Tzu Chi Medical Journal 2024; 36 (1): 83-91

Original Article

Factors affecting vancomycin-resistant *Enterococcus faecium* colonization of in-hospital patients in different wards

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Submission : 09-May-2023
Revision : 22-Aug-2023
Acceptance : 26-Sep-2023
Web Publication : 13-Dec-2023

Abstract

Objectives: The prevalence of vancomycin-resistant *Enterococcus faecium* (VRE) infection at a medical center in Eastern Taiwan rose to 80.6%, exceeding the average prevalence of 55.6% among all medical centers nationwide during the same period. In recent years, the number of cases of VRE infection detected among hospitalized patients has increased annually. However, most of these patients in different wards are asymptomatic carriers. Therefore, restricting active screening to high-risk units will not improve the current situation, and it is necessary to review the risk factors for VRE colonization to provide a reference for future infection control policies. **Materials and Methods:** Between 2014 and 2019, there were 3188 VRE-positive cultures reported at our institution, as per the electronic medical records system. **Results:** In the medical and surgical wards, patients who received penicillin (odds ratios [ORs]: 2.84 and 4.16, respectively) and third-generation cephalosporins (ORs: 3.17 and 6.19, respectively) were at higher risk of VRE colonization. In intensive care units, the use of carbapenems (OR: 2.08) was the most significant variable. **Conclusion:** This study demonstrated that the risk factors for VRE colonization differed between wards. Thus, policies should be established according to the attributes of patients in each ward, and active screening tests should be performed according to individual risks, instead of a policy for comprehensive mass screening.

Keywords: *Asymptomatic colonization, Colonization, Vancomycin-resistant Enterococcus*

Introduction

Enterococcus is a strain of Gram-positive, facultative anaerobic bacteria that can colonize humans and survive on environmental surfaces for a long time. Patient groups that are more susceptible to *Enterococcus* colonization include the elderly with multiple co-morbidities, patients receiving systemic antibiotics, and those with epithelial or mucosal barrier defects [1-4]. Although previously recognized as a low-virulence pathogen, enterococcus has emerged as one of the important culprit pathogens among healthcare-associated infections (HAI) in recent years [3,5]. Vancomycin-resistant *Enterococcus* (VRE) (known as *Micrococcus zymogenes* at that time) was first reported as the cause of a patient's endocarditis in Europe, and this patient died 18 days later from complications of his illness [6]. Prolonged infections in humans increase the risk of transmitting *Enterococcus* to others, which remains a critical issue in the public health sector because antimicrobial resistance (AMR) renders the treatment of infections more challenging. The most significant strain is VRE, a growing concern due to the increasing development of antibiotic resistance, increasing length of hospitalization, and excess mortality. There has also been an increase in the prevalence of HAIs worldwide.

The evolution of AMR in *Enterococcus* is complex. The adaptation of *Enterococcus* to the human host in the last four decades raised the concern for VRE within hospital systems. In 2017, the United States reported 54,500 VRE infections among hospitalized patients, and 5,400 of them ended up dying. In 2019, the US Centers for Disease Control and Prevention (CDC) classified VRE as a serious threat in its AR Threats Report (Antibiotic Resistance Threats in the United States) [7]. In Taiwan, previous studies have investigated and analyzed *Enterococcus* from different sources, and the results showed that *Enterococcus* infections were common in both

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How to cite this article: Wang YC, Wang LS, Hsieh TC, Chung HC. Factors affecting vancomycin-resistant *Enterococcus faecium* colonization of in-hospital patients in different wards. Tzu Chi Med J 2024;36(1):83-91.

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_117_23

hospitalized and ambulatory patients. Clinical research has revealed that *Enterococcus faecium* and *Enterococcus faecalis* were the two main strains responsible for these infections. In addition, the prevalence of VRE was found to have increased from 0.3% in 2004 to 24.9% in 2010, and significant differences existed in the prevalence rates between different age groups and geographic locations [5]. According to the statistics from the Taiwan Healthcare-associated infection and Antimicrobial resistance Surveillance, there has been an increase in the rate of AMR in recent years. The AMR rate of VRE in intensive care units (ICUs) at medical centers has increased from 46.1% in 2010 to 68.7% in the fourth quarter of 2019 [8]. When these infections occur, they are hard to treat. In addition to prolonging hospitalization and increasing medical costs, bacteremia will increase the risk of death in patients [9].

The fecal burden of *Enterococcus* in hospitalized patients is a concern, as VRE often dominates the gut microbiome and tends to displace commensal anaerobes [3,4]. VRE can survive for several weeks in the ambient environment primarily because they are more resistant to stressful conditions than other microorganisms. Environmental contamination can easily be found in the surroundings of patients, such as bed rails, curtains, drip racks, and door handles, and transmitted indirectly through the hands of medical staff, which poses a major threat to immunocompromised patients [4,10-13]. VRE colonization generally precedes the infection, and cases of asymptomatic gastrointestinal colonization outnumber those of the symptomatic disease by a ratio of approximately 10:1 [2].

