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Epidemiology of Vancomycin-Resistant *Enterococcus faecalis*: a Case-Case-Control Study

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Although much is known about vancomycin-resistant (VR) *Enterococcus faecium*, little is known about the epidemiology of VR *Enterococcus faecalis*. The predilection of VR *E. faecalis* to transfer the vancomycin resistance determinant to *Staphylococcus aureus* is much greater than that of VR *E. faecium*. The epidemiology of VR *E. faecalis* has important implications regarding the emergence of vancomycin-resistant *S. aureus* (VRSA); 8 of 13 reported VRSA cases have been from Michigan. A retrospective case-case-control study was conducted at the Detroit Medical Center, located in southeastern Michigan. Unique patients with VR *E. faecalis* infection were matched to patients with strains of vancomycin-susceptible (VS) *E. faecalis* and to uninfected controls at a 1:1:1 ratio. Five hundred thirty-two VR *E. faecalis* cases were identified and were matched to 532 VS *E. faecalis* cases and 532 uninfected controls. The overall mean age of the study cohort ($n = 1,596$) was 63.0 ± 17.4 years, and 747 (46.8%) individuals were male. Independent predictors for the isolation of VR *E. faecalis* (but not VS *E. faecalis*) compared to uninfected controls were an age of ≥65 years, nonhome residence, diabetes mellitus, peripheral vascular disease, exposure to cephalosporins and fluoroquinolones in the prior 3 months, and immunosuppressive status. Invasive procedures and/or surgery, chronic skin ulcers, and indwelling devices were risk factors for both VR *E. faecalis* and VS *E. faecalis* isolation. Cephalosporin and fluoroquinolone exposures were unique, independent predictors for isolation of VR *E. faecalis*. A majority of case patients had VR *E. faecalis* present at the time of admission. Control of VR *E. faecalis*, and ultimately VRSA, will likely require regional efforts focusing on infection prevention and antimicrobial stewardship.

Enterococci have emerged as one of the leading causes of health care-associated infections (1). The two most common species responsible for enterococcal infections in humans are *Enterococcus faecalis* and *E. faecium*. The increase in antibiotic resistance among enterococci, specifically to vancomycin, has become a major clinical and epidemiological problem (2).

At the Detroit Medical Center (DMC), located in southeastern Michigan, vancomycin-resistant *E. faecalis* (VR *E. faecalis*) is unusually common. More than 38% of vancomycin-resistant enterococci (VRE) at DMC were *E. faecalis* in 2009 (3), in contrast to the national prevalence of 11.7% (1), and the prevalence of VR *E. faecalis* has been growing (3). A recent study of skilled nursing facilities in southeastern Michigan also reported a high prevalence of VR *E. faecalis*, which accounted for 52% of total VRE isolates in the study (4).

Among patients cocolonized with VRE and *Staphylococcus aureus*, VRE strains can horizontally transfer the *vanA* gene complex to *S. aureus*, resulting in vancomycin-resistant *S. aureus* (VRSA) (5). In the majority of VRSA cases studied, VR *E. faecalis* served as the *vanA* donor for *S. aureus* (5). Eight of 13 cases reported in the United States since 2002 have occurred in southeastern Michigan (6, 7). It has remained unclear why VRSA has a predilection for this region, although clues have recently emerged (8). VRE strains with an Inc18-like *vanA* plasmid, which has been reported to facilitate the transfer of the *vanA* gene to *S. aureus*, were shown to be more prevalent in Michigan (3.9%) than in other U.S. states (0.6%) and were also much more common among VR *E. faecalis* isolates (identified in 12.5% of isolates in southeastern Michigan) than among VR *E. faecium* isolates (identified in 1.0% of isolates in southeastern Michigan) (8). A previous study also reported that VR *E. faecalis* was associated with cocolonization or coinfection with methicillin-resistant *Staphylococcus aureus* (MRSA) more commonly than the case for VR *E. faecium* (35% versus 17.3%) (9).

The epidemiology of VR *E. faecalis* has important implications regarding the emergence and spread of VRSA in Michigan. Past studies of the epidemiology and outcomes associated with VRE infections were conducted on cohorts consisting predominantly of individuals with *E. faecium* infections, and little is known about the epidemiology of VR *E. faecalis* (10). This study aimed to identify independent risk factors for the isolation of VR *E. faecalis* by using a case-case-control analysis. We also analyzed the outcomes of patients with VR *E. faecalis* isolation compared to those of pa-

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tients with vancomycin-susceptible (VS) *E. faecalis* isolation and those of uninfected controls.

