Infection Control & Hospital Epidemiology (2019), **40**, 414–419
doi:10.1017/ice.2019.15

Original Article

A retrospective cohort study of antibiotic exposure and vancomycin-resistant *Enterococcus* recolonization

Heather Y. Hughes MD MPH[1,2], Robin T. Odom MS[3], Angela V. Michelin MPH[3], Evan S. Snitkin PhD[4], Ninet Sinaii PhD, MPH[3], Aaron M. Milstone MD MHS[5], David K. Henderson MD[3] and Tara N. Palmore MD[3]

[1]The Ralph H. Johnson VAMC, Charleston, South Carolina, [2]The Medical University of South Carolina, Charleston, South Carolina, [3]National Institutes of Health, Bethesda, Maryland, [4]University of Michigan Medical School, Ann Arbor, Michigan and [5]Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Objective: In the National Institutes of Health (NIH) Clinical Center, patients colonized or infected with vancomycin-resistant *Enterococcus* (VRE) are placed in contact isolation until they are deemed "decolonized," defined as having 3 consecutive perirectal swabs negative for VRE. Some decolonized patients later develop recurrent growth of VRE from surveillance or clinical cultures (ie, "recolonized"), although that finding may represent recrudescence or new acquisition of VRE. We describe the dynamics of VRE colonization and infection and their relationship to receipt of antibiotics.

Methods: In this retrospective cohort study of patients at the National Institutes of Health Clinical Center, baseline characteristics were collected via chart review. Antibiotic exposure and hospital days were calculated as proportions of VRE decolonized days. Using survival analysis, we assessed the relationship between antibiotic exposure and time to VRE recolonization in a subcohort analysis of 72 decolonized patients.

Results: In total, 350 patients were either colonized or infected with VRE. Among polymerase chain reaction (PCR)-positive, culture (Cx)-negative (PCR+/Cx−) patients, PCR had a 39% positive predictive value for colonization. Colonization with VRE was significantly associated with VRE infection. Among 72 patients who met decolonization criteria, 21 (29%) subsequently became recolonized. VRE recolonization was 4.3 ($P = .001$) and 2.0 ($P = .22$) times higher in patients with proportions of antibiotic days and antianaerobic antibiotic days above the median, respectively.

Conclusion: Colonization is associated with clinical VRE infection and increased mortality. Despite negative perirectal cultures, re-exposure to antibiotics increases the risk of VRE recolonization.

(Received 1 October 2018; accepted 13 January 2019)

Vancomycin-resistant *Enterococcus faecium* (VRE) are an important cause of healthcare-associated infections.[1] Vancomycin resistance among *E. faecium* bloodstream isolates has increased in the United States from 57% in 2000 to >80% in 2010.[2] The odds of death from enterococcal bloodstream infection are more than doubled if the isolate is vancomycin resistant.[3] With increasing reports of resistance to additional antibiotics, infection control efforts must focus on preventing nosocomial spread of VRE.[4,5]

Factors contributing to colonization with VRE include prolonged hospital stay, immunosuppression, hematologic malignancy, residence in long-term care facilities, invasive procedures, proximity to colonized or infected patients, occupying a room vacated by a VRE-colonized patient, and use of third-generation cephalosporins, intravenous vancomycin, or antianaerobic antibiotics.[6–9] The likelihood of developing a bloodstream infection after VRE colonization is highest among immunosuppressed patients.[10] Infection control measures to prevent the spread of VRE include active microbiological surveillance and contact precautions.

