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Vancomycin-Resistant *Enterococcus* Acquisition in a Tertiary Care Hospital: Testing the Roles of Antibiotic Use, Proton Pump Inhibitor Use, and Colonization Pressure

Rishi Chanderraj,[1] Jess A. Millar,[1] Twisha S. Patel,[1] Andrew F. Read,[2] Laraine Washer,[1] Keith S. Kaye,[1] and Robert J. Woods[1]

[1]University of Michigan, Ann Arbor, and [2]Pennsylvania State University, State College

Background. Vancomycin-resistant *Enterococcus* (VRE) is a leading cause of healthcare-associated infections, and asymptomatic colonization precedes infection. VRE continues to spread despite widespread application of pathogen-specific control guidelines. A better understanding of the risk factors for transmission is needed.

Methods. A retrospective matched case-control study was performed from June 2013 through December 2016 in a single institution. Patients in 6 intensive care units, 1 hematology and oncology unit, and 1 bone marrow transplant unit were screened by means of rectal swab sampling on admission and weekly thereafter. Case patients had a negative swab sample followed by a positive sample >3 days after admission. Controls were closely matched to case patients based on time from admission to the second swab sample, unit in which the second sample was obtained, and date of admission. Comorbidity data, procedures, healthcare settings and exposures, culture data, and duration of antibiotic and proton pump inhibitor (PPI) therapy were abstracted from the electronic medical record. A multivariable risk factor model for conversion was generated using purposeful selection.

Results. A total of 551 case patients were matched with controls. The largest modifiable effects on VRE acquisition were ≥1 day of vancomycin therapy (odd ratio, 1.98; *P* < .001), ≥1 day of aerobic antibiotic therapy (1.90; *P* < .001), and a dose-dependent effect of PPI therapy (odds ratio per day of therapy, 1.09; *P* < .001). Colonization pressures from patients identified to be carriers and placed in contact precautions did not confer increased risk.

Conclusions. Decreasing PPI use and preventing the inappropriate initiation of antibiotic therapy are modifiable targets to decrease VRE transmission in the hospital.

Keywords. hospital acquisition; proton pump inhibitor; risk factors; vancomycin resistant *Enterococcus*.

Vancomycin-resistant *Enterococcus* (VRE) is a leading cause of nosocomial infections and results in higher morbidity and mortality rates than vancomycin-susceptible enterococci [1, 2]. First identified in 1988, VRE rapidly spread and now comprises >25% of all enterococcal bloodstream infections in the United States [3, 4]. It is a hospital-acquired pathogen, and the significant reservoirs for transmission are acute and long-term healthcare facilities [5, 6]. Molecular epidemiologic analyses have shown that cross-transmission between hospitalized patients is the primary means of VRE spread [7].

Colonization with VRE generally precedes infection [8, 9]. There may be 10 times more colonized than infected patients

[10]. Risk factors for VRE acquisition include colonization pressure, a measure of the exposure to patients colonized with VRE during a given period [11–13], host debility and comorbid conditions [7, 14], and antibiotic exposure. In particular, vancomycin, cephalosporins, and drugs with activity against anaerobes have all been shown to increase the risk for VRE acquisition [7, 14–16].

In the past 20 years, there has been a substantial effort to minimize the spread of VRE by targeting known risk factors for VRE acquisition [17, 18]. Despite the application of these extensive control measures, VRE remains endemic in many hospitals [19], emphasizing the need to identify new modifiable risk factors for VRE acquisition. It is unclear whether the previously identified risk factors remain important in the setting of current enhanced infection prevention and antibiotic stewardship practices. The current study examined whether colonization pressure remains a significant risk factor for VRE spread and reassessed modifiable risk factors.

METHODS

Study Setting and Design

A retrospective case-control investigation of risk factors was conducted at the University of Michigan Healthcare system

from 1 June 2013 through 31 December 2016. The University of Michigan Healthcare system consists of approximately 1000 inpatient beds and serves as a tertiary referral hospital for southeastern Michigan. The institutional review board at the University of Michigan approved the study before its initiation.

