Risk Factors Associated with Vancomycin-Resistant *Enterococcus faecium* Infection or Colonization in 145 Matched Case Patients and Control Patients

Nadia G. Tornieporth, Richard B. Roberts, Joylene John,* Alice Hafner, and Lee W. Riley

From the Division of International Medicine and Infectious Diseases, Department of Medicine, Cornell University Medical College, New York, New York

Risk factors and mortality associated with vancomycin-resistant *Enterococcus faecium* (VREF) infection or colonization were examined at a tertiary care hospital by comparing 145 patients who had VREF isolates (cases) to 145 patients with vancomycin-susceptible *Enterococcus faecium* (VSEF) isolates (controls). The number of deaths per 100 person-days of hospitalization after diagnosis did not differ significantly between VREF patients (1.2) and VSEF patients (0.8). Multivariate analyses found that the duration of hospitalization (⩾7 days), intrahospital transfer between floors, use of antimicrobials (i.e., vancomycin and third-generation cephalosporins), and duration of vancomycin use (⩾7 days) was independently associated with VREF infection or colonization. This study, which has a large sample size, confirms some earlier observations regarding risks for VREF infection or colonization and identifies factors that may be potentially exploited to develop interventional strategies for the control of this emerging nosocomial problem.

The increase in antimicrobial resistance observed in nosocomial infections worldwide constitutes a major public health problem [1]. The Centers for Disease Control and Prevention (CDC; Atlanta) reported a 20-fold increase nationwide in the percentage of nosocomial enterococci resistant to vancomycin between 1989 and 1993 [2]. This increase was even more dramatic among nosocomial enterococci isolated from patients in the intensive care unit (ICU) (34-fold). According to data from the National Nosocomial Infections Surveillance System, enterococci are now the fourth leading cause of nosocomial infections in the United States [3].

Emerging vancomycin resistance in enterococci further limits treatment options already diminished by the development of the organism's high-level resistance to the penicillins and aminoglycosides [4]. Since the initial reports of vancomycin-resistant *Enterococcus faecium* (VREF), published first in Europe and then in the United States in the late 1980s, attempts have been made to identify patient populations at increased risk for VREF infection or colonization [5–7].

Although certain patient populations, such as those with severe underlying illness or immunosuppression, have been identified to be at risk for VREF, the epidemiological information concerning VREF has been based largely on studies involving small numbers of patients in localized outbreaks [8–16]. However, recent reports have indicated that drug-resistant enterococci are rapidly becoming endemic in an increasing number of hospitals in the United States [17, 18], and adequate interventions remain to be identified [18]. Understanding the epidemiology of VREF infections in a large tertiary care hospital can provide useful information for effective infection control.

Between 1 March 1990 and 31 December 1992, VREF isolates were recovered from 183 patients at a single teaching hospital. This case-control study was undertaken to determine risk factors for vancomycin resistance and mortality in patients with *Enterococcus faecium* colonization or infection.

Methods

Patients. The study hospital is a 988-bed tertiary care referral hospital serving the New York metropolitan area. After the recognition of 183 cases of VREF infection or colonization at the hospital between March 1990 and December 1992, a case-control study was designed.

Definitions. Cases were defined as all hospitalized patients with VREF isolated from any source between 1 March 1990 and 31 December 1992. The patients were identified from the records of the clinical microbiology department. Both colonized and infected patients were included in the study. Colonization and infection with VREF or vancomycin-susceptible *E. faecium* (VSEF) were defined according to clinical and laboratory criteria previously published by the CDC [19]. Only the first VREF isolate from a patient was considered for analysis. Patients with isolates collected <72 hours after admission to the hospital were considered to have community-acquired strains unless they were known to have been hospitalized during the preceding 2 months or had acquired the organism perinatally [13, 19].

Controls were defined as hospitalized patients with VSEF isolates that were also identified from the records of the clinical microbiology laboratory and matched by date of specimen col-

Received 30 October 1995; revised 9 May 1996.