MATERIALS AND METHODS

Study settings and design. A retrospective case-case-control investigation of risk factors and a matched-outcomes analysis were conducted at DMC. The DMC health care system consists of 8 hospitals and >2,200 inpatient beds and serves as a tertiary referral hospital for metropolitan Detroit and southeastern Michigan. The institutional review boards at Wayne State University and DMC approved the study before its initiation.

Patients and variables. Patients who had clinical isolates of VR *E. faecalis* isolated from 1 January 2008 to 31 December 2009 were matched to patients with isolates of vancomycin-susceptible *E. faecalis* and to uninfected controls who did not have cultures with growth of enterococci, at a 1:1:1 ratio. Matching parameters for VS *E. faecalis* cases included (i) anatomic site of VRE isolation, (ii) hospital or outpatient facility where the patient was cared for, (iii) unit or clinic from which VRE was recovered, (iv) calendar year, and (v) time at risk (i.e., time from admission to culture for patients with enterococci). Time at risk for the VS *E. faecalis* case had to be at least as long as the time at risk for the matched VR *E. faecalis* case. Uninfected controls were matched to VR *E. faecalis* cases based on parameters ii to v, and for parameter v, the total duration of the hospital stay was considered to be the time at risk. Once an eligible pool of controls was identified, controls were randomly selected using the randomization function in Excel (Microsoft). Surveillance cultures for VRE were not conducted routinely at DMC during the study period and were excluded from the analysis. For patients who had >1 VR *E. faecalis*-positive culture during the study period, only the first episode of VR *E. faecalis* isolation was analyzed (i.e., the study included only unique-patient episodes).

Parameters retrieved from patient records included (i) demographics; (ii) background conditions and comorbid conditions (including Charlson's scores [11]); (iii) recent health care-associated exposures, such as a stay in a health care facility, invasive procedures, or the presence of indwelling devices; (iv) acute illness indices, including the McCabe score (12); (v) whether or not a VRE isolate was "present on admission," which was defined as isolation of VRE ≤2 days after hospital admission; (vi) cocolonization with MRSA, defined as isolation of MRSA from any body site within 7 days before or after VRE isolation (for uninfected controls, colonization of MRSA was defined as isolation of MRSA from any body site within 7 days before or after the admission date); (vii) recent (3 month) exposures to antimicrobials prior to VRE isolation (or prior to admission, for controls); (viii) outcomes, including in-hospital and 90-day mortality, length of hospital stay (LOS), functional status deterioration (defined as deterioration from admission to discharge in ≥1 activity of daily living [ADL] according to the Katz criteria [13]), and discharge to a long-term care facility (LTCF) after being admitted from home.

Microbiology. DMC has a single centralized clinical microbiology laboratory, which processes ~500,000 samples annually. Bacteria are identified to the species level, and susceptibilities to predefined antimicrobials are determined based on an automated broth microdilution system (MicroScan; Siemens AG, Germany) and in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria (14).

Statistical analysis. All analyses were performed by using IBM-SPSS Statistics 20 (2011) and SAS software, version 9.3 (SAS Institute). Matched bivariate analyses were conducted using a conditional logistic regression model. Matched multivariable models were constructed using Cox proportional hazards regression, accounting for clustering on matched pairs. All variables with a P value of <0.1 in the bivariate matched analyses were considered for inclusion in the multivariate matched analyses. A stepwise selection procedure was used to select variables for inclusion in the final model. The final selected model was tested for confounding. If a covariate affected the β-coefficient of a variable in the model by >10%, then the confounding variable was maintained in the multivariable model. Throughout the text, the percentages displayed are "valid percentages," which exclude missing data from the denominator, unless otherwise stated. A two-sided P value of <0.05 was considered statistically significant.

RESULTS

During the study period, 532 unique-patient isolates of VR *E. faecalis* were identified from urine (n = 319; 60%), wounds (n = 116; 21.8%), blood (n = 76; 14.3%), tips of central venous catheters (n = 20; 3.8%), and sputum (n = 1; 0.2%). The case patients were matched to 532 patients with VS *E. faecalis* isolation and 532 uninfected controls without enterococcal isolation. The overall mean age of the study cohort (n = 1,596) was 63.0 ± 17.4 years, 747 subjects (46.8%) were male, 1,189 subjects (74.5%) were African-American, and 501 subjects (31.6%) were admitted directly from long-term care facilities or transferred from other hospitals. VR *E. faecalis* isolates did not cluster in any single hospital location or at any particular time during the study period.

