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Journal

Infection Control and Hospital Epidemiology, 31(12)

ISSN

0899-823X

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Publication Date

2010-12-01

DOI

10.1086/657332

Published in final edited form as:
Infect Control Hosp Epidemiol. 2010 December ; 31(12): 1290–1293. doi:10.1086/657332.

Risk of Postdischarge Infection with Vancomycin-Resistant *Enterococcus* after Initial Infection or Colonization

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Abstract

Postdischarge risks of vancomycin-resistant *Enterococcus* (VRE) infection among carriers are unknown. We conducted a retrospective cohort study of 199 patients newly detected as VRE carriers. Fifteen patients (8%) developed 27 VRE infections in the 18 months after detection. Among 10 postdischarge infections, 2 involved bacteremia and 3 resulted in readmission.

As hospital length of stay shortens, it is increasingly important to evaluate postdischarge risks of healthcare-associated infection. Of the estimated 35 million hospital discharges in the United States in 2006, 58% involved hospitalizations of 3 days or less.[1] Vancomycin-resistant *Enterococcus* (VRE) is an important source of healthcare-associated infections and causes substantial morbidity and mortality among immunosuppressed patients.[2–5] Because VRE carriage is often prolonged,[6,7] studies assessing postdischarge risks of VRE infection are needed. We sought to assess the risk of VRE infection among all newly detected carriers both during hospitalization in and after discharge from an academic medical center.

METHODS

We identified a retrospective cohort of all adult patients from a 750-bed academic medical center in Boston, Massachusetts, who were newly detected with VRE colonization or infection during the period from September 1, 2003, through December 31, 2004. Using this cohort, we assessed the risk of VRE infection within 18 months after initial detection using in-patient and outpatient medical records at the same institution. Because rectal sample screening for VRE was performed at admission and weekly in all intensive care units (ICUs) using conventional cultures,[8] all VRE carriers newly detected by means of ICU screening cultures were evaluated as a subgroup. The Brigham and Women's Hospital institutional review board approved this study.

Demographic and antibiotic use data were obtained for all patients. Comorbidities were identified with use of *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes recorded during the year prior to and during the hospitalization in which VRE carriage was newly detected. All comorbidities were verified by means of medical record review. Malignancies were recorded only if treatment was received during the

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Presented in part: 18th Annual Meeting of the Society for Healthcare Epidemiology of America; Orlando, Florida; April 5–8, 2008; abstract 279.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

preceding year. Antibiotic administration was recorded from the time of detection to the time of infection, death, or the end of follow-up and grouped into the following classes: broad-spectrum penicillins, third-generation cephalosporins, fluoroquinolones, carbapenems, aminoglycosides, macrolides, and vancomycin. We also assessed whether patients were admitted to an ICU during the hospitalization in which VRE carriage was newly detected and whether patients underwent surgery during the prior 6 months. For patients whose initial positive culture results were detected during hospitalization, we assessed preadmission location, hospital length of stay, and discharge disposition.

Medical records were reviewed to identify the body site that had been colonized or infected when the initial VRE-positive culture sample was obtained and whether the detection represented colonization or infection on the basis of Centers for Disease Control and Prevention criteria.[9] All VRE isolates found within 18 months after initial detection were evaluated for evidence of discrete infection. Two trained reviewers separately verified whether infections represented distinct and unrelated events. Subsequent infections were described according to the infection site and days since initial detection.

We determined the proportion of patients who subsequently developed VRE infection within 18 months after initial detection of colonization or infection for all patients and for the subgroup of ICU patients newly detected as carriers by means of screening cultures. The proportion of patients who died within 18 months after detection, from all causes and from VRE, was also assessed. Death due to VRE was defined as VRE infection or bacteremia within 7 days of death and no other cause of death.

Potential predictors of VRE infection were assessed using a matched case-control design in which each VRE carrier who subsequently experienced infection was randomly matched to 5 VRE carriers who did not subsequently experience infection. Among control patients, the duration of follow-up was required to be at least as long as the time to infection for the matched case patients. Antibiotic receipt was evaluated for the month prior to infection among case patients and for the corresponding month since time of detection among matched control patients. Potential predictors that yielded $P < .10$ with the univariate Fisher exact test were entered into multivariate models in which predictors were retained at $\alpha = 0.05$.