Patients and Variables

The infection control practice throughout the study period was to perform routine surveillance for VRE on 8 adult units, including intensive care units, the hematology and oncology ward, and the bone marrow transplant ward. All patients were routinely screened on admission and weekly thereafter with rectal swab samples that were then applied to Bio-Rad VRE*Select* chromogenic medium, used to detect VRE. Case patients were those with an initial negative swab sample followed by a positive sample. Additional requirements were that the positive sample was collected 3 days after admission, and that case patients had no prior isolation of VRE from any previous screening swab samples or sterile site cultures. Thus, each case patient was unique, but the patient's first admission was not necessarily the admission that was used.

Controls were patients with an initial negative swab sample, followed by ≥1 negative samples. Their results remained negative on serial VRE screening and clinical culturing, with no isolation of VRE in any culture before inclusion in the study. Case patients were matched to controls at a 1:1 ratio. Each control was used only once. Matching parameters were (1) time at risk (within ±5%). (2) the unit from which the first positive VRE was recovered for case patients or the matched index swab samples for controls, and (3) calendar year (±365 days). Time at risk was defined for case patients as time elapsed between admission and positive VRE screening result. For controls, it was the time between admission and the index swab sample within the same time frame (±5% of the time at risk for the case patient).

Parameters retrieved from patient records included (1) demographics variables, (2) underlying conditions and comorbid conditions, (3) recent healthcare-associated exposures within 90 days before admission, (4) invasive procedures during the time at risk, (5) indwelling devices inserted or present during the time at risk, (6) isolation of *Clostridium difficile* during the time at risk, and (7) days of therapy for individual antimicrobials and proton pump inhibitor (PPI) during the time at risk.

Colonization pressure was analyzed with 2 different metrics. The first was defined as the number of patient-days of exposure for patients known to be VRE positive. For patient i in the study, this was calculated as the sum $\Sigma_j t_{ij}$ over all j other patients in the hospital, where t_{ij} was the time, in days, that patients i and j were in the same unit at the same time, and for which patient i was not yet VRE positive and patient j was VRE positive.

A second measure of colonization pressure, average prevalence during time at risk, was also calculated to compare our results with those of previous studies. Colonization pressure as average prevalence, for an individual patient i was calculated as $\Sigma_j t_{ij}/\Sigma_j c_{ij}$, where t_{ij} is as above and c_{ij} is the time, in days, that patients i and j were in the same unit at the same time, and for which patient i was not yet VRE positive but patient j was either positive or negative.

Statistical Analysis

Bivariable analysis was performed with conditional logistic regression, using the clogit package in R software (version 3.4.1) [20]. A conditional multivariable logistic regression model was built using purposeful selection in SAS Studio online, version 3.71 (Enterprise Edition). Purposeful selection is an iterative process of variable selection, in which covariates are removed from the model if they are nonsignificant and not confounders [21–23]. Significance was evaluated at the 0.1 α level, and confounding was defined as a change in any remaining parameter estimate >20%, compared with the full model.

Variables not selected for the original multivariable model were then added back one at a time, to identify those that made an important contribution in the presence of other variables. Any variables that were significant at the 0.1 α level were put back in the model, and the model was iteratively reduced as before, but only for the variables that were additionally added. Multiple correlations were calculated in R software using the lm package. In multiple correlation figures, squares are scaled based on significance ($P < .05$; false discovery rate corrected).

In multivariable analysis, antibiotic use was entered as a different type of dichotomous variables in 4 separate models: (1) as individual antibiotics, (2) by antibiotic class, (3) by categorizing antibiotics into either aerobic or anaerobic or vancomycin, and (4) by classifying antibiotics as either vancomycin or any other antibiotic. Vancomycin was considered independently of other classes regardless of categorization, owing to its unique importance to VRE. Colonization pressure was defined according the duration of exposure, in patient-days. The criteria for choosing the final model were the highest Cox and Snell R^2 value, the lowest Akaike information criterion, and the lowest correlation between variables. Based on these criteria, categorizing antibiotics by use of aerobic or anaerobic or vancomycin was chosen for the final model.

RESULTS

There were 22 572 patients with ≥1 screening swab sample over the 3.5-year study period, and 688 with an initial negative sample followed by a positive sample were identified as potential case patients. There were 6286 patients (with 7174 admissions) who could have served as controls. Of the potential case patients, 90 were excluded because they had prior isolation of VRE from sterile site cultures, 26 converted from VRE negative to positive in <72 hours, and 21 had no controls that met matching criteria. Thus, 551 case patients were included, and 551 matched controls were identified. The distribution of time to VRE conversion among case patients is displayed in Figure 1.

