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Risk factors for prolonged carriage of vancomycin-resistant *Enterococcus faecium* among patients in intensive care units: a case–control study

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Objectives: The aim of this study was to identify the risk factors for prolonged carriage of vancomycin-resistant *Enterococcus faecium* (VREF) in intensive care units (ICUs).

Methods: A retrospective case–control study was performed in the ICUs of a university hospital in Korea from September 2006 to July 2009. VREF carriage was identified through weekly active surveillance rectal cultures. Clinical characteristics and the risk factors for VREF acquisition were compared between cases with prolonged VREF carriage (≥5 weeks, $n=58$) and controls with shorter VREF carriage (<3 weeks, $n=36$) in a multivariate logistic regression model. The effect of vancomycin consumption on vancomycin-resistant enterococci (VRE) colonization pressure was investigated using time-series analysis with an autoregressive error model.

Results: Out of a total of 6327 rectal swab cultures examined, 1915 (30.3%) specimens from 266 patients were positive for VREF. The weekly VRE colonization pressure ranged from 0.77% to 42.42%. Vancomycin use after VREF acquisition significantly increased VREF carriage (adjusted odds ratio=4.09; 95% confidence interval=1.32–12.65). The case group had higher in-hospital mortality than the control group [21 (36.2%) versus 4 (11.1%), $P=0.007$]. Increment of VRE colonization pressure was significantly associated with vancomycin consumption of 1 week before (i.e. time $t-1$) ($P=0.0028$) and moderately associated with that of the corresponding week (i.e. time t) ($P=0.0595$).

Conclusions: Vancomycin use in patients with VREF colonization might prolong the duration of carriage. Restriction of vancomycin use should be strengthened in these patients through infection control measures.

Keywords: ICUs, infection control, time-series analysis

Introduction

The emergence of vancomycin-resistant enterococci (VRE) as an increasingly common nosocomial pathogen has created a formidable challenge for both clinicians and hospital infection control officers since it was first described in 1988.[1] Enterococci are intrinsically resistant to multiple antimicrobial agents, including cephalosporins, and can acquire resistance to penicillins, aminoglycosides and glycopeptides. VRE colonization occurs predominantly in the gastrointestinal tract of patients in high-risk units, such as intensive care units (ICUs), haemato-oncology and abdominal transplantation wards. It increases a patient's risk of developing subsequent VRE sepsis, which has been linked to very limited treatment options, and increased mortality and healthcare expenditure.[2–4] VRE carriage can also serve as a reservoir for the transmission of VRE to other patients and subsequent widespread colonization within hospitals. In particular, vancomycin resistance may be transferable from VRE to methicillin-resistant *Staphylococcus aureus* (MRSA),[5,6] resulting in the isolation of vancomycin-resistant *S. aureus* strains.

VRE colonization may persist for years.[7] Current infection control practices include contact isolation precautions for a patient colonized with VRE until VRE-negative results are documented from at least three consecutive cultures collected >1 week apart.[8] Spontaneous decolonization occurs infrequently.[9] There is limited success with effective antimicrobials

for VRE eradication.[10,11] Therefore, strategies to shorten the duration of VRE carriage might be important in the context of reducing the extra cost of strict isolation for prolonged VRE carriage. However, limited information about the duration and risk factors related to prolonged carriage is available.[7,12–15]

The purpose of this study was to determine the risk factors for prolonged vancomycin-resistant *Enterococcus faecium* (VREF) carriage among ICU patients and to provide prevention strategies to shorten the duration of VREF carriage in clinical practice.

Methods

Hospital setting

The study was conducted in the medical and surgical ICUs (23 beds per ICU) of an 850 bed tertiary care hospital in Korea. The hospital infection control practices for VRE carriers include strict contact isolation precautions (use of a private room or cohorting in ICUs, hand washing, gloving and gowning) and environmental cleansing, based on the published guidelines.[8,16] No specific therapy was attempted to clear VRE.[17] Weekly active surveillance rectal culture for VRE has continued since its launch in September 2006 for all patients who stayed in the ICUs for >24 h. The incidence of VRE in ICUs was calculated based on the results of surveillance and clinical cultures. VRE prevalence or colonization pressure was defined as the number of patients colonized with VRE on that day divided by the number treated in the ICUs on that day.[18]

The hospital has run a computerized antibiotic prescription program since 2002. Approval from infectious diseases specialists is required for the use of 15 agents, including vancomycin and third-generation cephalosporins. The consumption of individual antibiotics, expressed as the antimicrobial use density (AUD; defined daily dose per 1000 patient-days), was monitored.