Financial support: R.B.R. was supported in part by the Cary L. Guy Research Foundation; L.W.R. was supported in part by Pew Scholars in Biomedical Sciences.

* Present affiliation: Department of Family Medicine, University of Maryland, 29 South Paca Street, Baltimore, Maryland 21201.

Reprints or correspondence: Dr. Lee W. Riley, Division of International Medicine, Rm A-431, Cornell University Medical College, 1300 York Avenue, New York, New York 10021.

Clinical Infectious Diseases 1996;23:767–72

1058–4838/96/2304–0016$02.00

lection (within 1 month of the date that VREF was isolated from the case's specimen).

Patients with isolates that were initially susceptible to vancomycin but from whom VREF was subsequently isolated were included as cases. No VREF or VSEF isolates were obtained from routine surveillance cultures in this study.

The VanA glycopeptide resistance phenotype was defined according to Arthur et al. [20] as an MIC of $\geqslant 64$ μg/mL for vancomycin and $\geqslant 16$ μg/mL for teicoplanin. The VanB phenotype has MICs of 4–1,000 μg/mL for vancomycin and 0.5–1 μg/mL for teicoplanin. Empirical drug use was defined as drug therapy without microbiological confirmation of infection. Third-generation cephalosporins included cefotaxime, ceftazidime, and ceftizoxime.

Mortality was defined as number of deaths per 100 person-days of hospitalization after diagnosis.

Chart reviews. Hospital records were reviewed to obtain demographic and clinical information. Specific information was obtained regarding the treatment of patients with vancomycin and third-generation cephalosporins given alone or in combination before specimen collection. Microbiologic records were reviewed to obtain information on the source and drug susceptibility pattern of the isolate.

Bacteriologic identification and drug susceptibility tests. Enterococcus species were identified with use of conventional biochemical tests, and initial susceptibility tests for this organism were performed with freeze-dried Positive Breakpoint Combo type 6 panel (MicroScan; Baxter Health Care Corporation, West Sacramento, CA) [21]. This automated method to screen for vancomycin resistance was introduced into our hospital's clinical microbiology laboratory in 1987.

MICs were determined by broth macrodilution in tubes according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) [22, 23] and with cation-adjusted Mueller-Hinton II broth (Becton Dickinson Microbiology Systems, Cockeysville, MD) with an inoculum of 5×10^5 cfu/mL. A disk diffusion test was performed with vancomycin (Becton Dickinson Microbiology Systems) and teicoplanin (Marion Merrell Dow, Kansas City, MO) in Mueller-Hinton II agar according to NCCLS guidelines [23, 24].

Statistical analyses. Data entry and univariate statistical analyses were performed with the Epi-Info version 5 software (CDC). Since cases were matched with controls by the date of specimen collection, variables were analyzed by the McNemar χ^2 test for matched comparison. For nonmatched comparison, categorical variables were analyzed by the χ^2 or Fisher's exact test.

Student's *t*-test was used to assess statistically significant differences between case patients and control patients by comparing the means of continuous variables. The χ^2 test for rates was used to compare the difference between rates [25]. All *P* values were based on two-sided tests.

Multivariate statistics (logistic regression) were performed with SAS software version 6.04 (SAS Institute, Cary, NC) and were used to estimate the contribution of individual risk factors to vancomycin resistance or death (other variables were controlled for). Odds ratios and the corresponding 95% confidence intervals were calculated manually using the results obtained for the maximum likelihood estimates [26].

Results

Demographic characteristics. A total of 183 hospitalized patients with VREF were identified during the period from March 1990 through December 1992. Of these, 145 could be appropriately matched to 145 control patients; VSEF isolates from control patients were obtained within 1 month of the VREF isolates from the case patients. The remaining 38 case patients, who were excluded from the matched analysis because of the lack of appropriate control patients, were comparable to the study group with regard to demographic and clinical characteristics and mortality.