RESULTS

Among 56,317 hospital admissions, 199 patients (0.4%) were newly detected with VRE colonization or infection. Of these patients, 99 were newly detected as carriers by means of ICU screening cultures (1% of 10,151 ICU admissions). Patient characteristics are summarized in Table 1. The mean age of patients at the time of detection was 65 years. Among in-patients, the median hospital length of stay at the time of detection was 19 days (range, 1–139 days), although 52 (28%) of 187 inpatients had a VRE-positive culture result within 2 calendar days after admission. Among the 100 carriers detected with clinical cultures, 22 (22%) were colonized and 78 (78%) were infected at the time of detection.

Fifteen patients (8%) subsequently developed 27 discrete and unrelated VRE infections during the 18 months after detection. The proportion of patients who developed infection was similar among patients whose carriage was detected with ICU screening cultures (8 [8%] of 99) and patients whose carriage was detected with clinical cultures (7 [7%] of 100). The most common infections were urinary tract (10 [37%] of 27), primary bloodstream (7 [26%] of 27), soft-tissue (5 [19%] of 27), and gastrointestinal (2 [7%] of 27) infections. Eight infections (30%) involved bacteremia. More than one-third (10 [37%] of 27) of VRE infections developed after discharge, with 2 (20%) involving bacteremia and 3 (30%)

requiring rehospitalization. Most patients (14 [93%] of 15) developed infection at a site distinct from the site of detection. VRE infections occurred a median of 52 days (range, 2–525 days) after detection of VRE carriage.

Within 18 months after VRE detection, 89 (45%) of 199 patients experienced 217 readmissions. One hundred four patients (52%) died a median of 31 days after detection (range, 1–405 days). Of the 104 deaths, 88 (85%), 13 (13%), and 3 (3%) occurred during the first, second, and third 6-month periods after detection, respectively. One death was due to VRE.

The results of univariate testing are shown in Table 2. In multivariate analysis, only hematologic malignancy was significantly associated with VRE infection (odds ratio, 9.1 [95% confidence interval, 1.4–60.4]; $P = .02$).

DISCUSSION

Among studies evaluating the risk of VRE infection among hospitalized carriers, none have evaluated postdischarge risks of infection. We conducted a hospital-wide study of newly detected VRE carriers and assessed subsequently occurring disease over 18 months. Among all hospitalized patients, new VRE detection was rare, even with an active ICU screening program.

Overall, we observed an 8% risk of infection within 18 months after detection. The median time from detection to infection was 52 days, with more than one-third of infections occurring after discharge. Although the risk of later infection was relatively low, the risk of bacteremia, when infection occurred, was high (30%).

Similar to prior reports, our findings show that hematologic malignancy is a risk factor for VRE infection.[10] Our results also confirm that VRE carriage is commonly seen among severely ill patients. Among newly detected carriers, 52% died within 18 months. Moreover, the median time to death was shorter than the median time to infection. Thus, it is possible that the risk of infection may actually be higher in a less critically ill population.

This study has several limitations. First, our comparisons are limited because of a relatively small sample size. In addition, our findings may be an underestimate, because we could not account for infections that occurred at other medical facilities. Nevertheless, this study is one of the largest to investigate VRE carriers identified across an entire hospital population. Although numerous studies of VRE colonization have been performed, studies of VRE infection have been relatively small and limited to specialized subpopulations.[3,5]

We also note that although patients are described as “newly detected,” many newly detected carriers may actually be prevalent carriers, because VRE carriage is often prolonged.[7,8] In our study, 28% of inpatients with newly detected VRE carriage had a VRE-positive culture result within 2 days after admission, which suggests that some cases may not represent new acquisition. In addition, because strain typing was not performed, it is unknown whether subsequent infections were due to the same strain as the index infection or colonization event.

In summary, this study indicates that postdischarge VRE infection among newly detected carriers is not uncommon. Across a large academic medical center, although VRE was newly detected in only 0.4% of patients, newly detected carriage conferred an 8% risk of subsequent infection during the following 18 months. Importantly, more than one-third of VRE infections occurred after discharge. These postdischarge infections were often severe, with 20% involving bacteremia and 30% resulting in readmission. Future studies assessing

healthcare-associated morbidity due to VRE should consider evaluating postdischarge risks of infection.

Acknowledgments

Financial support. Centers for Disease Control and Prevention (CDC Prevention Epicenters Program, grant UR8/CCU115079) and the National Institutes of Health (grant K23AI64161).