Study design

The retrospective case–control study included all patients who were admitted to the two ICUs and had a positive culture for VREF during the study period from September 2006 to July 2009. Case patients were selected if they had prolonged VREF carriage for ≥5 weeks in active surveillance culture. Control patients were those who had shorter VREF carriage, which was defined as a duration of <3 weeks and a subsequent confirmation of 'eradication' (VREF-negative results on three or more consecutive rectal cultures). The weekly surveillance culture was also continued in the case patients to determine persistent VREF colonization or eradication until hospital discharge. Clinical characteristics and risk factors for VRE acquisition between the case group (≥5 weeks, range 35–133 days) and the control group (<3 weeks, range 7–20 days) were compared. For clear discrimination, patients with VREF carriage of intermediate length (21–34 days) were excluded.

Clinical data from a computerized hospital database were available for each patient, and included age, sex, co-morbid illnesses, receipt of procedures and medications, hospital days before VREF colonization, and microbial information. Antibiotic use (≥3 days) within 2 weeks prior to the identification of VREF colonization or after VREF colonization was reviewed. The data were obtained in a subset of ICU patients through a routine hospital surveillance programme for infection control purposes and, thus, ethical approval was not sought.

Microbiological methods

Rectal swab samples were plated on Enterococcosel culture plates (Difco Laboratories, Detroit, MI, USA) supplemented with 15 mg/L vancomycin and 8 mg/L clindamycin for the selection of vancomycin-resistant enterococcal species.[19,20] *Enterococcus* species were identified by conventional biochemical methods and by using the Vitek 2 GP card (bioMérieux, Marcy l'Étoile, France).

Statistical analysis

The sample size required to ensure 90% power was ≥45 cases and 23 controls, based on a group ratio of 2:1 with a two-sided 5% level of significance, in order to detect a 40% difference in the proportion of vancomycin use when that of controls was 30%. The PASS 2008 version 8.0.5 software (NCSS, Kaysville, UT, USA) was used for this power calculation. Demographic and clinical variables for case and control groups were summarized as the mean ± SD or number of subjects (percentage), and were compared using the χ^2 test, Mann–Whitney test or Student's *t*-test, as appropriate. Comparisons of risk factors and antibiotic use between the groups were made by using the χ^2 test or Fisher's exact test. Variables with $P<0.05$ were included in a multivariable logistic regression analysis. An odds ratio with its 95% confidence interval was estimated using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). To determine the effect of vancomycin consumption (an independent variable) on VRE colonization pressure (a dependent variable), a time-series analysis with an autoregressive error model up to autoregressive time $t-2$ for the VRE colonization pressure was performed.[21] In this model, an incidence of VRE outbreak in the ICUs during a 6 week period between October and November 2006 was used as a control, due to its possible association with an increase in the VRE colonization pressure. Five episodes of hospital accreditation were also used as a control, because they might increase adherence to infection control measures, such as strengthening of hand hygiene and environmental cleaning. For this analysis, the AUTOREG procedure with SAS version 9.2 (SAS Institute, Cary, NC, USA) was used.