Possible risk factors for VRE infection include prior use of antibiotics, surgery, and hemodialysis [4,6,14]. In 1995, the US Hospital Infection Control Practice Advisory Committee established guidelines for VRE infections, stating that the prevention of transmission depends on the rapid identification of carriers and that the initial focus can be placed on ICUs and other high-risk units [4,15]. Measures such as precautions for isolation, hand hygiene, and clean environment maintenance should be implemented for patients with VRE colonization or infections. For patients with VRE infections, and even those who are gradually recovering after receiving treatment, intestinal colonization may last for weeks or months. Thus, reducing the spread of VRE in hospitals is challenging [3].

Current policies that hospitals adopt to prevent VRE include the following: (1) A notice is posted on the information system to remind medical staff to use personal protective equipment (wearing gloves and protective clothing) when the laboratory confirms a case of VRE colonization/infection. (2) Active screening is performed for patients who are transferred from a long-term care facility to an ICU. (3) If there is a new case of VRE colonization or infection in a ward, patients who stay in the same room with the case for more than 48 h are required to undergo VRE screening and active isolation until the screening result comes back negative. (4) The first option in terms of arranging hospital beds for confirmed cases should be single-bed wards and the second option should be cohort care. (5) Medical carts should be cleaned with sodium dichloroisocyanurate wipes. (6) Compliance with hand hygiene routines and multiple drug resistance isolation measures among the healthcare staff is monitored regularly.

High-risk units include ICUs, nephrology, hematology/oncology, solid organ transplant units, and wards with patients linked to the single-strain outbreak in a healthcare facility [16,17]. However, in recent years, the number of patients with confirmed VRE (including patients in the same ward exposed to VRE infections) has been rising annually, and some clusters of incidents in general wards can be found, resulting in a shortage of single-bed rooms. In addition, the regulations on isolation beds have decreased the turnover of hospital beds, which has indirectly affected other patients' rights to receive medical services. With respect to the additional costs incurred by policy adherence, in 2018 alone, up to 392,504 isolation gowns (which translates to 1090 gowns per day on average) were used, and allocating single-bed rooms for the isolation of VRE patients at the public's expense can cost the hospital NT$8,000 per room in revenue. Although infection control guidelines for VRE are well established, the high proportion of inpatients requiring isolation means it is time to think about how patients' characteristics can help to focus on horizontal infection control strategies in the fight against the spread of VRE.

Routine hospital-wide admission screening is not recommended. Selective screening for high-risk inpatient groups should be undertaken [2-4]. We know that VRE colonization generally precedes infection; however, VRE is difficult to detect when the patient is asymptomatic. Therefore, it is necessary to accurately screen for potential cases of VRE colonization. There is a variety of modes of VRE transmission, and most infections are thought to be associated with transmission through indirect contact between a patient and health care providers. We identified our target group for screening based on the internal consistency of the contact precautions policy in patients who are either infected or colonized. Since there was no active Surveillance for general wards previously, this study aimed to re-investigate the risk factors for VRE colonization in different wards, hospital needs, and available resources, to achieve early detection of VRE colonization.

Materials and Methods

Study design, location, and patients

This cross-sectional study was conducted in the only medical center in Eastern Taiwan, where there were 30 wards with 971 beds, among which 713 were general beds (500 acute care beds, 40 acute psychiatric beds, and 173 chronic beds) and 258 were specialty beds (including beds for bone marrow transplantation, palliative care, intensive care, and intensive burn care). The study was conducted between 2014 and 2019, and the subjects were all hospitalized patients aged over 18 years who had VRE screen culture reports.

This study was approved by the Research Ethics Committee Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Approval number IRB108-237-B). Its design and conduct conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The subjects were not required

to provide informed consent to the study because the analysis used anonymous clinical data that had been obtained.

Patients had to meet the inclusion criteria established per the following objective: Surveillance definitions and guidance of the National Healthcare Safety Network of the CDC [18]; the date of the event, the infection window period (IWP), and the presence of VRE on admission. If patients who had VRE in other body sites also had VRE on rectal swabs ± 3 days, they were considered already infected during the same period. If there was no other source of information, their stool routine report (with a result showing fluid or semifluid) ±3 days from positive rectal swab positivity would be used to determine whether the patients had gastrointestinal symptoms. For those who had no available stool routine report, a prescription of antidiarrheals such as dioctahedral smectite (Smecta®) or 1operamide (Imolex®) during the period of IWP would be used as a reference. Patients who met any of the abovementioned criteria were excluded [Figure 1].