Full results of the bivariable logistic regression are included in the Supplementary Materials (Supplementary Table 1), with the notable results shown in Table 1. There were no significant differences in age, sex, race, or ethnicity between case patients and controls.

In the bivariable analysis, antibiotic use among all patients was widespread, with 495 of 551 controls (90%) and 536 of 551 case patients (97%) receiving a dose of antibiotic, a significant difference ($P < .01$; Table 1). There was no significant difference between case patients and controls in the duration of therapy, measured in days, for any individual antibiotic (Supplementary Table 1) or for the total duration of antibiotic treatment during the time at risk (mean, 20.4 days for case patients vs 19.4 days for controls; $P = .15$) (Table 1 and Figure 2). PPI use was more common in case patients than in controls, when analyzed as a dichotomous variable; 394 of 551 controls (72%) and 445 of 551 case patients (81%) received ≥1 day of PPI therapy during the time at risk ($P < .01$) (see Table 1). In contrast to antibiotic use, case patients had a longer duration of PPI therapy (mean, 10.5 days for case patients vs 8.5 days for controls; $P < .01$).

In the final multivariable model (Table 2), no candidate covariates were found to be confounders that changed the magnitude of the ratio coefficients by >20%. Notable modifiable risk factors that achieved significance were use of vancomycin (odds ratio, 1.98; 95% confidence interval, 1.39–2.82) or an aerobic antibiotic (1.90; 1.21–2.93]), total parenteral nutrition (1.56; 1.16–2.09), and duration of PPI therapy. Each day of PPI therapy increased the risk of VRE acquisition by 9% (odds ratio, 1.09; 1.06–1.13]). There was no significant difference in colonization pressure in bivariable analysis (Figure 3), and colonization pressure did not achieve significance in multivariable analysis and was removed from the final multivariable model. We noted that removing interaction terms included in the final multivariable model produced no qualitative difference in significant individual risk factors for VRE acquisition.

DISCUSSION

This study is the first to demonstrate the use of PPI therapy as a significant risk factor for VRE acquisition. It also showed that a single dose of antibiotic predisposes patients to VRE acquisition, but the duration of antibiotic treatment is not a significant risk factor. In contrast to previous findings, colonization pressure was not a significant risk factor for individual patients.

PPI therapy significantly increased the odds of acquiring VRE, and the effect was dose dependent. In the multivariable analysis, the odds of VRE acquisition for patients with prior PPI exposure is 9% more than that in a similar patient without exposure for each day of PPI treatment. This finding has biologic plausibility. The stomach acid barrier kills the vegetative forms of several enteric pathogens [24] and plays a vital role as a barrier to ingested bacteria. A mouse model of VRE acquisition showed that gastric acid suppression by PPI treatment facilitates colonization [25]. PPIs are often overprescribed without a clear clinical indication [26]. The findings of the current study suggest that reducing inappropriate PPI use could be a novel infection control strategy to limit the spread of VRE. A similar association has been proposed with *C. difficile* infection, but the results have been conflicting [27, 28]. The conflicting evidence in *C. difficile* infection highlights the need for additional studies on the association between PPI use and VRE acquisition. The final model had a significant interaction term between PPI use and sex, because the effect of PPI therapy was diminished in male patients. More study of the interaction between sex, PPI therapy, and the risk of VRE acquisition is needed.

Vancomycin or aerobic antibiotic therapy given for ≥1 day increased the odds of acquisition, but the duration of therapy had no impact. Antimicrobial stewardship programs have recently emphasized deescalation after antibiotic treatment is already initiated [29]. This study suggests that efforts to contain VRE acquisition should focus on unnecessary initiation of antibiotics rather than deescalation. Previous studies found that the use of anaerobic antibiotics is a risk factor for VRE colonization [30–32], but the current study did not replicate this finding. This discrepancy may be related to the high degree of overlap between vancomycin, anaerobic, and aerobic antibiotic use in the current study. Only a few patients received anaerobic antibiotics alone. Aerobic antibiotics and vancomycin accounted for the majority of antibiotic use.