Results

VREF colonization

Out of a total of 6327 rectal specimens submitted during the study period, 1915 (30.3%) samples from 266 patients were positive for VREF. Among them, 172 (64.7%) were excluded from the analysis due to their discharge from the hospital before confirmation of VREF eradication or their intermediate duration of VREF colonization. All of the remaining 94 (35.3%) patients who stayed in the ICUs for >24 h were included in the final analysis. Fifty-eight patients met the criteria for inclusion into the case group and 36 patients were included in the control group. Follow-up cultures on a weekly basis were used to determine the eradication or the duration of persistent VREF carriage in the case patients until hospital discharge. The duration of VREF carriage by the end-of-surveillance culture was distributed as follows: 5 weeks (number with persistent VREF, $n=18$; achievement of eradication, $n=6$); 6 weeks (11; 4); 7 weeks (11; 2); 8 weeks (2; 1); 9 weeks (3; 1); 10 weeks (3; 0); 11 weeks (2; 0); 12 weeks (3; 0); 13 weeks (2; 1); 15 weeks (1; 0); 17 weeks (1; 0); and 19 weeks (1; 1).

Meanwhile, the proportion of vancomycin-resistant *E. faecalis* accounted for only 0.6% (40/6327) of the isolates from the rectal surveillance cultures.

Risk factors associated with prolonged carriage of VREF

The demographic and clinical characteristics of the case and control groups were similar, except for mean age and mean

duration of VREF carriage, with values for both being significantly greater in the case group (Table 1). The parameters associated with clinical severity, such as the APACHE II score, underlying diseases and the Charlson score, showed no significant differences between the case and control groups. In the univariate analysis, the significant risk factors for prolonged VREF colonization identified included receipt of central venous catheterization and endotracheal intubation. In terms of specific antibiotic use, more patients in the case group received carbapenems, fluoroquinolones or vancomycin after VREF colonization than controls (Table 2). After controlling potential confounders, vancomycin use after VREF colonization showed 4.05 times higher odds of prolonged VREF carriage (Table 3).

In the outcome analysis of the two study groups, in-hospital mortality was significantly higher in the case group. One patient in each group developed VREF bacteraemic sepsis, with one death in the control group. In addition, length of ICU stay after VREF colonization was significantly longer in the case group, especially in survivors, compared with the control group (Table 1).

We further analysed the indications of vancomycin use in the two study groups. Among the 56 patients who received vancomycin treatment before or after VREF colonization, 30 patients (53.6%) were identified as having MRSA infections [case, 57.1% (24/42) versus control, 42.9% (6/14); $P=0.353$]. The remaining 26 patients were given vancomycin without other definite indications.

Analysis of glycopeptide use and VRE colonization pressure

In the ICUs during the study period, the weekly incidence of VRE colonization or infection was 4.61±3.80 (range, 0–38.96; median 3.44) per 100 patient-days. The weekly VRE colonization pressures were 11.35%±4.39% (range, 0.77%–42.42%; median, 10.43%). The average consumption of vancomycin per week was 121.46±50.85 AUD (range, 1.93–244.03; median, 122.77).

A time-series analysis was performed to assess the effect of vancomycin consumption on changes in VRE colonization pressure. Time-series data for the 150 week period and all of the related events were available from the hospital infection control unit, as shown in Figure 1. There was an occurrence of VRE outbreak in the ICUs between the second week of October (week 5)

Table 1. Comparison of demographic and clinical characteristics between the case group with prolonged VREF carriage and the control group with shorter VREF carriage[a]

	Case group, $n=58$ (%)	Control group, $n=36$ (%)	P value[b]
Male	35 (60.3)	23 (63.9)	0.73
Age (years)	65.2±18.0	56.9±13.5	0.01
Length of hospital stay before VREF colonization (days)	31.6±42.4	38.9±66.4	0.69[c]
Length of ICU stay before VREF colonization (days)	25.4±42.0	35.1±51.8	0.33[c]
Proximity of VREF-positive patients	18 (31.0)	6 (16.7)	0.27
Duration of VREF carriage (weeks)	7.6±3.2	1.3±0.5	<0.001
APACHE II score[d]	18.9±5.7	19.6±7.3	0.62
Charlson score[e]	4.4±2.6	4.0±2.7	0.49
Diabetes mellitus	20 (34.5)	7 (19.4)	0.12
Heart disease	15 (25.9)	5 (13.9)	0.17
Pulmonary disease	10 (17.2)	2 (5.6)	0.12[f]
Hepatic dysfunction	7 (12.1)	6 (16.7)	0.55[f]
Renal dysfunction	15 (25.9)	7 (19.4)	0.48
Malignancy	18 (31.0)	8 (22.2)	0.35
Neurological disease	27 (46.6)	22 (61.1)	0.17
Gastroduodenal ulcer disease	5 (8.6)	6 (16.7)	0.32[f]
Clinical outcome			
length of hospital stay after VREF colonization (days)	76.40±51.04	87.44±87.33	0.932[c]
survivors	74.1±43.4	88.2±91.2	0.876[c]
non-survivors	80.5±63.3	81.5±55.3	0.915[c]
length of ICU stay after VREF colonization (days)	41.5±53.5	24.7±32.6	0.028[c]
survivors	32.1±37.0	21.0±28.7	0.044[c]
non-survivors	58.1±72.4	54.8±50.5	0.915[c]