Data collection

Data (including sex, age, admission diagnosis, ward, hospital bed number, medical treatment, and antibiotic usage) were obtained from the bacterial test database and electronic medical records (EMRs) of the hospital under study. Antibiotic treatment, medical treatment, and invasive device use were defined within the 90 days that preceded our analysis. Because untreated VRE can evolve into long-term intestinal colonization and previous medical procedures may influence the duration of VRE colonization, several measures were adopted to make the samples more representative: Patients with multiple admissions were excluded; only new patients who were admitted from 2014 were enrolled; patients' first VRE screen culture (rectal swab) at admission with bacteria strain codes of D40 (VRE) or D22 (non-VRE) were used to evaluate their risk of VRE colonization.

Screening for VRE was performed on peri-rectal/anal swabs or stool specimens directly using selective chromogenic medium ChromID VRE agar combined with Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry identification for the detection and differentiation of VRE *faecium*.

Statistical analysis

We used Windows version 21.0 (IBM, Armonk, NY, USA) for all data analyses, and these analyses were performed by ward. Univariate analyses for comparing basic information, invasive devices, medical treatment, and antibiotic use between the VRE and no VRE groups were conducted using the Chi-squared test/Fisher's exact test and the unpaired *t*-test for categorical variables and continuous variables, respectively. We considered $P < 0.05$ statistically significant. For variables that showed statistical significance, the variance inflation factor (VIF) was introduced to determine whether there was collinearity between them. VIF > 10 was defined as strong collinearity, and variables showing strong collinearity were excluded. The remaining variables were included as independent variables in the multivariate logistic regression analysis to identify the risk factors for VRE colonization based on the ENTRY selection method. With the ENTRY selection method, all included independent variables remained in the model for evaluating their association with VRE without any selection. $P \geq 0.05$ obtained from the Hosmer–Lemeshow test was considered as the goodness-of-fit of data for the logistic regression model. According to the Hosmer–Lemeshow test method, the observations were categorized into 10 groups based on their predicting probability calculated using the logistic regression model. The overall expected number of events was compared with the observed number of events to evaluate the fit of the model. The adjusted odds ratios (ORs) with 95% confidence intervals were estimated.

Results

There were 3188 VRE screen culture tests during the study period, and 696 cases were included in the analysis. Patients who had been hospitalized more than once since 2014 (n = 2132), pediatric patients (n = 7), patients detected with VRE within 48 h of admission (n = 69), patients

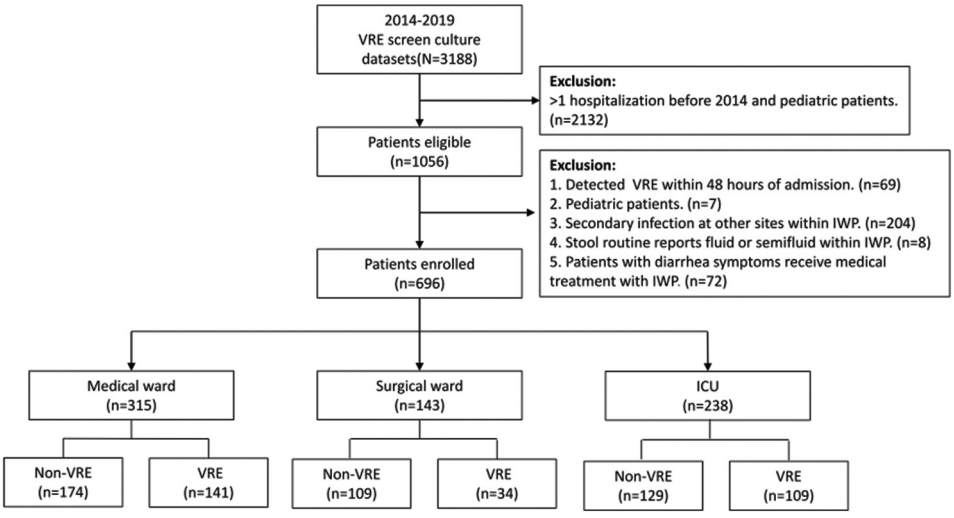

Figure 1: Flowchart of the participant recruitment process. ICU: Intensive care unit, IWP: Infection window period, VRE: Vancomycin-resistant *Enterococcus*

with secondary VRE infection at other sites during the IWP (n = 204), patients with a stool routine report of fluid/semifluid during the IWP (n = 8), and patients who were prescribed antidiarrheal agents (n = 72) were excluded. Of a total of 696 enrolled patients, 315 of them were from the medical ward, 143 of them were from the surgical ward, and 238 of them were from critical care units. The median age of patients in the VRE group was 65 years (Q1–Q3: 54–77), which was higher than that of the non-VRE group, 62.5 years (Q1–Q3:50–74).

