] Amberpet R, Sistla S, Parija SC, Thabab MM. Screening for intestinal colonization with vancomycin resistant enterococci and associated risk factors among patients admitted to an adult intensive care unit of a large teaching hospital. *J Clin Diagn Res* 2016;10:DC06–9.
- [18] Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke* 2009;40:2068–72.
- [19] Chiu D, Peterson L, Elkind MSV, et al. Comparison of outcomes after intracerebral hemorrhage and ischemic stroke. *J Stroke Cerebrovasc Dis* 2010;19:225–9.
- [20] Harbarth S, Cosgrove S, Carmeli Y. Effects of antibiotics on nosocomial epidemiology of vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002;16:19–28.
- [21] Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. *BMC Neurol* 2011;11:110.
- [22] Rogers MA, Mody L, Chenoweth C, Kaufman SR, Saint S. Incidence of antibiotic-resistant infection in long-term residents of skilled nursing facilities. *Am J Infect Control* 2008;36:472–5.
- [23] Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* 2018;6:121.