APACHE II, acute physiology and chronic health evaluation.
[a]Values represent the number of subjects (%) or mean±SD.
[b]P values are obtained from Student's t-test or χ^2 test, as appropriate.
[c]Mann–Whitney test was used.
[d]APACHE II score was confirmed on ICU admission.
[e]Charlson score was determined at the first identification of VREF colonization.
[f]Fisher's exact test was used.

Table 2. Comparison of risk factors and antibiotic use between case group with prolonged VREF carriage and control group with shorter VREF carriage

	Case group, $n=58$ (%)	Control group, $n=36$ (%)	P value[a]
Prior exposure to medical device			
central venous catheterization	49 (84.5)	24 (66.7)	0.04
Foley catheterization	55 (94.8)	33 (91.7)	0.54
enteral tube feeding	45 (77.6)	22 (61.1)	0.09
endotracheal intubation	48 (82.8)	23 (63.9)	0.04
Prior exposure to medication			
total parenteral nutrition	53 (91.4)	32 (88.9)	0.69
immunosuppressive agents	15 (25.9)	10 (27.8)	0.84
antacids	43 (74.1)	26 (72.2)	0.84
Prior exposure to instrument			
gastroscopic examination	13 (22.4)	12 (33.3)	0.24
bronchoscopic examination	11 (19.0)	5 (13.9)	0.52
Prior episode			
surgery	20 (34.5)	17 (47.2)	0.22
prior admission within 1 month	13 (22.4)	9 (25.0)	0.77
neutropenia (ANC 500/mm^3)	7 (12.1)	1 (2.8)	0.15[b]
Prior receipt of antibiotics before VREF colonization			
first-generation cephalosporins	1 (1.7)	3 (8.3)	0.16[b]
second-generation cephalosporins	1 (1.7)	2 (5.6)	0.56[b]
third-generation cephalosporins	26 (44.8)	18 (50.0)	0.63
fourth-generation cephalosporins	2 (3.4)	0 (0)	0.52[b]
aminoglycosides	3 (5.2)	2 (5.6)	1.00[b]
carbapenems	9 (15.5)	4 (11.1)	0.76[b]
vancomycin	19 (32.8)	7 (19.4)	0.16
fluoroquinolones	20 (34.5)	10 (27.8)	0.50
piperacillin/tazobactam	10 (17.2)	5 (13.9)	0.67
subtotal	51 (87.9)	25 (69.4)	0.03
Continuous receipt of antibiotics after VREF colonization			
first-generation cephalosporins	1 (1.7)	3 (8.3)	0.16[b]
second-generation cephalosporins	1 (1.7)	0 (0)	1.00[b]
third-generation cephalosporins	17 (29.3)	9 (25.0)	0.65
fourth-generation cephalosporins	5 (8.6)	0 (0)	0.15[b]
aminoglycosides	3 (5.2)	1 (2.8)	1.00[b]
carbapenems	13 (22.4)	1 (2.8)	0.01
vancomycin	40 (69.0)	10 (27.8)	<0.001
fluoroquinolones	23 (39.7)	7 (19.4)	0.04
piperacillin/tazobactam	7 (12.1)	7 (19.4)	0.33
subtotal	51 (87.9)	25 (69.4)	0.03