Patients at the National Institutes of Health (NIH) Clinical Center, a 200-bed hospital, are enrolled in research studies. Most patients are immunosuppressed from their underlying illnesses or from therapy, including chemotherapy, hematopoietic stem cell transplantation (HSCT), and immunotherapy. Patients who have VRE colonization or infection are placed in contact isolation, which is discontinued when the patient appears to be "decolonized," that is, after 3 consecutive negative surveillance cultures at least 1 week apart.[11,12] One challenge in the subsequent management of VRE is the patients' dynamic state of colonization, which affects clinical care and isolation status. Recent literature on the natural history of VRE recolonization is sparse.[13–15] Whether the same risk factors that promote initial colonization also encourage recolonization with VRE is not well understood. Antibiotic exposure after decolonization could apply selective pressure in the setting of low-level persistent colonization, or it could alter the intestinal microbiome in a manner conducive to recolonization. Here, we present descriptive epidemiology and natural

Author for correspondence: Tara N. Palmore, Email: tpalmore@mail.nih.gov

PREVIOUS PRESENTATION: Part of these data were presented as an abstract at ID Week 2014 on October 9, 2014, in Philadelphia, Pennsylvania, and as a poster presentation at ID Week 2015 on October 9, 2015, in San Diego, California.

Cite this article: Hughes HY, *et al.* (2019). A retrospective cohort study of antibiotic exposure and vancomycin-resistant *Enterococcus* recolonization. *Infection Control & Hospital Epidemiology*, 40: 414–419, https://doi.org/10.1017/ice.2019.15

history of VRE colonization and infection as well as the results of our investigation of whether receipt of inpatient antibiotics is associated with time to VRE recolonization.

Methods

Patients and setting

All patients who had VRE infection or colonization identified from active surveillance or clinical cultures between January 2007 and December 2015 were included in the study. Starting in July 2009, surveillance perirectal swabs were collected on admission and then weekly from all patients receiving HSCT and on medical oncology wards (regardless of diagnosis), except those already known to be colonized with VRE. The institutional review board waived approval for this study.

Definitions

Patients met criteria for VRE infection if VRE grew in culture from a clinical specimen other than urine. Patients who had positive perirectal cultures or PCR for VRE or who had VRE grown from urine were considered colonized. Patients off antibiotics ≥4 weeks who had 3 consecutive negative perirectal swabs at least 1 week apart were considered decolonized. After they were decolonized, patients were classified as recolonized if they later had clinical cultures or surveillance swabs positive for VRE. Decolonized patients who had no further microbiological evidence of VRE were considered to have remained decolonized.

The primary exposure variables were total antibiotic and antianaerobic antibiotic days. An antibiotic day was defined as receipt of at least 1 inpatient antibiotic per 24-hour period. Outpatient antibiotics were excluded because we were unable to confirm administration definitively. Antibiotics most likely to be prescribed for intra-abdominal infections were included in the group of antianaerobic antibiotics. Ampicillin/sulbactam, amoxicillin/clavulanate, meropenem, imipenem, ertapenem, metronidazole, and piperacillin/tazobactam were classified as antianaerobic antibiotics. Because clindamycin is not recommended as a first-line antibiotic for these infections, it was not included.

Possible confounding variables were selected based on literature review and clinician experience and included age at the time of VRE decolonization, race, gender, and inpatient hospitalization days.

The primary outcome variable was VRE recolonization. The at-risk period was the duration of VRE decolonization, defined as the number of days between the first negative perirectal culture and the date of recolonization or the last known negative culture.

VRE screening and clinical cultures

Throughout the study period, clinical specimens were inoculated onto selective media (bile esculin azide agar containing 6 μg/mL vancomycin). From July 2009 to July 2010, perirectal swabs were also inoculated onto selective media. Starting in July 2010, swabs were first tested by rapid *VanA/VanB* PCR (Cepheid), which, due to low positive predictive value, was replaced in December 2010 with rapid *VanA* PCR (Cepheid). Swabs with positive PCR results were inoculated onto selective media. Colonies were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS) and underwent automated antimicrobial susceptibility testing using the Phoenix (Becton Dickinson, Franklin Lakes, NJ) and Vitek (bioMèrieux, Marcy-l'Étoile, France) systems.