In contrast to previous studies, colonization pressure was not identified as a risk factor in either the bivariable or the multivariable analysis. Our data suggest that 20 years after widespread implementation of infection control practices targeted at VRE acquisition, individual patient risk factors play a larger role than environmental exposure to VRE. This suggests that future interventions directed at controlling the acquisition and
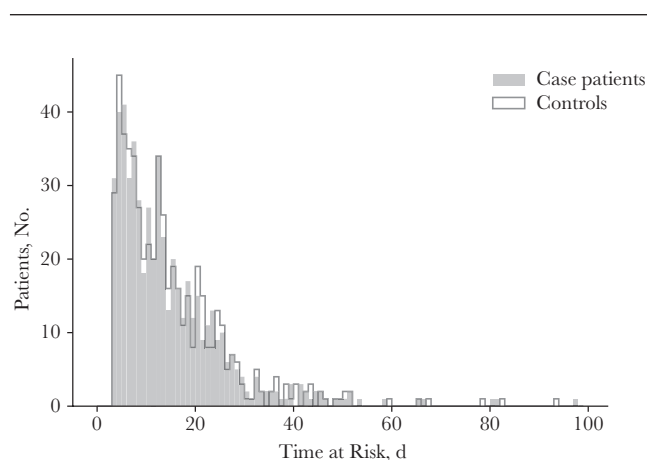

Figure 1. Distribution of time at risk for case patients and controls, with time at risk defined as the time from admission until time to positive vancomycin-resistant *Enterococcus* screening results for case patients, and time from admission to index swab sample for controls.

Table 1. Notable Findings of Univariable Analysis and Complete Final Multivariable Model

Variable	Patients, No. (%)[a]		OR (95% CI)	
	Control (n = 551)	Case Patients (n = 551)	Univariable Analysis	Multivariable Analysis[b]
Age, mean, y	58	59	1.00 (.99–1.01)	…
Nonwhite race	107 (19)	96 (17)	0.87 (.65–1.20)	…
Time at risk, mean, d	14.9	14.9	1.25 (.93–1.68)	…
Colonization pressure, mean, patient-days of exposure	46	48	1.00 (.99–1.01)	…
Total duration of antibiotic treatment, mean, d	19.3	20.4	1.00 (.99–1.01)	…
Any antibiotic use	495 (89)	536 (97)	4.72 (2.47–9.05)	…
Any PPI use	394 (72)	445 (81)	1.75 (1.30–2.36)	…
Final multivariable model				
Vancomycin	358 (65)	421 (76)	1.94 (1.44–2.60)	1.98 (1.39–2.82)
Aerobic antibiotic	433 (79)	493 (89)	2.66 (1.81–3.91)	1.90 (1.21–2.93)
Duration of PPI use, mean, d	8.6	10.5	1.06 (1.03–1.08)	1.09 (1.06–1.13)
Total parenteral nutrition	173 (31)	201 (36)	1.26 (.98–1.62)	1.56 (1.16–2.09)
Congestive heart failure	79 (14)	105 (19)	1.46 (1.04–2.05)	1.54 (1.04–2.28)
Pulmonary hypertension	53 (10)	75 (14)	4.72 (2.47–9.05)	3.50 (1.54–7.95)
Chronic renal failure	76 (14)	93 (17)	1.27 (.91–1.77)	1.79 (1.15–2.78)
Hypertension	45 (8)	32 (6)	0.68 (.42–1.10)	0.32 (.17–.62)
Hemiplegia	64 (12)	85 (15)	1.40 (.98–2.00)	2.54 (1.40–4.68)
Vascular surgery	48 (9)	36 (7)	0.71 (.44–1.14)	0.57 (.34–.98)
Central catheter placement	395 (72)	348 (63)	0.66 (.51–.86)	0.99 (.61–1.38)
Transfer outside hospital	279 (51)	247 (45)	0.77 (.61–.99)	1.93 (1.15–3.17)
Male sex	325 (59)	307 (56)	0.86 (.68–1.11)	1.09 (.75–1.60)
Interaction terms				
Pulmonary hypertension and vancomycin	…	…	…	0.27 (.10–.71)
Duration of PPI use and sex	…	…	…	0.96 (.93–.98)
Central catheter and transfer outside hospital	…	…	…	0.36 (.20–.64)
Transfer outside hospital and hemiplegia	…	…	…	0.41 (.18–.94)