ANC, absolute neutrophil count.
[a]*P* values were obtained by χ^2 test unless otherwise indicated.
[b]Fisher's exact test was used.

and the third week of November (week 10) in 2006, a span of 6 weeks. The hospital also had five episodes of hospital accreditation: weeks 5–10 (September to November 2006); weeks 62–72 (November 2007 to January 2008); weeks 93–99 (June to July 2008); weeks 122–127 (January to February 2009); and weeks 142–149 (May to July 2009). After controlling for these incidences, the vancomycin consumption of 1 week before (i.e. the independent variable with time $t-1$) was significantly associated with an increment of VRE colonization pressure (%) ($P=0.0028$), while that of the corresponding week (i.e. the independent variable with time t) increased the pressure moderately ($P=0.0595$) (Table 4). The resulting model can be represented by the equation:

$$\mathrm{VRE}(t) = 8.344 + 0.011\ \mathrm{VC}(t) + 0.017\ \mathrm{VC}(t-1) + 18.916\ \mathrm{OUTBR} - 4.076\ \mathrm{HSPAC} + \mathrm{v}(t)$$

with $v(t) = -0.896\ v(t-1) + 0.193\ v(t-2) + e(t)$, and where VRE($t$) represents the VRE colonization pressure at time t; VC(t) and VC($t-1$) are the vancomycin consumption at time t and $t-1$, respectively; OUTBR is an incidence of outbreak; and HSPAC is an incidence of hospital accreditation. The term v(t) represents an autoregressive error term at time t, while e(t) is for white noise. The estimated error variance for e(t) is 7.59, and the coefficient of determination (R^2) of the equation is 78.7%.

In addition, the time-series analysis disclosed that the percentages of VRE colonization pressure for both the previous week (AR1) and 2 weeks before (AR2) significantly affected that of the current week.

Table 3. Multivariable logistic regression analysis of risk factors associated with prolonged VREF carriage

Risk factors	OR	95% CI	*P* value
Vancomycin use after VREF colonization	4.05	1.280–12.793	0.02
Central venous catheterization	1.50	0.449–4.972	0.51
Endotracheal intubation	1.92	0.580–6.324	0.14
Carbapenems	5.74	0.636–51.856	0.12
Fluoroquinolones	2.56	0.761–8.593	0.13
Continuous receipt of antibiotics after VREF colonization	0.67	0.162–2.810	0.59
Age	1.02	0.990–1.053	0.18
Length of ICU stay after VREF colonization	1.01	0.997–1.021	0.16

OR, odds ratio; CI, confidence interval.

Discussion

In this case–control study, we investigated the risk factors associated with prolonged carriage of VREF among ICU patients. We determined that vancomycin administration in patients already colonized with VREF significantly increased the risk of prolonged VREF carriage compared with that in patients who were not exposed to vancomycin. In particular, the time-series analysis supported that vancomycin consumption played a critical role in the nosocomial epidemiology of VRE. Thus, restriction of vancomycin use might be helpful to shorten the duration of VREF carriage in ICU patients.

In the present study, we observed that VREF carriage persisted for up to 133 days on the follow-up cultures. Previous studies have reported the persistence of VRE carriage for up to a 3 year period.[7,12] VRE colonization can persist not only due to a relapse with a closely related strain, but also due to the acquisition of a new strain. Exposure to contaminated equipment and proximity to a VRE carrier might influence the duration of VRE colonization through cross-colonization.[22] The concentration of VRE in the stool has been described as another major factor in