Medical wards

A total of 315 subjects were from medical wards and 44.7% (n = 141) of them were VRE-colonized. Univariate analysis was conducted to screen potential risk factors associated with VRE. In the univariate analysis, the median age significantly higher (P = 0.007) in the VRE group (65 years) than in the non-VRE group (63.5 years). Patients in the VRE group were significantly more likely to have used invasive devices in the past 3 months (Foley tube: 47.5% vs. 25.3%, P < 0.001; nasogastric tube: 42.6% vs. 18.4%, P < 0.001; central venous catheters [CVCs]: 27.0% vs. 10.9%, P < 0.001; ventilator: 11.3% vs. 3.4%, P = 0.006; chest tube drainage: 10.6% vs. 2.9%, P = 0.005) and be admitted to ICUs before 3 months (29.1% vs. 15.5%). VRE colonization was significantly associated with having four patient beds in the same room (82.3% vs. 64.9%, P = 0.002). Patients in the VRE group were more likely to have had wound dressings compared with those in the non-VRE group (2.9%). For antibiotic use in the past 3 months, the use of penicillin (56.7% vs. 30.5%, P < 0.001), third-generation cephalosporins (36.9% vs. 16.1%, P < 0.001), carbapenems (26.2% vs., 9.8%, P < 0.001), and vancomycin (20.6% vs. 10.9%, P = 0.018) were significantly more common in the VRE group than in the non-VRE group. The VIFs of all significant variables were < 10. Thus, using the ENTRY selection method, all aforementioned significant variables were included in the logistic regression model to perform multivariate analysis without selection procedure. By the Hosmer–Lemeshow test, the data showed acceptable goodness-of-fit for the logistic regression model, with P = 0.156 (>0.05). As a result, for medicine wards, patients' age (OR = 1.02, P = 0.016), the use of penicillin (OR = 2.84, P < 0.001), and the use of third-generation cephalosporins (OR = 3.17, P < 0.001) were found to have significant correlations with VRE colonization [Table 1].

Surgical wards

In surgical wards, 23.8% (n = 34) of 143 subjects were VRE-colonized. Univariate analysis revealed that patients in the VRE group were significantly more likely to have used invasive devices than those in the non-VRE group (nasogastric tube: 41.7% vs. 23.9%, P = 0.009; CVC: 44.1% vs. 15.6%, P < 0.001). Receiving medical treatments such as proton-pump inhibitors (PPIs) (35.3% vs. 12.8%, P = 0.003), wound dressing (50.0% vs. 22.9%) and surgery (97.1% vs. 74.3%) in the previous 3 months was significantly more common in the VRE group than in the non-VRE group. In terms of antibiotics used in the previous 3 months, penicillin (38.2% vs. 14.7%, P = 0.003), the third-generation of cephalosporins (64.7% vs. 22.0%, P < 0.001), quinolones (20.6% vs. 4.6%, P = 0.008), and vancomycin (23.5% vs. 10.1%, P = 0.044) attained statistical significance. All the above significant variables were included in the logistic regression model for multivariate analysis since their corresponding VIFs were all <10. Per the Hosmer–Lemeshow test, the data showed acceptable goodness-of-fit for the logistic regression model, with P = 0.115 (>0.05). According to our findings, the use of penicillin (OR = 4.16, P = 0.014), the use of third-generation cephalosporins (OR = 6.19, P < 0.001), and surgery (OR = 14.2, P = 0.031) were found to have significant correlations with VRE colonization [Table 2].

Intensive care unit

In ICUs, 45.8% (n = 109) of 238 subjects were VRE-colonized. Univariate analysis revealed that patients in the VRE group were significantly more likely to use of invasive devices such as Foley tubes (87.2% vs. 65.9%, P < 0.001), nasogastric tubes (97.2% vs. 76.7%, P < 0.001), CVC (76.1% vs. 58.9%, P = 0.005), and ventilators (76.1% vs. 62.8%) in the previous 3 months than those in the non-VRE group. Medical treatment in the previous 3 months such as hemodialysis (11.0% vs. 3.9%, P = 0.033) and PPI (45% vs. 26.4%) was more common in the VRE group than in the non-VRE group. The level of exposure to the following antibiotics in the previous 3 months differed significantly between the groups: tetracyclines (14.7% vs. 3.9%, P = 0.003), third-generation cephalosporins (40.5% vs. 28.7%, P = 0.009), carbapenems (46.8% vs. 18.6%, P < 0.001), and vancomycin (46.8% vs. 19.4%, P < 0.001).

The abovementioned variables were sent for logistic regression after the VIF > 10, where the generalized Hosmer–Lemeshow test indicated that all data showed positive goodness-of-fit, with P = 0.281 (P > 0.05). Only two variables proved to be risk factors for VRE colonization as presented in Table 3. The use of nasogastric tubes in the previous 3 months and the use of carbapenems were found to have significant correlations with VRE colonization.