Table 1. Baseline Characteristics of Patients With VRE Colonization and/or Infection

Characteristic	Total (n=350)
Age, mean y (SD)	44.4 (17.3)
Age, median y (IQR)	46 (29–59)
Female, no. (%)	162 (46.3)
Race, no. (%)	
White	179 (51.1)
Black	83 (23.7)
Hispanic	67 (19.1)
Asian	13 (3.7)
Other	7 (2.0)
Missing	1 (0.29)
Underlying diagnosis, no. (%)	
Leukemia/lymphoma	309 (88.3)
Sickle cell disease	7 (2.0)
HIV	8 (2.3)
Immunodeficiency disorder	22 (6.3)
Other	4 (1.1)
Receipt of transplant, no. (%)	190 (54.3)
Type of first transplant (%)	
Myeloablative HSCT	17.1
Reduced intensity HSCT	30.9
Autologous HSCT	4.3
HSCT, type unknown	0.87
Solid organ	1.1
Not available	45.7
>1 transplant, %	18.6
Mortality, no. (%) deceased	163 (46.6)

Note. SD, standard deviation; IQR, interquartile range; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant.

Statistical analysis

To standardize antibiotic exposure during the at-risk period, the median proportions of total antibiotic days per VRE decolonized days and antianaerobic antibiotic days per VRE decolonized days were calculated for each patient and analyzed in regression models. The median proportions of antibiotic days per VRE decolonized days were then analyzed separately in survival analyses as binary variables either above or below the respective medians. The proportion of inpatient days per VRE decolonized days was calculated for each patient then analyzed as a binary variable either above or below the respective subcohort (n = 72) median.

We used Stata version 13.1 statistical software (StataCorp, College Station, TX) for all analyses. Baseline characteristics were compared using the Student *t* test for means and the Fisher exact test and the Pearson $\chi 2$ test for categorical values. Percentage of median total antibiotic days, antianaerobic antibiotic days, and inpatient hospital days were compared using the median Fisher exact test. Hazard ratios and significance determinations were calculated using Cox proportional hazards models with time-fixed covariates and robust estimation. Statistical significance was defined as a

https://doi.org/10.1017/ice.2019.15 Published online by Cambridge University Press

Table 2. Baseline Characteristics of Patients With VRE Infection[a] Versus Colonization[b]

Variable	Colonized (n=217)	Infected (n=133)	Total (n=350)	*P* Value
Age, mean y (SD)	45.6 (17.4)	42.3 (16.9)	44.4 (17.3)	.08[c]
Female, %	45.2	48.1	46.3	.66[d]
Race, %				.96[d]
White	51.2	51.1	51.1	
Black	22.6	25.6	23.7	
Hispanic	19.4	18.8	19.1	
Asian	4.2	3.0	3.7	
Other	2.3	1.5	2.0	
Missing	0.5	0.0	0.3	
Underlying diagnosis, %				.03[d]
Leukemia/Lymphoma	87.5	88.9	88.1	
Sickle cell disease	3.3	0.0	2.0	
HIV infection	4.0	0.0	2.4	
Congenital immunodeficiency	4.6	9.1	6.4	
Other	0.66	2.0	1.2	
HSCT transplant, %	52.1	57.9	54.3	.32[d]
>1 transplant, %	15.2	24.1	18.6	.05[d]
Mortality, % deceased	38.3	60.2	46.6	<.0001[d]

Note. VRE, vancomycin-resistant *Enterococcus*; SD, standard deviation.
[a]VRE growth in culture from a clinical specimen other than urine.
[b]VRE detection/growth in surveillance or urine culture.
[c]Student *t* test.
[d]Fisher exact test.

2-sided *P* value < .05. The Kaplan-Meier survival curve *P* values were calculated using log-rank tests.

Results

Overall cohort results

Between 2007 and 2015, 350 patients were identified as either colonized or infected with VRE. Most patients had an underlying diagnosis of leukemia or lymphoma (88%), and 54% had undergone HSCT. Patients with a VRE infection had a higher mortality rate than those who were colonized (60% vs 38%). Patient characteristics and comparisons are summarized in Table 1 and Table 2.