Cases and controls were comparable in sex as well as in race and ethnicity. Their age distribution is shown in table 1. The median age was 67 years for cases and 46 years for controls. The risk of vancomycin resistance was significantly associated with age $\geqslant 50$ years. Stratification by age eliminated any association between race and isolation of VREF.

Specimen sources. Cases and controls did not differ significantly by the proportion of colonized (55% and 59%, respectively) and infected patients (45% and 41%, respectively) or by specimen source. Most enterococcal specimens were isolated from urine samples, followed by wounds and blood (table 1).

A total of 24 case patients and 23 control patients with at least one positive *E. faecium* blood culture were identified. Mortality among these bacteremic patients did not differ significantly between those with VREF (58%) and those with VSEF (43%) isolates.

Hospitalization. Only 11 of 145 patients with VREF had been hospitalized for <72 hours before specimen collection, and all had a history of preceding hospitalizations, either immediately before the current hospital admission or within 2 months before this admission. Among 48 of 50 VSEF patients with this background, 20 had been hospitalized recently and 28 met the criteria for having community-acquired strains. Data were not available for two patients with VSEF.

The mean duration of hospitalization as well as the mean duration of hospitalization from admission to the date of specimen collection was significantly longer for cases than for controls (both, $P < .01$) (table 1). Seventy-three patients with VREF were in one of our eight ICUs at the time of specimen collection compared with 47 controls ($P < .01$). Intrahospital transfer of patients to more than one ICU or to more than one floor throughout their hospital stay increased the risk for acquisition of VREF ($P < .05$ and $P < .001$, respectively).

Underlying illness and therapeutic procedures. Major primary and secondary discharge diagnoses are listed in table 1. A diagnosis of vascular disease, which included patients with peripheral vascular disease, valvular heart disease, and, in particular, coronary artery disease, was found to be sig-

Table 1. Comparison of the characteristics of cases (patients with VREF) and controls (patients with VSEF) and the risk factors for VREF by univariate analysis.

Variable	Cases (n = 145)	Controls (n = 145)	OR (95% CI)
Age distribution			
No. of persons <10 y	5	38	0.13 (0.05–0.33)
No. of persons 10–50 y	25	37	NS
No. of persons ⩾50 y	115	70	3.50 (2.07–5.91)
Mean age in y (range)	62.3 (3 mo–99)	43.7 (<1 mo–91)*	
Sex			
No. (%) of females	91 (63)	90 (62)	NS
No. (%) of males	54 (37)	55 (38)	NS
No. of days of hospitalization			
Mean (range)	64.5 (2–290)	40.8 (2–248)†	
Median	48	26	
No. of person-days of hospitalization	4,679	3,363	
No. (%) of persons hospitalized ⩾7 d	137 (94)	122 (84)	2.88 (1.29–6.43)
No. (%) of persons hospitalized ⩾14 d	128 (88)	105 (72)	2.53 (1.39–4.61)
No. of days from admission to specimen collection			
Mean (range)	32.5 (0–142)	17.7 (0–158)†	
Median	25	8	
No. (%) of persons hospitalized ⩾7 d	126 (87)	76 (52)	5.17 (2.78–9.59)
No. (%) of persons hospitalized ⩾14 d	110 (76)	53 (37)	4.56 (2.66–7.84)
Service			
Medicine	73 (50)	45 (31)	2.22 (1.36–3.63)
Surgery	57 (39)	38 (26)	1.73 (1.07–2.80)
Pediatrics	2 (1.4)	36 (25)	0.06 (0.01–0.23)
Burn unit	10 (7)	12 (8)	NS
Location of patient			
ICU	73 (50)	47 (30)	2.08 (1.28–3.39)
More than one ICU	58 (40)	27 (19)	2.25 (1.25–4.05)
More than one floor	43 (30)	23 (16)	3.07 (1.71–5.49)
Source of specimen			
Urine	57 (39)	61 (42)	NS
Wound	52 (36)	38 (26)	NS
Blood	24 (17)	23 (16)	NS
Underlying illness			
Vascular disease	40 (28)	22 (15)	2.0 (1.12–3.58)
Coronary artery disease	24 (17)	13 (9)	NS
Benign GI disorder	35 (24)	25 (17)	NS
Neoplastic disease	28 (19)	29 (20)	NS
End-stage renal disease	12 (8)	5 (3)	NS
AIDS	11 (8)	8 (6)	NS
Burn	10 (7)	12 (8)	NS
Obstetric, gynecologic, or neonatal disorder	1 (0.7)	21 (6)	0.04 (0–0.26)
Procedures			
Surgery	89 (61)	60 (41)	2.38 (1.35–4.25)
Hemodialysis	32 (22)	10 (7)	3.44 (1.48–8.52)
Mortality‡	1.2	0.8	NS§