Discussion

VRE colonization requires no special treatment until infectious symptoms occur; however, long-term VRE colonization can easily lead to opportunistic infections. If these potential VRE patients in hospitals are not detected early, they may also threaten patients in neighboring beds in the same room and other wards [13,19,20]. In past studies, units where patients are at high risk of VRE colonization or infection (ICUs, malignant hematology wards, transplant wards, wards for chronic dialysis patients, and long-term care facilities) also have a higher prevalence of cluster infections [10,15,21,22]. According to the literature, age > 65 years is a common risk factor for VRE infection or colonization [23]. In our study, the average age of patients in medical wards is higher, and it attained statistical significance only in subjects from medical wards whose median age was 65 years (OR: 1.02; P = 0.016). However, Taiwan is transforming into an aging society since 2018, with people aged over 65 years of age accounting for

Table 1: Factors associated with vancomycin-resistant *Enterococcus faecium* acquisition in medical wards

Variable	Patients (%)		Univariate analysis (*P*)	Multivariate analysis	*P*
	Non-VRE (*n*=174)	VRE (*n*=141)			
Basic information					
Male sex, *n* (%)	102 (58.6)	78 (55.3)	0.556		
Age (years), median (Q1–Q3)	63.5 (52–74.25)	65 (55–80)	0.007*	1.02 (1.004–1.039)	0.016*
CCI, *n* (%)			0.605		
0	69 (39.7)	49 (34.8)			
1–2	86 (49.4)	73 (51.8)			
>2	19 (10.9)	19 (13.5)			
Number of beds in a room, *n* (%)			0.002*		
1	15 (8.6)	7 (5.0)		Reference	
2	39 (22.4)	11 (7.8)		0.67 (0.176–2.597)	0.569
3	7 (4.0)	7 (5.0)		1.44 (0.266–7.783)	0.672
4	113 (64.9)	116 (82.3)		2.66 (0.873–8.157)	0.085
Activities of daily living[a], *n* (%)			0.224		
Independent	98 (56.3)	66 (46.8)			
Need help	38 (21.8)	35 (24.8)			
Bedridden	38 (21.8)	40 (28.4)			
Admitted to ICU before[†]	27 (15.5)	41 (29.1)	0.004*	1.86 (0.871–3.984)	0.109
Invasive devices[†], *n* (%)					
Foley tube	44 (25.3)	67 (47.5)	<0.001*	1.15 (0.606–2.208)	0.658
Nasogastric tube	32 (18.4)	60 (42.6)	<0.001*	1.86 (0.952–3.643)	0.069
Tracheotomy	3 (1.7)	4 (2.8)	0.505		
CVC	19 (10.9)	38 (27.0)	<0.001*	1.35 (0.587–3.142)	0.475
Ventilator	6 (3.4)	16 (11.3)	0.006*	0.57 (0.161–2.021)	0.384
Chest tube drainage	5 (2.9)	15 (10.6)	0.005*	2.70 (0.760–9.653)	0.124
Medical treatment†, *n* (%)					
Hemodialysis	11 (6.3)	16 (11.3)	0.113		
Chemotherapy	3 (1.7)	1 (0.7)	0.631		
Total parenteral nutrition	1 (0.6)	2 (1.4)	0.589		
Proton-pump inhibitor	51 (29.3)	53 (37.6)	0.12		
Immunosuppressive drugs	3 (1.7)	4 (2.8)	0.386		
Wound dressing	5 (2.9)	16 (11.3)	0.003*	2.53 (0.744–8.602)	0.137
Surgery	44 (25.3)	34 (24.1)	0.81		
Antibiotics[†], *n* (%)					
Tetracyclines	11 (6.3)	5 (3.5)	0.311		
Penicillin	53 (30.5)	80 (56.7)	<0.001*	2.84 (1.613–5.028)	<0.001*
Cephalosporins[1st]	42 (24.1)	25 (17.7)	0.167		
Cephalosporins[2nd]	6 (3.4)	7 (5.0)	0.575		
Cephalosporins[3rd]	28 (16.1)	52 (36.9)	<0.001*	3.17 (1.796–5.291)	<0.001*
Cephalosporins[4th]	6 (3.4)	6 (4.3)	0.773		
Sulfonamides	8 (4.6)	6 (4.3)	1		
Aminoglycosides	8 (4.6)	12 (8.5)	0.17		
Quinolones	30 (17.2)	37 (26.2)	0.057		
Carbapenems	17 (9.8)	37 (26.2)	<0.001*	1.78 (0.809–3.946)	0.151
Vancomycin	19 (10.9)	29 (20.6)	0.018*	0.76 (0.337–1.739)	0.524

**P*<0.05; CI; OR; mean (SD); CVC, [†]The previous 3 months, [a]Activities of daily living are defined using the admission nursing assessment record form (subjective assessment). CVC: Central venous catheter, ICU: Intensive care unit, VRE: Vancomycin-resistant *Enterococcus*, CI: Confidence interval, OR: Odds ratio, SD: Standard deviation, CCI: Charlson comorbidity index

14% of the total population, and the number of elderly people will only continue to increase. In the context of an aging population, identifying risk factors for VRE colonization that are specific to the elderly is important.