Active surveillance results

Surveillance perirectal swabs identified VRE colonization in 230 of the 350 patients (66%): 146 had positive VRE PCR and culture (PCR+/Cx+), and 84 had positive VRE PCR but negative culture (PCR+/Cx−). No patients had negative PCR and positive culture (PCR−/Cx+).

Clinical culture results

Clinical cultures growing VRE were the first manifestation of VRE acquisition in 120 patients: 54 (45%) in urine, 28 (23%) in blood, 25 (21%) in wounds and 13 (11%) other sources.

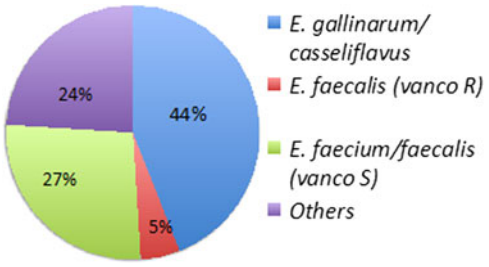

Fig. 1. Organisms cultured from swabs that were PCR positive and culture negative (PCR+/Cx−) for VRE (n = 75). Among 84 patients whose surveillance swabs were PCR+/Cx−, 75 had subsequent swabs collected. Of these 75 patients, 23 (30%) later grew VRE in culture from surveillance swabs, while the remaining patients' swabs (n=52) grew 41 other isolates: vancomycin-susceptible (vanco S) *E. faecium/faecalis* (27%), vancomycin-resistant (vanco R) *E. faecalis* (5%), *E. gallinarum/casseliflavus* (44%), and others (24%).

PCR-positive/Culture-negative analysis

Among the 84 PCR+/Cx− patients, 75 had subsequent swabs collected. Only 23 (30%) of these 75 patients ever grew VRE in culture. The remaining patients' PCR+/Cx− swabs grew 41 other isolates (Fig. 1). PCR had a positive predictive value of 39%, and 95% of the identified organisms were not VRE.

VRE infection

Of the 350 patients included in this study, 133 developed a VRE infection. A significantly higher rate of infection was observed in patients whose initial detection was from a positive clinical culture (67%) or PCR+/Cx+ swab (32%) than in patients with PCR+/Cx− swabs (8%).

Subcohort analysis of VRE recolonization

Among the 350 patients, 72 (23%) eventually met decolonization criteria, but 21 (29%) later became recolonized with VRE. Most recolonized patients had leukemia or lymphoma, and the majority had undergone HSCT (Table 3).

Nearly all patients received inpatient antibiotics in the interval after VRE decolonization (Table 3). Median total antibiotic days per VRE decolonized days and median antianaerobic antibiotic days per VRE decolonized days were 3.5 and 5.6 times higher, respectively, in recolonized patients than among those who remained decolonized.

Crude and adjusted hazard ratios of time to VRE recolonization are presented in Table 4. After adjusting for median percentage of inpatient days in the final model, the hazard of VRE recolonization was 4.3-fold higher ($P = .001$) in patients whose percentage of total antibiotic days was higher than the subcohort median. These relationships are graphically represented in Kaplan-Meier curve estimates in Figure 2.

Discussion

Our cohort of patients with VRE infection and colonization largely comprised patients who had underlying hematologic malignancies and/or had undergone HSCT, similar to previous reports.[16] Only 15% of 350 patients appeared to become decolonized over the course of this study; this finding underscores the tenacity of VRE colonization. In our population, higher rates of VRE infection were seen in culture-positive colonized patients than culture-negative

https://doi.org/10.1017/ice.2019.15 Published online by Cambridge University Press

Table 3. Baseline Characteristics and Comparative Antibiotic Exposure of Decolonized Patients Who Became Recolonized With VRE or Remained Decolonized