NOTE. GI = gastrointestinal; NS = not significant. Unless otherwise indicated, all values represent no. (%) of patients.

* $P < .01$ by Student's t test.

† $P < .005$ by Student's t test.

‡ Per 100 person-days of hospitalization after diagnosis.

§ $P < .2$ (χ^2 test for rates).

nificantly associated with VREF ($P < .05$) by univariate analysis. Patients who underwent a surgical procedure or who received hemodialysis treatment during their hospital stay were 2–3 times more likely to acquire VREF than were patients who did not undergo a procedure or receive treatment (both, $P < .01$), while VSEF was more frequently isolated from patients with gynecologic, obstetric, or neonatal disorders.

Antimicrobial therapy. Patients who received either vancomycin or a third-generation cephalosporin before specimen collection had a more than five-fold greater risk for isolation of VREF (OR, 5.54; 95% CI, 3.07–10.0; $P < .00001$) than did patients who did not receive this therapy (table 2). Of these patients, only two case patients and two control patients received oral preparations of vancomycin. Vancomycin was given empirically, i.e., without microbiological confirmation of infection, to >60% of both VREF and VSEF patients. The mean duration of vancomycin treatment before specimen collection did not differ significantly between cases and controls, but treatment with vancomycin for ⩾7 days before specimen collection was significantly associated with vancomycin resistance ($P < .00001$).

Mortality. Overall, 54 (37%) of the patients with VREF died during hospitalization compared with 28 (19%) of the patients with VSEF. When the duration of hospitalization after diagnosis was controlled for, the number of deaths per 100 person-days of hospitalization were 1.2 for patients with VREF and 0.8 for patients with VSEF ($P < .2$). The overall mortality among a subset of patients with VREF (49%) compared with that among a subset of VSEF patients (28%) admitted to any ICU was not significantly different by matched analysis.

Mortality among VREF patients who were ⩾50 years old was significantly associated with being in an ICU at the time of specimen collection (OR, 2.97; 95% CI, 1.26–7.04; $P < .05$) and with the use of a third-generation cephalosporin before specimen collection (OR, 3.31; 95% CI, 1.32–8.43; $P < .01$). This association was not significant for VREF patients under 50 years of age. Increased mortality was also noted among hemodialysis patients with VREF who were ⩾50 years old (OR, 3.16; 95% CI, 1.16–8.71; $P < .05$) and among those with VSEF (OR, 6.28; 95% CI, 1.03–44.33; $P = .02$). Mortality among VSEF patients who were ⩾50 years old was associated with a duration of hospitalization of ⩾7 days before specimen collection (OR, 6.34; 95% CI, 1.20–61.12; $P < .05$). Isolation of VSEF from blood was associated with increased mortality among VSEF patients who were under 50 years of age (OR, 7.13; 95% CI, 1.36–38.99; $P = .01$).

Multivariate analysis. All variables significantly associated ($P < .05$) with vancomycin resistance or mortality by univariate analysis were included in multivariate models (table 3). A duration of hospitalization of ⩾7 days between admission and the time of isolation of VREF was independently associated with vancomycin resistance in all models tested (OR, 1.61–2.06).