Results of bivariate analyses comparing VR *E. faecalis* patients and uninfected controls or VS *E. faecalis* patients and uninfected controls are displayed in Table 1. Patients with *E. faecalis* had higher frequencies of dependent functional status and comorbid conditions than those of uninfected controls, and patients with VR *E. faecalis* had higher degrees of dependent functional status and comorbid conditions than those of patients with VS *E. faecalis*. Patients with VR *E. faecalis* were more likely than uninfected controls to be immunosuppressed (neutropenic status, steroid use in the past month, chemotherapy or radiotherapy in the past 3 months, HIV infection, posttransplantation status, or anti-tumor necrosis factor alpha [anti-TNF-α] therapy in the past 3 months). Exposures to health care settings and environments, such as recent surgery or invasive procedures, recent hospitalization, or the presence of indwelling permanent devices, were more common among patients with VR *E. faecalis* and, to a lesser degree, patients with VS *E. faecalis* than among uninfected controls. Compared to uninfected controls, chronic hemodialysis was significantly more common among patients with VR *E. faecalis* but not among those with VS *E. faecalis*. Exposures to antibiotics such as cephalosporins, penicillins, fluoroquinolones, and vancomycin were more common among VR *E. faecalis* subjects than among uninfected controls. The number of antibiotic exposures was significantly higher in the VR *E. faecalis* group than among uninfected controls (median number [interquartile range {IQR}] of antibiotic exposures in VR *E. faecalis* group, 2 [1 to 3], with a range of 0 to 9; median number [IQR] of antibiotic exposures in uninfected controls, 0 [0 to 1], with a range of 0 to 7) ($P < 0.01$). However, the risk for the isolation of VR *E. faecalis* did not increase as the number of antibiotic exposures increased. Patients with VS *E. faecalis* and uninfected controls had similar frequencies of exposures to antibiotics.

Thirty-one (5.8%) VR *E. faecalis* isolates and 2 (0.4%) VS *E. faecalis* isolates were resistant to ampicillin; 8 (1.5%) VR *E. faecalis* isolates and 1 (0.3%) VS *E. faecalis* isolate were resistant to linezolid; 3 (1.9%) VR *E. faecalis* isolates and no VS *E. faecalis* isolates were resistant to daptomycin; 482 (90.9%) VR *E. faecalis* isolates and 158 (30.1%) VS *E. faecalis* isolates demonstrated high-level resistance to gentamicin (i.e., MIC of ≥500 mg/liter); and 385 (72.9%) VR *E. faecalis* isolates and 121 (23.2%) VS *E. faecalis* isolates demonstrated high-level resistance to streptomycin (i.e., MIC of ≥2,000 mg/liter).

The median length of hospital stay before isolation of VR *E.*

TABLE 1 Bivariate analysis of risk factors and outcomes for isolation of VR *E. faecalis* (VREF) and VS *E. faecalis* (VSEF), Detroit Medical Center, 2008–2009[a]