Nearly all VRE infections begin with the colonization of the GI tract by bacteria that are ingested from the hospital environment [24], if these enteric devices were contaminated by bacteria from an endogenous or an exogenous source, which increases the risk of colonization of VRE strains, a potent threat to immunocompromised patients. Previous studies in ICU patients have suggested environmental room contamination and a higher percentage of other VRE-colonized patients in the unit as other risk factors [10,12,15]. However, although it has been difficult to prove that this kind of surface contamination is an important factor in VRE transmission, it is possible to consider increasing the frequency of cleaning the surrounding

Table 2: Factors associated with vancomycin-resistant *Enterococcus faecium* acquisition in surgical wards

Variable	Patients (%)		Univariate analysis (*P*)	Multivariate analysis	*P*
	Non-VRE (*n*=109)	VRE (*n*=34)			
Basic information					
Male sex	80 (73.4)	24 (70.6)	0.748		
Age (years), median (Q1–Q3)	59 (45–69)	59 (47.5–65)	0.736		
CCI			0.888		
0	56 (51.4)	16 (47.1)			
1–2	48 (44.0)	16 (47.1)			
>2	5 (4.6)	2 (5.9)			
Number of beds in a room, *n* (%)			0.42		
1	4 (3.7)	0			
2	8 (7.3)	2 (5.9)			
3	57 (52.3)	15 (44.1)			
4	40 (36.7)	17 (50.0)			
Activities of daily living[a]			0.528		
Independent	66 (60.6)	18 (52.9)			
Need help	22 (20.2)	10 (29.4)			
Bedridden	21 (19.3)	6 (17.6)			
Admitted to ICU before[†]	39 (35.8)	14 (41.2)	0.569		
Invasive devices[†], *n* (%)					
Foley tube	48 (44.0)	20 (58.8)	0.132		
Nasogastric tube	26 (23.9)	16 (47.1)	0.009*	1.19 (0.374–3.828)	0.762
Tracheotomy	8 (7.3)	4 (11.8)	0.48		
CVC	17 (15.6)	15 (44.1)	<0.001*	2.19 (0.693–6.919)	0.182
Ventilator	10 (9.2)	5 (14.7)	0.35		
Chest tube drainage	6 (5.5)	3 (8.8)	0.444		
Medical treatment[†], *n* (%)					
Hemodialysis	0	2 (5.9)	0.055		
Chemotherapy	1 (0.9)	0	1		
Total parenteral nutrition					
Proton pump inhibitor	14 (12.8)	12 (35.3)	0.003*	2.08 (0.640–6.773)	0.223
Immunosuppressive drugs					
Wound dressing	25 (22.9)	17 (50.0)	0.002*	2.27 (0.789–6.540)	0.128
Surgery	81 (74.3)	33 (97.1)	0.004*	14.2 (1.262–161.05)	0.031*
Antibiotics[†], *n* (%)					
Tetracyclines	5 (4.6)	2 (5.9)	0.671		
Penicillin	16 (14.7)	13 (38.2)	0.003*	4.16 (1.328–12.63)	0.014*
Cephalosporins[1st]	57 (52.3)	19 (55.9)	0.714		
Cephalosporins[2nd]	15 (13.8)	8 (23.5)	0.176		
Cephalosporins[3rd]	24 (22.0)	22 (64.7)	<0.001*	6.19 (2.233–17.20)	<0.001*
Cephalosporins[4th]	0	2 (5.9)	0.055		
Sulfonamides	1 (0.9)	1 (2.9)	0.42		
Aminoglycosides	17 (15.6)	7 (20.6)	0.497		
Quinolones	5 (4.6)	7 (20.6)	0.008*	2.62 (0.588–11.676)	0.206
Carbapenems	16 (14.7)	9 (26.5)	0.114		
Vancomycin	11 (10.1)	8 (23.5)	0.044*	0.76 (0.198–2.992)	0.705

**P*<0.05; CI; OR; mean (SD); CVC, [†]The previous 3 months, [a]Activities of daily living are defined using the admission nursing assessment record form (subjective assessment). CVC: Central venous catheter, CI: Confidence interval, OR: Odds ratio, SD: Standard deviation, ICU: Intensive care unit, VRE: Vancomycin-resistant *Enterococcus*, CCI: charlson comorbidity index

environment of the ICU. The relative risks involving invasive devices have been described in previous studies, such as the use of CVCs, Foley tubes, and mechanical ventilation [14,15,22]. Our study showed that these risks differ in the different wards in the univariate analysis, while only the use of nasogastric tubes in the ICU was found to be significant in the multivariate analysis (OR = 6.83, P = 0.006). The use of other invasive devices did not differ significantly between the three groups.