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TABLE 1

Characteristics of Patients Newly Detected as Carrying Vancomycin-Resistant *Enterococcus* (VRE)

Characteristic	Proportion (%) of patients			*P*
	Total	Detected with clinical culture	Detected with ICU screening culture	
Positive culture result	199/199 (100)	100/100 (100)	99/99 (100)	
Male sex	119/199 (60)	55/100 (55)	64/99 (65)	.17
Race				.16
White	160/199 (80)	82/100 (82)	78/99 (79)	
Black	16/199 (8)	10/100 (10)	6/99 (6)	
Other or unknown	23/199 (12)	8/100 (8)	15/99 (15)	
Hospitalized at time of VRE detection	187/199 (94)	88/100 (88)	99/99 (100)	<.001
Preadmission location[a]				.12
Home	86/187 (46)	45/88 (51)	41/99 (41)	
Other hospital	65/187 (35)	25/88 (28)	40/99 (40)	
Rehabilitation or skilled nursing facility	36/187 (19)	18/88 (20)	18/99 (18)	
Discharge disposition[a]				.03
Home	58/187 (31)	36/88 (41)	22/99 (22)	
Other hospital	9/187 (5)	1/88 (1)	8/99 (8)	
Rehabilitation or skilled nursing facility	74/187 (40)	32/88 (36)	42/99 (42)	
Deceased	46/187 (25)	19/88 (22)	27/99 (27)	
Index culture species				.06
Enterococcus faecium	181/199 (91)	90/100 (90)	91/99 (92)	
Enterococcus faecalis	13/199 (7)	5/100 (5)	8/99 (8)	
Other *Enterococcus* species	5/199 (3)	5/100 (5)	0/99 (0)	
Immunosuppression				
Solid cancer	41/199 (21)	20/100 (20)	21/99 (21)	.83
Hematologic malignancy	32/199 (16)	22/100 (22)	10/99 (10)	.02
Receipt of solid-organ transplant	30/199 (15)	23/100 (23)	7/99 (7)	.002
Chronic disease				
Diabetes mellitus	50/199 (25)	26/100 (26)	24/99 (24)	.78
End-stage renal disease	30/199 (15)	15/100 (15)	15/99 (15)	.98
End-stage liver disease	7/199 (4)	6/100 (6)	1/99 (1)	.06
Other comorbidities				
ICU stay[a]	136/187 (73)	37/88 (42)	99/99 (100)	<.001
Surgery during prior 6 months	117/199 (59)	53/100 (53)	64/99 (65)	.10

NOTE. ICU, intensive care unit.

[a] During the hospitalization in which the patient was newly detected as a VRE carrier.

TABLE 2

Univariate Association with Subsequent Infection among Patients Newly Detected as Carrying Vancomycin-Resistant *Enterococcus* (VRE)

Variable	No. (%) of VRE carriers		*P*
	Control patients without infection (*n* = 75)	Case patients who developed infection (*n* = 15)	
Demographic characteristics			
Male sex	38 (51)	12 (80)	.05
Age			.52
18–44 years	4 (5)	3 (20)	
45–54 years	11 (15)	1 (7)	
15–64 years	13 (17)	2 (13)	
65–74 years	15 (20)	4 (27)	
75–84 years	23 (31)	4 (27)	
≥85 years	9 (12)	1 (7)	
White race	56 (75)	13 (87)	.51
Preadmission location[a]			.71
Home	34 (45)	7 (47)	
Other hospital	19 (25)	6 (40)	
Rehabilitation center	8 (11)	1 (7)	
Skilled nursing facility	7 (9)	1 (7)	
Outpatient clinic	7 (9)	0 (0)	
Detected with ICU surveillance culture	36 (48)	8 (53)	.78
Immunosuppression			
Solid cancer	18 (24)	2 (13)	.51
Hematologic malignancy	2 (3)	3 (20)	.03
Receipt of solid-organ transplant	8 (11)	3 (20)	.38
Chronic disease			
Diabetes mellitus	20 (27)	6 (40)	.35
End-stage renal disease	11 (15)	2 (13)	>.99
End-stage liver disease	3 (4)	0 (0)	>.99
Other comorbidities			
ICU stay[a]	46 (61)	12 (80)	.24
Surgery during prior 6 months	43 (57)	9 (60)	>.99
Antibiotic use			
Broad-spectrum penicillins	12 (16)	0 (0)	.21
Third-generation cephalosporins	12 (16)	2 (13)	>.99
Fluoroquinolones	22 (29)	1 (7)	.10
Carbapenems	5 (7)	1 (7)	>.99
Aminoglycosides	9 (12)	0 (0)	.35
Macrolides	1 (5)	0 (0)	>.99
Vancomycin	30 (40)	3 (20)	.24

NOTE. ICU, intensive care unit.

[a] During the hospitalization in which the patient was newly detected as a VRE carrier.