Variable	Value for group			VREF cases vs uninfected controls		VSEF cases vs uninfected controls	
	VREF cases (n = 532)	VSEF cases (n = 532)	Uninfected controls (n = 532)	OR (95% CI)	P value	OR (95% CI)	P value
Demographics							
Age (yr) (mean [SD])	66.0 (16.5)	62.4 (18.1)	60.6 (17.2)	NA	0.001	NA	0.108
No. (%) of males	241 (45.3)	259 (48.7)	247 (46.4)	0.95 (0.75–1.22)	0.707	1.09 (0.86–1.38)	0.472
No. (%) of African-Americans	417 (78.4)	399 (75.1)	373 (70.1)	**1.8 (1.30–2.50)**	**0.001**	**1.39 (1.02–1.90)**	**0.036**
No. (%) of individuals in nonhome residence	265 (50.2)	143 (27.1)	93 (17.6)	**5.05 (3.63–7.03)**	**<0.001**	**1.82 (1.34–2.48)**	**<0.001**
Acute and chronic conditions on admission							
No. (%) of individuals with condition							
Dependent functional status	382 (72.8)	311 (58.6)	219 (41.2)	**3.75 (2.81–4.99)**	**<0.001**	**2.06 (1.59–2.66)**	**<0.001**
Impaired consciousness	226 (43)	169 (31.8)	101 (19)	**3.23 (2.40–4.36)**	**<0.001**	**2 (1.50–2.68)**	**<0.001**
Rapidly fatal McCabe score	84 (16.5)	42 (7.9)	48 (9.1)	**2.18 (1.45–3.29)**	**<0.001**	0.85 (0.53–1.35)	0.481
Cerebrovascular accident	148 (27.8)	145 (27.3)	73 (13.7)	**2.5 (1.80–3.47)**	**<0.001**	**2.47 (1.77–3.44)**	**<0.001**
COPD	136 (25.6)	72 (13.6)	98 (18.5)	**1.49 (1.12–1.99)**	**0.006**	**0.71 (0.51–0.98)**	**0.035**
Congestive heart failure	222 (41.7)	143 (27.1)	116 (21.8)	**2.80 (2.08–3.77)**	**<0.001**	**1.34 (1.01–1.78)**	**0.045**
Diabetes mellitus	281 (52.8)	209 (39.5)	165 (31.1)	**2.63 (2–3.46)**	**<0.001**	**1.48 (1.14–1.92)**	**0.003**
Dementia	171 (32.1)	84 (15.9)	43 (8.1)	**5.57 (3.73–8.33)**	**<0.001**	**2.08 (1.41–3.06)**	**<0.001**
Chronic skin ulcer	258 (48.9)	128 (24.2)	45 (8.5)	**11.14 (7.13–17.41)**	**<0.001**	**3.44 (2.35–5.04)**	**<0.001**
Peripheral vascular disease	175 (32.9)	82 (15.5)	57 (10.7)	**4.58 (3.14–6.67)**	**<0.001**	**1.58 (1.08–2.32)**	**0.019**
Peptic ulcer disease	159 (29.9)	56 (10.6)	58 (10.9)	**3.3 (2.35–4.62)**	**<0.001**	0.96 (0.65–1.42)	0.842
Any liver disease	85 (16)	69 (13)	40 (7.5)	**2.29 (1.54–3.4)**	**<0.001**	**1.91 (1.24–2.92)**	**0.003**
Any renal disease	253 (47.6)	168 (31.8)	136 (25.7)	**2.68 (2.03–3.54)**	**<0.001**	**1.37 (1.04–1.80)**	**0.026**
Active malignant disease	52 (9.8)	72 (13.6)	56 (10.5)	0.91 (0.58–1.4)	0.655	1.43 (0.94–2.18)	0.093
Immunosuppressive state[b]	196 (36.8)	109 (20.6)	89 (16.8)	**2.98 (2.18–4.07)**	**<0.001**	1.29 (0.94–1.77)	0.113
Charlson's weighted index of comorbidity (median [IQR])	5 (3–7)	3 (1–5)	2 (1–5)	NA	**<0.001**	NA	**<0.001**
No. (%) of individuals with exposure to health care settings and environments before VRE isolation							
Chronic hemodialysis	89 (16.8)	51 (9.6)	60 (11.3)	**1.68 (1.16–2.44)**	**0.006**	0.8 (0.52–1.21)	0.288
Permanent devices[c]	373 (70.5)	243 (45.9)	113 (21.2)	**8.25 (5.84–11.66)**	**<0.001**	**3.15 (2.36–4.2)**	**<0.001**
Hospitalized in the past 3 months	400 (76)	267 (50.4)	226 (42.6)	**4.18 (3.12–5.61)**	**<0.001**	**1.37 (1.07–1.75)**	**0.012**
Surgery or invasive procedure[d] in the past 6 months	423 (80)	276 (52.1)	197 (37.2)	**7.05 (5–9.95)**	**<0.001**	**1.91 (1.48–2.47)**	**<0.001**
ICU stay in the past 3 months	194 (37.2)	184 (34.7)	125 (23.7)	**2.92 (2.0–4.26)**	**<0.001**	**2.06 (1.49–2.85)**	**<0.001**
Microbiology							
No. (%) of individuals with cocolonization with MRSA[e]	85 (16.0)	36 (6.8)	9 (1.7)	**10.5 (5.08–21.68)**	**<0.001**	4.38 (2.03–9.43)	**<0.001**
No. (%) of individuals with antimicrobial exposure within 3 months before VRE isolation							
Any antibiotics	410 (78.7)	187 (35.3)	180 (34.1)	**8.93 (6.08–13.11)**	**<0.001**	1.07 (0.82–1.40)	0.628
Penicillins[f]	171 (33.3)	29 (5.5)	40 (7.6)	**6.96 (4.45–10.87)**	**<0.001**	0.68 (0.40–1.15)	0.148
Ampicillin	56 (11.1)	2 (0.4)	7 (1.3)	**9.33 (4.02–21.66)**	**<0.001**	0.29 (0.06–1.38)	0.118
Ampicillin-sulbactam	50 (9.9)	12 (2.3)	18 (3.4)	**3.46 (1.87–6.42)**	**<0.001**	0.65 (0.30–1.38)	0.261
Piperacillin-tazobactam	63 (12.5)	14 (2.7)	12 (2.3)	**9.67 (4.17–22.40)**	**<0.001**	1.17 (0.54–2.52)	0.696
Amoxicillin	28 (5.5)	0	1 (0.2)	27.0 (3.67–198.68)	0.001	0.00	0.986
Amoxicillin-clavulanate	5 (1)	3 (0.6)	5 (0.9)	1 (0.29–3.45)	1	0.6 (0.14–2.51)	0.484
Cephalosporins	276 (55.6)	99 (18.7)	77 (14.6)	**7.09 (4.93–10.21)**	**<0.001**	1.4 (0.99–1.98)	0.057
Cefepime	195 (38.5)	42 (7.9)	42 (8)	**9.61 (5.92–15.62)**	**<0.001**	1 (0.63–1.58)	**<0.001**
Ceftriaxone	125 (24.7)	44 (8.3)	35 (6.6)	**3.90 (2.63–5.79)**	**<0.001**	1.3 (0.81–2.09)	0.280
Cefazolin	58 (11.4)	13 (2.5)	12 (2.3)	**6.22 (3.08–12.58)**	**<0.001**	1.08 (0.49–2.37)	0.842
Carbapenem	32 (6.2)	19 (3.6)	22 (4.2)	1.667 (0.88–3.16)	0.118	0.85 (0.45–1.62)	0.623
Vancomycin	252 (49)	77 (14.5)	85 (16.1)	**5.69 (4–8.12)**	**<0.001**	0.97 (0.62–1.52)	0.909
Daptomycin	6 (1.2)	5 (0.9)	8 (1.5)	0.75 (0.26–2.16)	0.594	0.63 (0.2–1.91)	0.410
Linezolid	26 (5)	7 (1.3)	11 (2.1)	**2.78 (1.3–5.95)**	**0.009**	0.64 (0.25–1.64)	0.350
Fluoroquinolones	134 (26.1)	42 (7.9)	43 (8.1)	**4.6 (2.99–7.09)**	**<0.001**	0.97 (0.62–1.52)	0.909
Trimethoprim-sulfamethoxazole	57 (11.1)	22 (4.2)	19 (3.6)	**3.24 (1.88–5.57)**	**<0.001**	1.16 (0.63–2.14)	0.640
Metronidazole	71 (13.8)	27 (5.1)	31 (5.9)	**2.6 (1.64–4.12)**	**<0.001**	0.86 (0.51–1.47)	0.587
Clindamycin	37 (7.2)	21 (4)	14 (2.7)	**3 (1.56–5.77)**	**0.001**	1.5 (0.76–2.95)	0.240