Variable	Recolonized (n=21)	Remained Decolonized (n=51)	Total (n=72)	*P* Value
Age, mean y (SD)	41.1 (17.8)	41.3 (19.3)	41.3 (18.8)	.96[a]
Female, %	42.9	39.2	40.3	.80[b]
Race, %				.13[b]
White	42.9	54.9	51.4	
Black	42.9	15.7	23.6	
Hispanic	14.2	19.6	18.1	
Other	0	9.8	7.0	
Underlying diagnosis, %				.50[b]
Leukemia/lymphoma	90.5	82.4	84.7	
Sickle cell disease	4.8	0	1.4	
HIV	0	2.0	1.4	
Congenital immunodeficiency	4.8	11.8	9.7	
Other	0	3.9	2.8	
HSCT transplant (%)	100	68.6	77.8	.004[b]
Received antibiotics (%)	100	80.4	86.1	.03[b]
Total antibiotic days				
Mean (SD)	94 (60)	44 (54)	59 (60)	.001[a]
(min, max)	(28, 275)	(0, 243)	(0, 275)	
Median (IQR)	80 (49–108)	27 (2–75)	44 (10–90)	.001[c]
Total antianaerobic antibiotic days				
Mean (SD)	39 (42)	17 (24)	22 (32)	.007[a]
(min, max)	(0, 187)	(0, 96)	(0, 187)	
Median (IQR)	28 (12–52)	5 (0–24)	11 (0–35)	.009[c]
Proportion of inpatient days to decolonized days (%)				
Mean (SD)	36 (27)	22 (31)	26 (30)	.074[a]
(min, max)	(1, 103)	(0, 108)	(0, 108)	
Median (IQR)	37 (14–47)	7 (0–30)	14 (2–41)	.037[c]
Proportion of total antibiotic days to total decolonized days (%)				
Mean (SD)	48 (38)	46 (77)	46 (67)	.895[a]
(min, max)	(6, 169)	(0, 422)	(0, 422)	
Median (IQR)	45 (19–57)	13 (2–47)	23 (7–56)	.037[c]
Proportion of total antianaerobic antibiotic days to total decolonized days (%)				
Mean (SD)	19 (16)	16 (28)	17 (25)	.697[a]
(min, max)	(0, 51)	(0, 97)	(0, 98)	
Median (IQR)	19 (5–30)	3.4 (0–16)	6 (0–25)	.037[c]

Note. SD, standard deviation; HIV, hum immunodeficiency virus; IQR, interquartile range.
[a]Student *t* test.
[b]Fisher exact test.
[c]Median Fisher exact test.

colonized patients, consistent with studies evaluating colonization as a risk factor for VRE bacteremia.[17,18]

When comparing the characteristics of patients with and without VRE infection, increased mortality appeared to be associated with VRE infection, although unmeasured confounding may have contributed to this finding.[3]

The link between VRE colonization and infection in immunosuppressed patients is an important consideration, particularly for infection prevention practices. Detectable colonization appears to be transient, and VRE may persist in the intestinal flora below the threshold of detection of PCR testing. The vacillation of PCR and culture detection over time creates a practical challenge for determining when a patient may be removed from contact isolation. As others have shown, 3 negative weekly VRE PCR tests or cultures are insufficient to conclude that patients are no longer colonized with VRE.[19–21] However, as shown in our study, the low positive

https://doi.org/10.1017/ice.2019.15 Published online by Cambridge University Press

Table 4. The Relationship of Antibiotic Exposure per VRE Decolonized Days and Time to VRE Recolonization

	Crude			Adjusted[a]		
Variable	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value
% total antibiotic days[c]	**6.39**	(2.49–16.41)	<0.0001	**4.29**	(1.78–20.38)	0.001[b] <0.0001[d]
Age	0.60	(0.24–1.49)	0.268			
Race	0.94	(0.59–1.48)	0.779			
Gender	1.36	(0.58–3.22)	0.481			
Median % inpatient days[c]	4.52	(1.83–11.2)	0.001	1.93	(0.87–4.28)	0.106[b]
% antianaerobic antibiotic days[e]	**4.01**	(1.75–9.19)	0.001	1.95	(0.67–5.67)	0.222[b] 0.0021[d]
Age	0.60	(0.24–1.49)	0.268			
Race	0.94	(0.59–1.48)	0.779			
Gender	1.36	(0.58–3.22)	0.481			
Median % inpatient days[e]	4.52	(1.83–11.1)	0.002	2.78	(0.84–9.23)	0.095[b]