Since 2013, our institution has promoted CVC, catheter-associated urinary tract infection, and ventilator-associated pneumonia bundle care, daily assessment of the necessity of indwelling catheters, and early (as soon as possible) catheter removal. Now, we have also started promoting swallow training for swallowing disorders in older patients, and we recommended that nasogastric tubes be removed as soon as possible. Besides, patients with nasogastric tubes in Eastern Taiwan are generally hospitalized

Table 3: Factors associated with Vancomycin-resistant *Enterococcus faecium* acquisition in the intensive care units

Variable (%)	Patients (%)		Univariate analysis (*P*)	Multivariate analysis	*P*
	Non VRE (*n*=129)	VRE (*n*=109)			
Basic information					
Male sex	84 (61.5)	83 (76.1)	0.064		
Age (years), median (Q1–Q3)	64 (48–77)	63 (54.5–74)	0.327		
CCI			0.337		
0	69 (53.5)	54 (49.5)			
1–2	54 (41.9)	53 (48.6)			
>2	6 (4.7)	2 (1.8)			
Number of beds in a room, *n* (%)					
1	129 (100)	109 (100)			
2					
3					
4					
Activities of daily living[a]			0.074		
Independent	82 (63.6)	56 (51.4)			
Need help	13 (10.1)	21 (19.3)			
Bedridden	34 (26.4)	32 (29.4)			
Admitted to ICU before[†]	109 (84.5)	91 (83.5)	0.832		
Invasive devices[†]					
Foley tube	85 (65.9)	95 (87.2)	<0.001*	1.60 (0.632–4.082)	0.32
Nasogastric tube	99 (76.7)	106 (97.2)	<0.001*	6.83 (1.727–27.06)	0.006*
Tracheotomy	7 (5.4)	3 (2.8)	0.351		
CVC	76 (58.9)	83 (76.1)	0.005*	0.95 (0.484–1.863)	0.881
Ventilator	81 (62.8)	83 (76.1)	0.027*	0.52 (0.221–1.257)	0.149
Chest tube drainage	12 (9.3)	9 (8.3)	0.777		
Medical treatment[†]					
Hemodialysis	5 (3.9)	12 (11.0)	0.033*	1.57 (0.475–5.251)	0.457
Chemotherapy					
Total parenteral nutrition	1 (0.8)	1 (0.9)	1		
Proton-pump inhibitor	34 (26.4)	49 (45.0)	0.003*	1.35 (0.707–2.589)	0.362
Immunosuppressive drugs	1 (0.8)	0	1.000		
Wound dressing	23 (17.8)	19 (17.4)	0.936		
Surgery	76 (58.9)	57 (52.3)	0.305		
Antibiotics[†]					
Tetracyclines	5 (3.9)	16 (14.7)	0.003*	1.55 (0.486–4.986)	0.456
Penicillin	68 (52.7)	68 (62.4)	0.133		
Cephalosporins[1st]	60 (46.5)	38 (34.9)	0.069		
Cephalosporins[2nd]	2 (1.6)	5 (4.6)	0.167		
Cephalosporins[3rd]	37 (28.7)	49 (40.5)	0.009*	1.44 (0.778–2.683)	0.243
Cephalosporins[4th]	10 (7.8)	9 (8.3)	1		
Sulfonamides	9 (7.0)	14 (12.8)	0.127		
Aminoglycosides	38 (29.5)	23 (21.2)	0.141		
Quinolones	34 (26.4)	41 (37.6)	0.063		
Carbapenems	24 (18.6)	51 (46.8)	<0.001*	2.08 (1.031–4.212)	0.041*
Vancomycin	25 (19.4)	51 (46.8)	<0.001*	1.98 (0.989–3.797)	0.054

**P*<0.05; CI; OR; mean (SD); CVC, [†]The previous 3 months, [a]Activities of daily living are defined using the admission nursing assessment record form (subjective assessment). CVC: Central venous catheter, ICU: Intensive care unit, CI: Confidence interval, OR: Odds ratio, SD: Standard deviation, VRE: Vancomycin-resistant *Enterococcus*, CCI: Charlson comorbidity index

in long-term care facilities. With the transfer of increasing numbers of patients colonized with MDROs between hospitals and nursing facilities. This confirms the benefit of policies in favor of the active screening of patients who are transferred from long-term care facilities to ICUs.

For patients in these surgical wards, prior surgery was found to be significantly associated with VRE. Up to 42.2% (n = 14) of VRE patients had undergone plastic surgery, and most of the surgical approaches were debridement, fasciotomy, and free flap. The ranked second note is general surgery (n = 7), and the majority of laparoscopy.