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TABLE 1 (Continued)

Variable	Value for group			VREF cases vs uninfected controls		VSEF cases vs uninfected controls	
	VREF cases ($n = 532$)	VSEF cases ($n = 532$)	Uninfected controls ($n = 532$)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Macrolides	43 (8.3)	13 (2.5)	13 (2.5)	**3.9 (1.95–7.81)**	**<0.001**	1 (0.43–2.31)	1.000
Aminoglycosides	66 (12.8)	18 (3.4)	24 (4.5)	**3.28 (1.93–5.56)**	**<0.001**	0.73 (0.38–1.39)	0.332
Tetracyclines	30 (5.8)	15 (2.8)	18 (3.4)	1.87 (1–3.5)	0.051	0.83 (0.42–1.65)	0.603
Oral vancomycin	24 (4.7)	4 (0.8)	5 (0.9)	**5.5 (1.9–15.95)**	**0.002**	0.80 (0.22–2.98)	0.740
Outcomes							
No. (%) of individuals with outcome							
In-hospital mortality	52 (9.8)	39 (7.4)	35 (6.6)	**1.81 (1.06–3.08)**	**0.029**	1.12 (0.7–1.79)	0.633
3-month mortality	90 (18.3)	69 (13.5)	52 (10.1)	**2.58 (1.64–4.05)**	**<0.001**	1.43 (0.97–2.1)	0.068
Functional status deterioration	74 (15.8)	102 (20.8)	26 (6.8)	**2.38 (1.43–3.96)**	**0.001**	**4.93 (2.77–8.75)**	**<0.001**
Dependent functional status at discharge	377 (80.6)	323 (65.8)	193 (38.8)	**6.81 (4.7–9.87)**	**<0.001**	**3.24 (2.42–4.35)**	**<0.001**
Discharge to LTCF after being admitted from home	84 (33.9)	91 (23.5)	51 (11.4)	**2.76 (1.68–4.55)**	**<0.001**	**2.21 (1.42–3.46)**	**0.001**
Additional hospitalizations within 6 months following VREF/VSEF isolation[g]	345 (74.5)	288 (59.9)	247 (50.8)	**2.86 (2.12–3.87)**	**<0.001**	**1.44 (1.1–1.88)**	**0.008**
Invasive procedure or surgery within 3 months following VREF/VSEF isolation[g]	276 (55.2)	175 (33.9)	174 (34.7)	**2.25 (1.72–2.95)**	**<0.001**	1.01 (0.77–1.33)	0.945
Total length of hospital stay (days) (median [IQR])	11.4 (5.6–21.4)	9.9 (4.7–22.1)	4.2 (1.1–11.9)	NA	**<0.001**	NA	**<0.001**
Total length of hospital stay, excluding deaths[h] (days) (median [IQR])	6.6 (1.4–17.6)	6.4 (1.8–17.0)	2.0 (0.9–7.8)	NA	**<0.001**	NA	**<0.001**