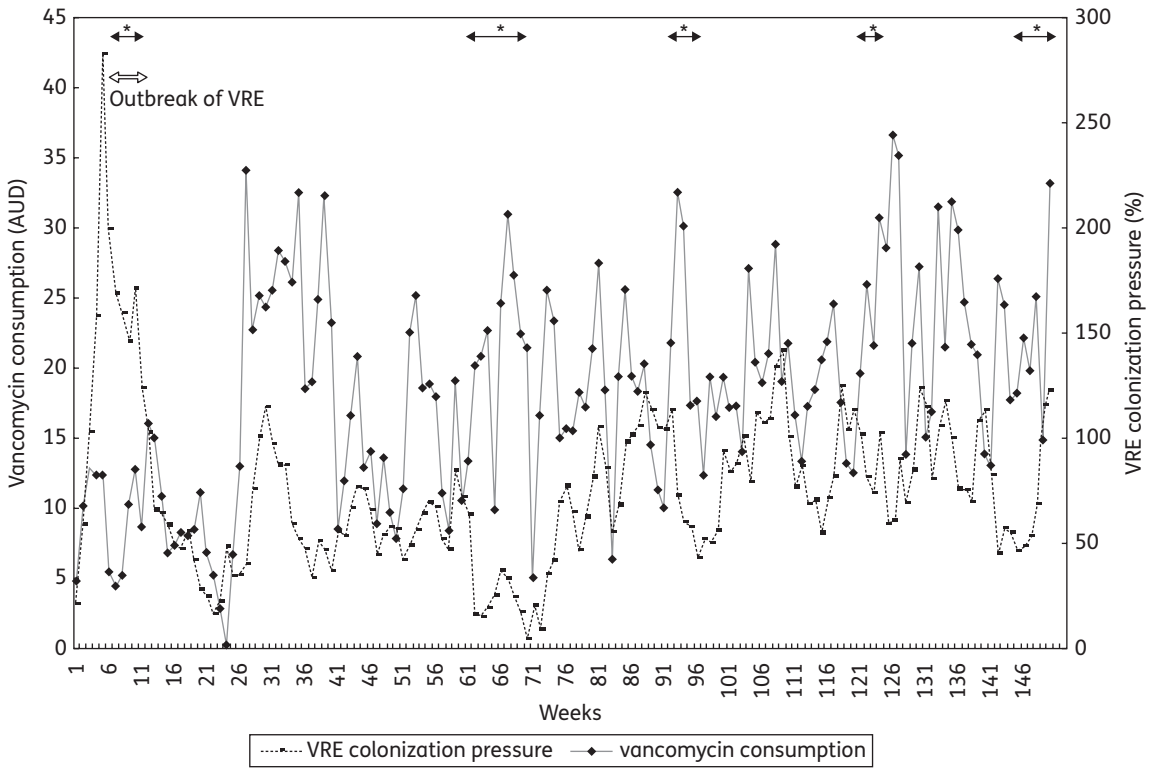

Figure 1. Trends of VRE colonization pressure (%) and vancomycin consumption (AUD, defined daily dose per 1000 patient-days) in the ICUs during the study period. *Episodes of hospital accreditation.

Table 4. Time-series analysis with an autoregressive error model for the effect of vancomycin consumption on VRE colonization pressure[a]

Independent variables	Coefficient[b]	SE	*t* value	*P* value
Vancomycin consumption				
at time *t*	0.011	0.006	1.90	0.06
at time *t* − 1	0.017	0.006	3.04	0.003
Outbreak	18.916	2.320	8.15	<0.001
Hospital accreditation	−4.076	1.040	−3.92	<0.001
Autoregressive error				
at time *t* − 1 (AR1)	−0.896	0.084	−10.65	<0.001
at time *t* − 2 (AR2)	0.193	0.085	2.26	0.03
Durbin–Watson	1.949			

VRE, vancomycin-resistant enterococci.
[a]VRE colonization pressure was expressed as the percentage of patients colonized with VRE.
[b]Total coefficient of determination (R^2) is 78.6%.

persistent colonization. Green *et al.*[23] reported that having $\geq 10^6$ cfu of VRE per mL of stool was associated with persistent colonization.

In this study, central venous catheterization or endotracheal intubation was identified as a risk factor for prolonged VREF colonization in univariate analysis, but not in multivariate analysis. However, the presence of an invasive device before VRE isolation predicted VRE colonization in multivariate models.[24] Moreover, prior invasive procedures were identified as strong clinical risk factors for VRE invasive infections in a recent study.[25] Therefore, these factors should be considered in infection control practice to prevent VREF colonization and to reduce its duration.