As most patients (78%) had received one or more antibiotics, we could not accurately determine the independent association of each antibiotic with VREF acquisition in a single model. However, in models that included each antimicrobial agent separately controlled for age, intrahospital transfer, or duration of hospitalization, vancomycin and use of third-generation cephalosporins as well as a duration of ⩾7 days of vancomycin therapy before specimen collection were independently associated with acquisition of VREF.

Among VREF patients who were ⩾50 years old, mortality was independently associated with being in an ICU at the time of VREF isolation (OR, 1.64; 95% CI, 1.15–2.36) and with the preceding use of third-generation cephalosporins (OR, 1.73; 95% CI, 1.15–2.54). For control patients who were <50 years old, death was independently associated with isolation of VSEF from blood (OR, 1.81; 95% CI, 1.09–3.02).

Discussion

From September 1989 to October 1991, the number of New York City hospitals reporting vancomycin-resistant enterococci (VRE) increased from 1 to 38 [27]. In the study hospital, the number of vancomycin-resistant strains among enterococcal isolates identified from January 1990 through December 1992 increased from 15 (0.85%) of 1,763 to 170 (6.6%) of 2,581. This increase was seen predominantly among *E. faecium* species, and vancomycin resistance occurred in >50% of these isolates in 1992. VREF infections in hospitalized patients in-

Table 2. Comparison of type and days of antimicobial therapy for cases (patients with VREF) and controls (patients with VSEF).

Variable	Cases (n = 145)	Controls (n = 145)	OR (95% CI)
Vancomycin*†	101 (70)	33 (23)	5.86 (3.32–10.32)
No. of days of vancomycin therapy before specimen collection			
Mean (range)	12.50 (0–66)	12.27 (1–70)	NS
Median	10	7	
⩾7 d	66 (65)	19 (58)	4.92 (2.64–9.15)
⩾14 d	43 (43)	9 (27)	5.86 (2.63–13.06)
Third-generation cephalosporin*‡	86 (59)	47 (32)	3.29 (1.80–6.16)
Vancomycin or third-generation cephalosporin*	119 (82)	60 (41)	5.54 (3.07–10.0)
Vancomycin and third-generation cephalosporin*	68 (47)	20 (14)	6.33 (3.14–12.79)

NOTE. Values represent no. (%) of patients unless indicated otherwise. NS = not significant.

* Antibiotic administered before specimen collection.

† Time point of vancomycin use was not known for 6 of 111 VREF patients and 2 of 73 VSEF patients who received vancomycin during their hospital stay.

‡ During the study period, the relative percentage of the use of third-generation cephalosporins at the study hospital was as follows: ceftriaxone, 51%; ceftazidime, 46%; and cefotaxime, 3%.

Table 3. Odds ratios and 95% confidence intervals for risk factors independently associated with vancomycin resistance, as determined by multivariate analysis, among cases (patients with VREF) and controls (patients with VSEF).

Variable	OR (95% CI)
Duration of hospitalization from admission to specimen collection	
⩾7 d	2.06 (1.51–2.81)
Intrahospital transfer	
To >1 floor	1.73 (1.50–2.34)
Antimicrobial treatment*	
Vancomycin	2.35 (1.67–3.31)
Third-generation cephalosporin	1.93 (1.49–2.50)
⩾7 days of vancomycin therapy	1.87 (1.37–2.26)

* Before specimen collection.

creased 14-fold from 0.3/1,000 patient discharges in 1990 to 4.2/1,000 patient discharges in 1992.

These observations prompted us to examine risk factors for acquisition of VREF by comparing patients who had VREF to patients who had VSEF during the same period. Previous analyses of risk factors have examined mostly outbreaks involving a maximum of 46 VREF patients with control groups that did not always include VSEF patients [8–16].