Note. VRE, vancomycin-resistant *Enterococcus*; HR, hazard ratio; CI, confidence interval.
[a]Based on Cox proportional hazards with robust estimation, adjusting for median percentage of inpatient days.
[b]Based on significance level of $P < .05$.
[c]Calcuated during each patient's VRE decolonization period; analyzed as binary variable above and below cohort median % of total antibiotic days (median, 23; IQR, 7–56).
[d]Based on the log-rank test for equality of survivor functions.
[e]Calcuated during each patient's VRE decolonization period; analyzed as binary variable above and below cohort median % of total antianaerobic days (median, 6; IQR 0–25).

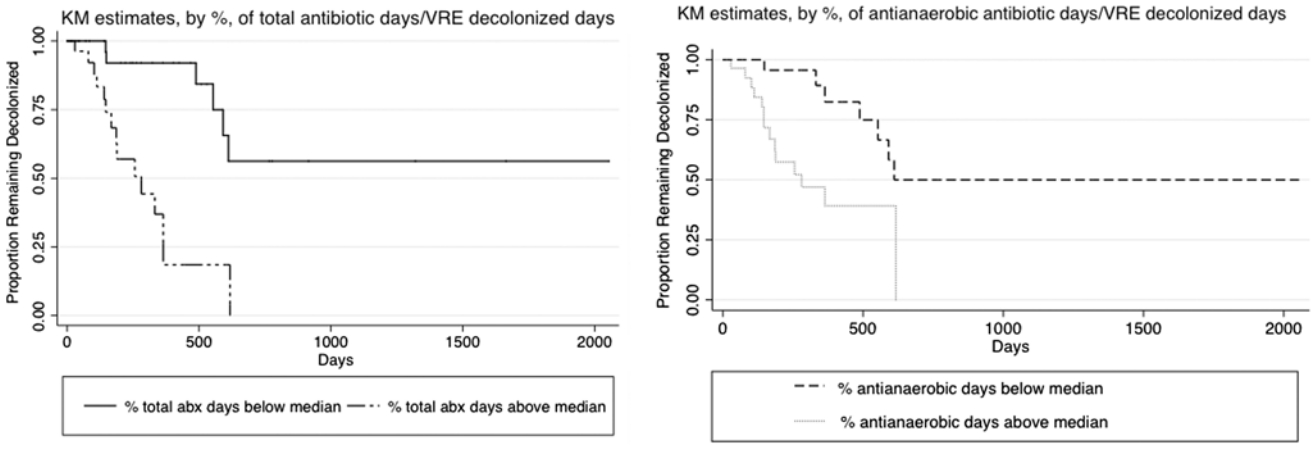

Fig. 2. Kaplan-Meier estimates of VRE decolonized state by proportion of total antibiotic days (left) and antianaerobic antibiotic days (right). The hazard of VRE recolonization was 4.29-fold higher ($P = .001$) in patients who received a higher proportion of total antibiotic days than the subcohort median (median, 23; IQR, 7–56). The hazard of VRE recolonization was 1.95 times higher ($P = .222$) in patients who received a higher proportion of antianaerobic antibiotic days than the subcohort median (median, 6; IQR, 0–25).

predictive value of PCR testing may be influenced by detection of *VanA* genes in other intestinal flora and likely results in unnecessary isolation of some patients. The limitations of existing surveillance testing illustrate that a better understanding of the dynamics of VRE colonization is essential for reducing its prevalence in hospitalized patient populations.

The relationship between VRE colonization and gut microbiome disruption following antibiotic exposure has been previously reported.[13,19,22,23] Our data show that the risk of VRE recolonization is significantly associated with receiving antibiotics on a higher proportion of days following decolonization. Similar to Donskey *et al.*,[14] our results provide evidence for the impact of antimicrobials on the risk of VRE recolonization and the importance of antimicrobial stewardship in immunosuppressed patients. Our results suggest that decolonized patients receiving antibiotics should be screened for asymptomatic recolonization. Identifying these patients quickly could prevent transmission and improve clinical care.