[a] Data include percentages of patients for whom data were available, i.e., excluding the missing cases. Statistically significant data are shown in bold. Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; LTCF, long-term care facilities; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, data not available; OR, odds ratio; SD, standard deviation.

[b] Includes one or more of the following: (i) neutropenia (<500 neutrophils) at time of culture, (ii) glucocorticoid/steroid use in the past month, (iii) chemotherapy in the past 3 months, (iv) radiotherapy in the past 3 months, (v) posttransplantation status, (vi) anti-TNF-α therapy in the past 3 months, and (vii) HIV infection.

[c] Chronic or permanent devices (e.g., tracheotomies, central lines, urinary catheters, and orthopedic external fixators) that were in place at time of VREF/VSEF isolation (on admission for uninfected controls).

[d] Includes percutaneous interventions, endoscopies, and biopsies.

[e] Cocolonization with MRSA was defined as isolation of MRSA from any body site within 7 days before or after the isolation of VRE (for uninfected controls, MRSA colonization was defined as isolation of MRSA within 7 days before or after the admission date).

[f] Penicillins include β-lactam–β-lactamase inhibitor combinations.

[g] After admission for uninfected controls.

[h] Excluding data for patients who died during hospitalization.

faecalis or VS *E. faecalis* was relatively short, and the lengths of stay were similar between the two groups (median [IQR] of 1.9 days [0.26 to 8.81 days] versus 2 days [0.31 to 8.76 days], respectively) ($P = 0.767$). Two hundred eighty-nine (54.3%) patients with VR *E. faecalis* and 284 (53.4%) patients with VS *E. faecalis* had enterococcal isolates present on admission. Patients with VR *E. faecalis* or VS *E. faecalis* were colonized with MRSA (i.e., cocolonized with VRE and MRSA) more frequently than uninfected controls were ($n = 85$ [16.0%], 36 [6.8%], and 9 [1.7%], respectively; for the VR *E. faecalis* group versus controls, the odds ratio [OR] and 95% confidence interval [95% CI] were 10.5 and 5.1 to 21.7, respectively [$P < 0.01$]; for the VS *E. faecalis* group versus controls, the OR and 95% CI were 4.4 and 2.0 to 9.4, respectively [$P < 0.01$]). Patients with VR *E. faecalis* isolation were cocolonized with MRSA more frequently than were patients with VS *E. faecalis* (OR and 95% CI of 3.0 and 1.9 to 4.7, respectively [$P < 0.01$]).

In multivariate analyses (Table 2), independent predictors for the isolation of VR *E. faecalis* compared to uninfected controls were an age of ≥65 years, nonhome residence (transferred from another hospital or admitted from an LTCF), diabetes mellitus, chronic skin ulcer, peripheral vascular disease, invasive procedure and/or surgery in the past 6 months, exposure to cephalosporins and fluoroquinolones in the 3 months prior to VR *E. faecalis* isolation, immunosuppressive status on admission, and the presence of indwelling permanent devices at the time of VR *E. faecalis* isolation (Table 2). Independent predictors for isolation of VS *E. faecalis* compared to uninfected controls were the presence of indwelling permanent devices at the time of VS *E. faecalis* isolation, surgery or an invasive procedure in the past 6 months, intensive care unit (ICU) stay in the past 3 months, chronic skin ulcer, history of cerebrovascular accident (CVA) prior to admission, and liver disease or dysfunction.

Independent predictors for VR *E. faecalis* but not VS *E. faecalis* included an age of ≥65 years, nonhome residence, diabetes mellitus, peripheral vascular disease, immunosuppressive status on admission, and exposure to cephalosporins and fluoroquinolones in the 3 months prior to admission.