It has been unclear whether vancomycin resistance in *E. faecium* contributes to increased patient mortality. Frieden et al. reported an overall mortality of 42% for patients with VRE in New York City hospitals [27]. In single outbreaks, mortality among patients with VREF has ranged from 50% to 70% [11, 12, 15]. However, previous studies did not always compare the mortality among patients with VREF to that among patients with VSEF colonization or infection. We observed that the overall mortality among patients with VREF (37%) was twice that for patients with VSEF (19%). However, patients with VSEF included 38 children <10 years old, and stratification by age eliminated significant differences in mortality between cases and controls.

Furthermore, the difference in the number of deaths per 100 person-days of hospitalization after diagnosis in the two groups was also not statistically significant. Therefore, if mortality is an indicator of severity of illness, these two groups were comparable. We cannot exclude the possibility that other differences in the severity of illness may have confounded our results. However, controlling for these variables by matching would have eliminated the possibility of recognizing them as risk factors.

The median length of hospitalization of 27 days before VREF isolation in our study group is similar to that reported for VRE patients from other hospitals in New York City [27]. Prolonged hospitalization was identified as a risk factor for vancomycin resistance in earlier studies [8–11].

We analyzed several time points in the duration of hospitalization and found that the risk of VREF was significantly increased in our patients when the overall duration of hospitalization as well as the duration of hospitalization from admission to specimen collection was ⩾7 days. The mean length of stay for all patients admitted to the hospital services where the study patients resided was 12.6 days between March 1990 and December 1992. Thus, as the problem of VREF increases in hospitals, the likelihood of VREF acquisition can increase even during a relatively short hospital stay.

ICUs may serve as reservoirs for nosocomial pathogens and may enable them to spread throughout the hospital [28]. After January 1992, our medical, cardiothoracic, and surgical ICUs regularly had 1–2 new cases of VREF infection or colonization each month, suggesting that this organism may be endemic, a problem that has been noted in other hospitals in the United States [2, 18, 28]. Intrahospital spread of VREF may have been facilitated by patients who were transferred to more than one ICU or more than one floor during their hospitalization. These patients had a two- to threefold higher risk of acquiring VREF.

Prior use of antimicrobial therapy, including that with vancomycin and cephalosporin, has been shown to be associated with acquisition of VREF [8–10, 12, 14–18, 29]. However, our results must be interpreted with caution since the selection of controls based on VSEF isolates would have biased towards selection of patients not likely to receive vancomycin. Furthermore, although antimicrobial use did show the strongest association with vancomycin resistance, this study found several other risk factors for vancomycin resistance with odds ratios between 1.7 and 2.4. This finding may further help to explain why Morris et al. did not observe a significant reduction in the prevalence of VREF infection or colonization after instituting measures for restriction of vancomycin [18].

Severe and immunocompromising illness has been associated with increased susceptibility to VREF, but no specific underlying condition has been associated with the isolation of this resistant pathogen. Impaired renal function has been previously implicated as a risk factor in outbreaks of VREF [10, 15].

In the present study, which had a sample size larger than that of previous studies, the association between hemodialysis and acquisition of VREF was significant. In addition, our results indicated an association between vascular disease and VREF by univariate analysis but not by multivariate analysis. This association may be related to the spread of VREF strains among patients with vascular disease (61%) who require intensive care.

In summary, our data suggest that prolonged hospitalization, intrahospital transfers, and antimicrobial use place patients at risk for VREF infection or colonization. With the spread of VREF continuing unabatedly throughout hospitals in the United States and Europe, research efforts must now be focused on the identification of effective intervention strategies.

Acknowledgements

The authors thank Mrs. Katharine Gross and Mrs. Dottie Brown and her staff for technical and logistic support.