Whether recolonization represents recrudescence or new acquisition of VRE in our cohort is uncertain without genomic analysis. Even with whole-genome sequencing, analysis of single colonies may miss the heterogeneity of colonizing strains. Recent studies suggest that VRE transmission is more complex than previously thought. Sequencing of *E. faecium* isolates within one facility revealed numerous clusters of highly related isolates, indicating multiple introductions with subsequent clonal expansion.[24] The presence of genetically diverse VRE combined with persistence and transmission over time could explain the findings of Ford *et al.*,[17] in which

https://doi.org/10.1017/ice.2019.15 Published online by Cambridge University Press

typing of VRE isolates from recolonized HSCT patients revealed that in 55% of patients the newly detected strains differed from the original strains.

Even without genomic evidence, the supposition that some patients in our cohort were truly decolonized seems reasonable. Overall, 86% of our decolonized subcohort received antibiotics during their decolonized periods, yet 51 patients did not become recolonized, suggesting that these patients effectively cleared intestinal VRE carriage. The natural history of VRE recolonization most likely involves other factors in addition to antibiotic exposure and bacterial transmission.

The results of this study may not be generalizable to all patient populations. Additional factors associated with initial VRE colonization such as immunosuppressive medications, proximity to other VRE patients, and invasive procedures were not evaluated. The variability of antibiotic administration could have influenced study outcomes. Changes in VRE testing procedures and targeted surveillance could have introduced selection bias.

In summary, VRE colonization is tenacious and increases the likelihood of VRE infection in immunocompromised patients. Infection control measures are essential, but their effectiveness is diminished by testing limitations and the complexity of nosocomial acquisition of VRE. We have shown that higher total antibiotic days as a proportion of VRE decolonized days is associated with shorter time to VRE recolonization. VRE decolonization is a fragile state during which monitoring antimicrobial usage metrics could aid in screening and isolation decisions among patients who appear to have become decolonized.

Author ORCIDs. Heather Y. Hughes, 0000-0002-9733-3172

Acknowledgments. We thank the staff of the NIH Clinical Center Microbiology Service for their critical contributions to this project.

Financial support. This research was supported by the NIH Clinical Center, and the intramural research program of the National Institute of Allergy and Infectious Diseases.

Conflicts of interest. Dr Milstone reports grants from Sage Products outside the submitted work. All other authors report no conflicts of interest relevant to this article.