In-hospital mortality and total mortality within 3 months following VR *E. faecalis* isolation (following admission for controls) were higher among patients with VR *E. faecalis* than among controls, and no statistically significant difference in mortality rate was noted between the VS *E. faecalis* group and uninfected controls. Functional deterioration, discharge to an LTCF, and additional hospitalization within 6 months occurred more commonly

TABLE 2 Multivariate analysis of risk factors for isolation of VR *E. faecalis* (VREF) and VS *E. faecalis* (VSEF), Detroit Medical Center, 2008–2009[a]

Variable	VREF group vs uninfected controls[b]		VSEF group vs uninfected controls[c]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Chronic skin ulcer	6.10 (2.92–12.75)	<0.001	2.62 (1.73–3.98)	<0.001
Presence of permanent devices[d] at VRE isolation	4.50 (2.51–8.06)	<0.001	2.26 (1.63–3.13)	<0.001
Surgery or invasive procedures[e] in the past 6 months	2.48 (1.31–4.18)	0.005	1.42 (1.05–1.92)	0.024
Immunosuppressive state[f] on admission	3.69 (1.87–7.23)	<0.001		
Diabetes mellitus	2.83 (1.56–5.14)	0.001		
Peripheral vascular disease	2.41 (1.21–4.78)	0.012		
Age of ≥65 yr	1.89 (1.09–3.30)	0.025		
Nonhome residence	2.03 (1.14–3.60)	0.010		
Cephalosporin exposure in the past 3 months	3.01 (1.51–6.01)	0.002		
Fluoroquinolone exposure in the past 3 months	2.80 (1.16–6.78)	0.022		
Cerebrovascular accident			1.89 (1.29–2.76)	0.001
Any liver disease			2.09 (1.27–3.44)	0.004
ICU stay in the past 3 months			1.62 (1.11–2.35)	0.012

[a] Abbreviations: CI, confidence interval; HR, hazard ratio.
[b] Controlled for the confounding effects of vancomycin, penicillins, and metronidazole in the past 3 months, a rapidly fatal McCabe score, and chronic hemodialysis.
[c] Controlled for the confounding effects of dementia on admission, nonhome residence, and age of ≥65 years.
[d] Chronic or permanent devices (e.g., tracheotomies, central lines, urinary catheters, and orthopedic external fixators) that were in place at time of VREF/VSEF isolation (on admission for uninfected controls).
[e] Including percutaneous interventions, endoscopies, and biopsies.
[f] Includes one or more of the following: (i) neutropenia (<500 neutrophils) at time of culture, (ii) glucocorticoid/steroid use in the past month, (iii) chemotherapy in the past 3 months, (iv) radiotherapy in the past 3 months, (v) posttransplantation status, (vi) anti-TNF-α therapy in the past 3 months, and (vii) HIV infection.

in the VR *E. faecalis* and VS *E. faecalis* groups than among uninfected controls. The total duration of hospitalization (LOS) was longer among the VR *E. faecalis* and VS *E. faecalis* groups than among uninfected controls. In-hospital mortality did not differ significantly between the VR *E. faecalis* and VS *E. faecalis* case groups ($P = 0.113$), although total mortality within 3 months following enterococcal isolation was higher among patients with VR *E. faecalis* isolation than among patients with VS *E. faecalis* isolation ($P = 0.02$; OR = 1.58 [95% CI = 1.09 to 2.29]). Total LOS were similar among patients in the VR *E. faecalis* and VS *E. faecalis* groups ($P = 0.25$).

DISCUSSION

To our knowledge, this is the first study to evaluate specific predictors for the isolation of VR *E. faecalis* by using the case-case-control study design (15). A key finding in this study was that exposures to cephalosporins in the 3 months prior to VR *E. faecalis* isolation were independent risk factors for VR *E. faecalis* isolation, but not VS *E. faecalis* isolation, after controlling for confounding variables. Exposure to cephalosporins was reported as a VRE risk factor in past studies, although none of these studies evaluated VR *E. faecalis* exclusively (16, 17). We recently reported that patients with bacteremia due to VR *E. faecalis* were exposed to cephalosporins more frequently than were patients with VR *E. faecium* bacteremia (18). Fluoroquinolones were also independently associated with isolation of VR *E. faecalis*, and this association was demonstrated by other investigators with regard to VRE (16).