In terms of antibiotic use in the previous 3 months, the use of third-generation cephalosporins was significantly associated with VRE colonization in medical and surgical wards. Although there are fewer references made to general wards, it is still noteworthy [5,10,15,22]. The rates of use of

third-generation cephalosporins in the previous 3 months in the two groups were 5.7% and 6.5%, and the rest were started on antibiotics when they were admitted to the hospital. This reminds us to focus on antibiotics that are administered during hospitalization. Such antibiotics can be included in the medical record spot-check project. In addition, the use of penicillin was also correlated with VRE colonization in medical and surgical wards, which deviates from the findings of other studies. Penicillins are generally used in infections caused by *staphylococcus, streptococcus, pneumococcus, meningococcus*, and other susceptible bacteria. They are broad-spectrum antibiotics and are one of the most used antibiotics in clinical practice. This finding deviates from those of previous studies but is in line with the results of a study conducted at our hospital from 2007 to 2012 regarding the risk factors for opportunistic VRE infections [8]. One possible explanation is that different hospitals had different policies on antibiotic use and different antibiotics on their formularies.

Among the 284 patients with VRE colonization, only one was diagnosed with VRE-induced HAI during a single hospitalization. Two patients were confirmed to have contracted VRE caused by bloodstream infection and arterial or venous infection when re-admitted to the hospital in 2–3 months. This finding shows that VRE colonization can persist in human bodies for a long time and cause opportunistic infections once the immunity of the patient weakens.

In hospital-wide data, the number of hospital beds in a room was significantly correlated with VRE colonization. However, our findings unexpectedly showed that this was true in only medical wards. The average time-lapse from admission to VRE confirmation in hospitalized patients is 16.8 days. During this period, the infected patients may have contact with 1–3 other patients during a single hospitalization. Based on Hamel's study on patient exposure in hospital wards, for every 1–6 cases of patient exposure, the likelihood of contracting an infection increases by a scale factor of 1–1.9 [19]. According to previous cluster infections, if an index case was not isolated and hand hygiene routines or environmental cleaning was not thoroughly implemented among healthcare staff, the possibility of the transmission of microorganisms increased [17,25]. However, this may be a selection bias because we excluded infected patients. According to the hospital's VRE prevention and control policy, all patients with or without symptoms were placed under isolation protection measures (wearing gloves, isolation gowns, and specifically designed items) and had a dedicated cleaning team to carry out terminal disinfection. Is this policy cost effective? We observed that nearly 50% of patients with VRE colonization could still perform activities of daily living regularly. The guidelines from the CDC suggest that all VRE-infected patients be restricted to single isolation units due to the concerns of microbial transmission through shared toilets. However, our policies did not differentiate between infected and asymptomatic patients. At present, it is uncertain whether asymptomatic carriers are also likely to transmit microorganisms, which may be a direction for further research in the future. Until then, it may only be possible to rely on proper hand hygiene.

Our findings demonstrate that hospitalized patients in different wards also had different risk factors. Designing the VRE scoring by different wards could facilitate early diagnosis. Attention should be paid to high-risk patients with negative VRE results to determine whether medical treatment would increase the risk of conversion to positive results. Our study's findings may serve as a basis for the revision of VRE infection control policies in hospitals.

Limitations

We know that VRE can colonize the intestines for an extended period. Unless there is a cluster infection event, active screening for VRE is not conducted for all inpatients. Past studies have revealed that some VRE cases were outpatients [5], which may underestimate the risk in communities. Where the patient comes from is obviously an important factor; however, this field is not mandatory in the EMRS; so, the information was missing in some patients. In addition, given the sample size, this study only divided subjects into three groups: medical wards, surgical wards, and ICUs. It is impossible to determine which specific ward had the highest prevalence. Regarding antibiotics, no statistical data are available on the consumption of nonregulatory antibiotics by patients in each ward. This study did not consider prophylactic antibiotics; whether or not this manner of data recording affected the result of this study regarding antibiotics requires further review. Due to the retrospective nature of this study, there is a possible selection bias and mentioning recall bias that may affect the current study's results. A prospective study will be designed and conducted as our next step for accurately exploring risk factors for colonization. Finally, the data collected in this study were all from a single hospital; thus, our findings cannot be generalized.

Conclusion

Effective control of VRE transmission in hospitals relies on the active screening of high-risk subjects. The findings of this study show that risk factors for VRE colonization differed among wards. Thus, different management policies should be formulated according to the characteristics of patients in each ward. Screening tests should be conducted according to patients' individual risks of VRE infections, instead of implementing a policy that favors mass screening. For medical wards, screening should be focused on patients from long-term care facilities and elderly patients who are frequently admitted. For surgical patients, more attention should be paid to patients undergoing certain types of procedures. For the ICU, the frequency of environmental cleaning should be considered as part of infection control. Finally, we believe that nasogastric tubes should be removed as soon as possible, and we should promote swallow training for older patients.

We have also demonstrated that the regulation of antibiotic use is an important risk factor, and offering antibiotic stewardship to clinicians requires planning and education. Building antimicrobial stewardship programs through the integration of EMRs is a goal for future efforts. In addition, it is worth reviewing whether it is necessary to completely isolate patients with long-term VRE colonization but no signs

of infection. Such patients only have a 1% of possibility of developing HAI. More research on whether asymptomatic carriers of VRE can be freed from isolation should be conducted in Taiwan.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Tsung-Cheng Hsieh, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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