Although antecedent treatment with antibiotics is a well-described risk factor for VRE acquisition,[26,27] the role of antibiotic exposure in patients who are already VRE colonized has been less well defined. It has been suggested that multiple types of antibiotics, including antianaerobic agents, may disrupt the normal bowel flora and lead to selective VRE growth. In this study, the continuous receipt of fluoroquinolones after VREF colonization was a significant risk factor for prolonged VREF colonization in univariate analysis. Some fluoroquinolones have deleterious effects on faecal anaerobes in certain immunosuppressive populations.[28,29] Interestingly, high-level ciprofloxacin resistance has been detected among the global hospital-adapted *E. faecium* clone (complex 17),[30,31] suggesting the potential role of fluoroquinolones in the nosocomial epidemiology of *E. faecium*.

In this case–control study, vancomycin exposure after VREF colonization, as the only independent risk factor, conferred 4.05-fold increased odds ratio for prolonged VREF colonization. However, length of ICU stay after VREF colonization in case patients was significantly longer than in control patients, which might be associated with an increased receipt of vancomycin in the case group, and attenuate the correlation between vancomycin use and prolonged carriage of VREF. Although current guidelines for the control of VRE include the prudent use of vancomycin,[8,16] the precise association between vancomycin use and VRE colonization or infection remains unclear. Vancomycin exposure may increase VRE detection in colonized patients by eliminating other colonizing bacteria and allowing VRE to flourish.[32,33] Vancomycin inhibits *Bacteroides* species in humans when administered orally,[34] and even parenteral vancomycin, which is thought to have poor bowel penetration, has been demonstrated to have biliary concentrations sufficient to disrupt the normal bowel flora after 5 days of therapy.[35]

In this study, many patients (44.6%, 25/56) received empirical vancomycin therapy before or after VREF acquisition, without evidence of MRSA infection or other indications. As the ICU settings of this study had a high endemicity of MRSA, vancomycin was frequently included in the initial empirical antibiotic therapy for febrile critical patients. It is easy to start empirical vancomycin therapy, but it is more difficult to decide when to stop it.

In the time-series analysis of this study, the vancomycin consumption of 1 week before and that of the corresponding week were strongly and moderately associated with an increase in VRE colonization pressure, respectively. It was possible to estimate the time lags between variations in vancomycin use and subsequent variations in VRE pressure: effect-delay ranges between 0 and 1 week for vancomycin use were positively correlated with VRE prevalence. The time-series analysis also identified the past levels of VRE colonization pressure, such as those in the previous week (AR1) and 2 weeks before (AR2), as another force driving current VRE pressure. Although the effect of vancomycin intervention on VRE incidence or prevalence was inconclusive in a recently published systematic review,[36] our results strongly suggest that vancomycin use should be a target of policies aimed at controlling VRE, as recommended by current guidelines.

Our study has limitations. We did not consider the potential cross-transmission or reacquisition of VREF from the environment, which might be a confounding factor for the prolonged VREF carriage. However, almost all of the patients with prolonged VREF carriage analysed were isolated in a single private room under strict isolation precaution, which should reduce the chance for cross-colonization. Finally, our findings may not be generalizable to other hospitals, as our ICUs have been in high endemicity of MRSA. The monthly prevalence of MRSA was 32.6 ± 0.8 (range, 21.6–43.0) per 1000 patient-days.

In conclusion, this study indicates that vancomycin use may contribute to the prolonged carriage of VREF among ICU patients and VRE colonization pressure. Therefore, more restricted vancomycin use for patients colonized with VREF, along with close monitoring of vancomycin consumption in ICUs, may be required to shorten the duration of VREF carriage and to control the spread of VREF.

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Transparency declarations

None to declare.

Author contributions

Y. K. Y. collected and analysed the data and wrote the manuscript. J. L. revised the important intellectual content and statistical analysis. S. E. L. and H. J. K. participated in the epidemiological surveillance. J. W. S., D. W. P. and J. Y. K. collected and assembled the data. M. J. K. coordinated the study and revised the manuscript. All authors read and approved the final manuscript.

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