Eight of 13 patients with reported cases of VRSA (6 of 8 patients with reported cases of VRSA were from Michigan) were diabetic. An important finding in this study was that diabetes mellitus was identified as a unique, independent risk factor for isolation of VR *E. faecalis*. Diabetes prevalence in Michigan has consistently been higher than that in the nation as a whole; an estimated 1.65 million Michigan citizens (16.7% of the estimated population in 2011) have diabetes, as opposed to 25.8 million (8.3%) Americans (19). Other independent risk factors uniquely associated with VR *E. faecalis* isolation in this study, such as the presence of indwelling permanent devices and chronic skin ulcers, overlap the epidemiological characteristics of patients with VRSA isolation. Wounds were the anatomic culture source of VRSA in 11 of 13 cases, and isolations of VRSA were associated with infections of foreign devices in 2 cases (6, 7). A recent prospective study conducted in a skilled nursing facility in southeastern Michigan identified individuals with indwelling devices who also had functional disability or wounds as being at greatest risk for MRSA-VRE cocolonization (4). Indeed, in our study, patients with VR *E. faecalis* were frequently cocolonized with MRSA to a greater degree than patients with VS *E. faecalis* and uninfected controls. Furthermore, our team recently reported that the severity of illness, presence of indwelling devices, and chronic wounds are independent predictors for cocolonization with VR *E. faecalis* and MRSA (20). These findings, together with the growing prevalence of VR *E. faecalis* and the relatively high prevalence of Inc18-like plasmids in Michigan, might partially explain the endemicity of VRSA in this region (3, 8).

Donskey et al. previously reported that antianaerobe antibiotics, including penicillins, promote high-density colonization of VRE in patients' stools (21), which might have been related to the inhibiting effects of these antibiotics to anaerobic flora, which compete with or inhibit VRE (22). This study did not find an association between exposure to penicillin antibiotics and VR *E. faecalis* isolation, possibly because few of the VR *E. faecalis* isolates in this study were resistant to ampicillin ($n = 31$; 5.8%). Previous studies have reported metronidazole exposure to be a risk factor for VRE, but this study did not identify metronidazole use as a risk factor for VR *E. faecalis*. A previous meta-analysis reported an association between vancomycin exposure and VRE that did not reach statistical significance (23). This study did not find a significant association between vancomycin exposure and VR *E. faecalis*.

An additional multivariate analysis using the variable "any antibiotic exposure" in the place of individual antibiotics was conducted. In the resultant model, "any antibiotic exposure" was an independent predictor for the isolation of VR *E. faecalis* compared to the uninfected control group (OR = 5.45 [95% CI = 3.03 to 9.81]; $P < 0.001$).

Clinical isolates of VR *E. faecalis* from this study displayed frequencies of high-level resistance to gentamicin ($n = 482$; 90.9%) and ampicillin ($n = 31$; 5.8%) that were higher than previously reported levels (24). Notably, the number of VR *E. faecalis* isolates in the current study was much greater than those in previous studies (24, 25).

Multiple studies have evaluated risk factors for isolation of VRE; however, these studies included predominantly VR *E. faecium* isolates and/or did not differentiate VR *E. faecalis* from VR *E. faecium*. Furtado et al. evaluated the risk factors for VR *E. faecalis* bacteremia by using two control groups (VS *E. faecalis* cases and uninfected controls), and they identified vancomycin exposure as the major risk factor for VR *E. faecalis* bacteremia in Brazil (25). There are several important differences between the former study and our study which may explain the disparate results. Furtado et al.'s study did not compare VS *E. faecalis* cases to uninfected controls, which limited the evaluation of the predictors specifically associated with isolation of VR *E. faecalis*. Also, the study included a limited number of bacteremia cases ($n = 34$), assessed fewer risk factors (for example, chronic skin ulcers and nonhome residence were not analyzed), and used a narrow period (3 weeks) for evaluation of previous antibiotic exposures.

In this study, the median length of hospital stay prior to isolation of VR *E. faecalis* was relatively short (less than 2 days), and the majority of subjects with VR *E. faecalis* had VR *E. faecalis* isolates present at the time of admission. This indicates the presence of a reservoir of VR *E. faecalis* in health care settings other than hospitals. The potential role of selective antimicrobial pressure of agents such as cephalosporins in the high prevalence of VR *E. faecalis* and VRSA in a variety of health care and institutional settings needs to be explored. Control of VR *E. faecalis*, and ultimately VRSA, will likely require regional efforts across the entire health care continuum, focusing on both infection prevention and antimicrobial stewardship.

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K. Hayakawa and K. S. Kaye were responsible for overseeing the work as a whole, including the study design, the retrieval of medical records, and data analyses. The other contributions were as follows. D. Marchaim, E. T. Martin, and M. Palla were responsible for the data analyses. J. M. Pogue, K. Sukayogula, and M. Joseph were responsible for the retrieval and review of medical records. P. R. Lephart and R. Policherla were responsible for the retrieval and review of microbiological data. M. J. Rybak was responsible for editing the manuscript and reviewing the data. All authors not listed were responsible for the retrieval and review of medical records.

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