Abbreviations: CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]Results shown for the variables included in final multivariable analysis. For full analysis of all factors displayed, see Supplementary Table 1. Values were as follows for the multivariable analysis: pseudo R^2, 0.11 (maximum, 0.5); concordance, 0.66; and Akaike information criterion, 666.3.

spread of VRE should target the individual patient and not the hospital population as a whole—for instance, emphasizing the appropriate use of antibiotics and PPI therapy for an individual patient. We do note that prior studies of VRE acquisition
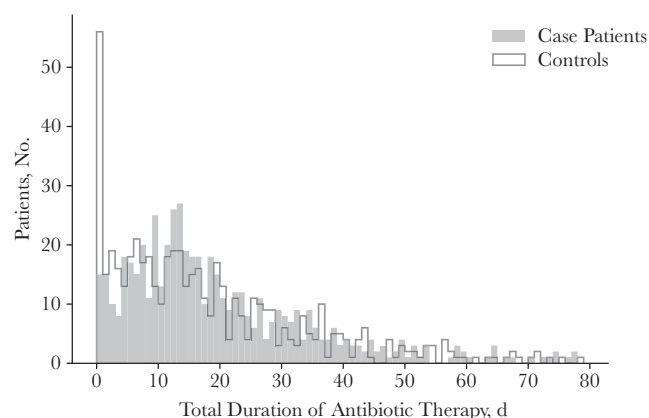

Figure 2. Total duration of antibiotic therapy. The mean was 19.3 days for controls and 20.4 days for case patients (P = .14 in bivariable analysis).

had higher overall colonization pressure. The mean point prevalence of VRE in the current study was 17%, compared with a range of 25%–38% in other studies [11, 12, 33–37]. Our study was conducted in a different era of infection control for the VRE epidemic, an era with more widespread adoption of infection control measures. Future study of the impact of infection prevention strategies, comparing strategies aimed at the population level and individual level, may be helpful.

Our final multivariable model contained several significant interaction terms. These terms were included to account for complex covariation in observational data, although some were not readily interpretable. A sensitivity analysis, in which the interaction terms included in the final multivariable model were each individually removed, produced no qualitative difference in the effect of antibiotic use, PPI use, and colonization pressure on VRE acquisition found in our model.

The weaknesses of the current study include its retrospective, single-center design and lack of access to physiologic data to categorize the severity of illness. A major strength of the study is a data-driven, purposeful selection approach to model building. This algorithmic approach reduced selection bias for known
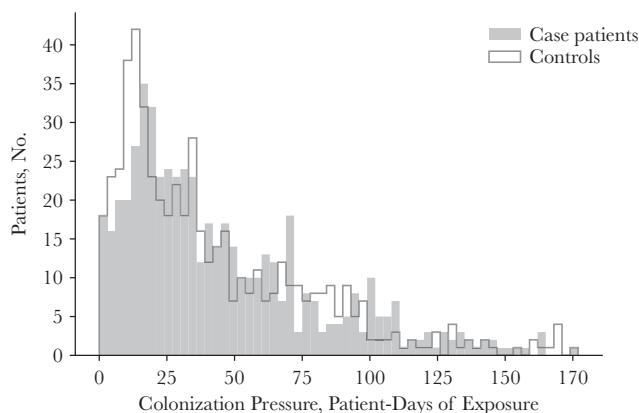
Figure 3. Colonization pressure measured as patient-days of exposure. The mean was 46 patient-days for controls and 48 patient-days for case patients (P = .08 in bivariable analysis).

risk factors and allowed for discovery of new findings. Other strengths of the study are its large sample size, larger than any previous single-center case-control study of VRE acquisition [7, 10, 38], as well as its rigorous matching protocol. It is also among the few studies performed in the context of the modern aggressive infection control protocols targeted at VRE.

It has been >2 decades since the first studies of VRE colonization, and in that time infection control practices have changed dramatically. In this setting, colonization pressure was not a risk factor for VRE acquisition for the individual patient. PPI use is newly identified as a modifiable target to decrease VRE transmission in the hospital. Our findings also suggest that stewardship efforts directed at stopping the spread of VRE should focus on avoiding the inappropriate initiation of antibiotics rather than on antibiotic deescalation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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