References

1. Cohen ML. Antimicrobial resistance: prognosis for public health. Trends Microbiol **1994**;2:422–5.
2. Centers for Disease Control and Prevention. Nosocomial enterococci resistant to vancomycin—United States, 1989–1993. MMWR Morbid Mortal Wkly Rep **1993**;42:597–9.
3. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev **1993**;6: 428–42.
4. Murray BE. The life and times of the enterococcus. Clin Microbiol Rev **1990**;3:46–65.
5. Uttley AHC, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci [letter]. Lancet **1988**;1:57–8.
6. Bingen EH, Denamur E, Lambert-Zechovsky NY, Elion J. Evidence for the genetic unrelatedness of nosocomial vancomycin-resistant *Enterococcus faecium* strains in a pediatric hospital. J Clin Microbiol **1991**;29: 1888–92.
7. Kaplan AH, Gilligan PH, Facklam RR. Recovery of resistant enterococci during vancomycin prophylaxis. J Clin Microbiol **1988**;26:1216–18.
8. Karanfil LV, Murphy M, Josephson A, et al. A cluster of vancomycin-resistant *Enterococcus faecium* in an intensive care unit. Infect Control Hosp Epidemiol **1992**;13:195–200.
9. Rubin LG, Tucci V, Cercenado E, Eliopoulos G, Isenberg HD. Vancomycin-resistant *Enterococcus faecium* in hospitalized children. Infect Control Hosp Epidemiol **1992**;13:700–5.
10. Handwerger S, Raucher B, Altarac D, et al. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. Clin Infect Dis **1993**;16:750–5.
11. Boyle JF, Soumakis SA, Rendo A, et al. Epidemiologic analysis and genotypic characterization of a nosocomial outbreak of vancomycin-resistant enterococci. J Clin Microbiol **1993**;31:1280–5.
12. Montecalvo MA, Horowitz H, Gedris C, et al. Outbreak of vancomycin-, ampicillin-, and aminoglycoside-resistant *Enterococcus faecium* bacteremia in an adult oncology unit. Antimicrob Agents Chemother **1994**; 38:1363–7.
13. Boyce JM, Opal SM, Chow JW, et al. Outbreak of multidrug-resistant *Enterococcus faecium* with transferable *vanB* class vancomycin resistance. J Clin Microbiol **1994**;32:1148–53.
14. Livornese LL Jr, Dias S, Samel C, et al. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. Ann Intern Med **1992**;117:112–6.
15. Edmond MB, Ober JF, Weinbaum DL, et al. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis **1995**;20:1126–33.
16. Shay DK, Maloney SA, Montecalvo M, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis **1995**;172:993–1000.
17. Wells VD, Wong ES, Murray BE, Coudron PE, Williams DS, Markowitz SM. Infections due to beta-lactamase-producing, high-level gentamicin-resistant *Enterococcus faecalis.* Ann Intern Med **1992**;116:285–92.
18. Morris JG Jr, Shay DK, Hebden JN, et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin. Establishment of endemicity in a university medical center. Ann Intern Med **1995**;123:250–9.
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control **1988**;16:128–40.
20. Arthur M, Courvalin P. Genetics and mechanisms of glycopeptide resistance in enterococci. Antimicrob Agents Chemother **1993**;37:1563–71.
21. Facklam R, Hollis D, Collins MD. Identification of gram-positive coccal and coccobacillary vancomycin-resistant bacteria. J Clin Microbiol **1989**;27:724–30.
22. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard. 2nd ed. NCCLS document M7-A2. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, **1990.**
23. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing: approved standard. Third informational supplement M100-S3. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, **1991.**
24. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests: approved standard. 4th ed. NCCLS document M2-A4. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, **1990.**
25. Smith PG, Morrow RH, eds. Methods for field trials of interventions against tropical diseases: a 'toolbox'. New York: Oxford University Press, **1991**:289–94.
26. Rothman KJ. Modern epidemiology. Boston: Little, Brown & Co., **1986**: 285–311.
27. Frieden TR, Munsiff SS, Low DE, et al. Emergence of vancomycin-resistant enterococci in New York City. Lancet **1993**;342:76–9.
28. Centers for Disease Control and Prevention. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Morb Mortal Wkly Rep **1995**;44(RR-12):1–13.
29. Nichols RL, Muzik AC. Enterococcal infections in surgical patients: the mystery continues. Clin Infect Dis **1992**;15:72–6.