References

1. Cattoir V, Leclercq R. Twenty-five years of shared life with vancomycin-resistant enterococci: Is it time to divorce? *J Antimicrob Chemother* 2013;68:731–742.
2. Arias CA, Mendes RE, Stilwell MG, Jones RN, Murray BE. Unmet needs and prospects for oritavancin in the management of vancomycin-resistant enterococcal infections. *Clin Infect Dis* 2012;54 Suppl 3:S233–S238.
3. DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clin Infect Dis* 2005; 41:327–333.
4. Arias CA, Panesso D, McGrath DM, *et al.* Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med* 2011;365:892–900.
5. Diaz L, Kiratisin P, Mendes RE, Panesso D, Singh KV, Arias CA. Transferable plasmid-mediated resistance to linezolid due to cfr in a human clinical isolate of *Enterococcus faecalis*. *Antimicrob Agents Chemother* 2012;56:3917–3922.
6. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med* 2000;342:710–721.
7. Calderwood MS, Mauer A, Tolentino J, Flores E, van Besien K, Pursell K, Weber SG. Epidemiology of vancomycin-resistant enterococci among patients on an adult stem cell transplant unit: observations from an active surveillance program. *Infect Control Hosp Epidemiol* 2008;29: 1019–1025.
8. Almyroudis NG, Lesse AJ, Hahn T, *et al.* Molecular epidemiology and risk factors for colonization by vancomycin-resistant *Enterococcus* in patients with hematologic malignancies. *Infect Control Hosp Epidemiol* 2011;32:490–496.
9. Ford CD, Lopansri BK, Haydoura S, *et al.* Frequency, risk factors, and outcomes of vancomycin-resistant *Enterococcus* colonization and infection in patients with newly diagnosed acute leukemia: different patterns in patients with acute myelogenous and acute lymphoblastic leukemia. *Infect Control Hosp Epidemiol* 2015;36:47–53.
10. Weinstock DM, Conlon M, Iovino C, *et al.* Colonization, bloodstream infection, and mortality caused by vancomycin-resistant *Enterococcus* early after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant* 2007;13:615–621.
11. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control* 2007;35:S165–S193.
12. Banach DB, Bearman G, Barnden M, *et al.* Duration of contact precautions for acute-care settings. *Infect Control Hosp Epidemiol* 2018;39:127–144.
13. Bhalla A, Pultz NJ, Ray AJ, Hoyen CK, Eckstein EC, Donskey CJ. Antianaerobic antibiotic therapy promotes overgrowth of antibiotic-resistant, gram-negative bacilli and vancomycin-resistant enterococci in the stool of colonized patients. *Infect Control Hosp Epidemiol* 2003;24: 644–649.
14. Donskey CJ, Hoyen CK, Das SM, Helfand MS, Hecker MT. Recurrence of vancomycin-resistant *Enterococcus* stool colonization during antibiotic therapy. *Infect Control Hosp Epidemiol* 2002;23:436–440.
15. Lee WG, Park IJ, Jin HY, Park MH. Relapse and reacquisition of rectal colonization by vancomycin-resistant *Enterococcus faecium* after decolonization. *Epidemiol Infect* 2010;138:1449–1453.
16. Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, Papanicolaou G. The changing epidemiology of vancomycin-resistant *Enterococcus* (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. *Biol Blood Marrow Transplant* 2010;16: 1576–1581.
17. Ford CD, Gazdik MA, Lopansri BK, *et al.* Vancomycin-resistant enterococcus colonization and bacteremia and hematopoietic stem cell transplantation outcomes. *Biol Blood Marrow Transpl* 2017;23:340–346.
18. Hefazi M, Damlaj M, Alkhateeb HB, *et al.* Vancomycin-resistant *Enterococcus* colonization and bloodstream infection: prevalence, risk factors, and the impact on early outcomes after allogeneic hematopoietic cell transplantatoin in patients with acute myeloid leukemia. *Transpl Infect Dis* 2016;18:913–920.
19. Donskey CJ, Chowdhry TK, Hecker MT, *et al.* Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med* 2000;343:1925–1932.
20. Baden LR, Thiemke W, Skolnik A, *et al.* Prolonged colonization with vancomycin-resistant *Enterococcus faecium* in long-term care patients and the significance of "clearance." *Clin Infect Dis* 2001;33:1654–1660.
21. Henard S, Lozniewski A, Aissa N, Jouzeau N, Rabaud C. Evaluation of the duration of vanA vancomycin-resistant *Enterococcus faecium* carriage and clearance during a large-scale outbreak in a region of eastern France. *Am J Infect Control* 2011;39:169–171.
22. Stiefel U, Pultz NJ, Helfand MS, Donskey CJ. Increased susceptibility to vancomycin-resistant *Enterococcus* intestinal colonization persists after completion of antianaerobic antibiotic treatment in mice. *Infect Control Hosp Epidemiol* 2004;25:373–379.
23. Ubeda C, Taur Y, Jenq RR, *et al.* Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest* 2010;120:4332–4341.
24. Raven KE, Gouliouris T, Broderick H, *et al.* Complex routes of nosocomial vancomycin-resistant *Enterococcus faecium* transmission revealed by genome sequencing. *Clin Infect Dis* 2017;64:886–892.

https://doi.org/10.1017/ice.2019.15 Published online by Cambridge University Press