

Association between Resistance to Vancomycin and Death in Cases of *Enterococcus faecium* Bacteremia

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We conducted a retrospective cohort study to determine the association between resistance to vancomycin and mortality among hospitalized patients with *Enterococcus faecium* bacteremia. We compared outcomes for patients infected with vancomycin-resistant versus vancomycin-susceptible *E. faecium* among 69 patients with bacteremia defined according to the National Nosocomial Infections Surveillance system. The univariate odds ratio (OR) for death associated with vancomycin resistance was 2.1 ($P = .172$). After controlling for severity of illness, we found that vancomycin resistance was not associated with mortality (OR, 1.74; 95% confidence interval, 0.5–6.12; $P = .39$). Vancomycin resistance does not independently increase mortality among patients with *E. faecium* bacteremia.

Over the past 10 years, enterococci have become the third most common nosocomial bloodstream pathogens, but their significance in nosocomial bloodstream infections is controversial [1–5]. Several studies of enterococcal bacteremia have shown increased mortality, morbidity, hospitalization, and costs [6–10], whereas others have suggested that enterococcal bacteremia merely represents skin contamination [11] or severe underlying disease with no additional mortality risk [12].

Differences in enterococcal species and antimicrobial resistance may affect mortality risk. *E. faecium* is now the strain most often associated with nosocomial bacteremia [1] and has been associated with greater mortality than has *Enterococcus faecalis* [13, 14]. Bacteremia due to vancomycin-resistant enterococci has been characterized as a disease of severely debilitated patients [1, 5, 7, 8, 10, 13], but it is unclear whether vancomycin resistance is an independent predictor of death. Crude mortality estimates for patients with bacteremia due to VRE range from 37% to 76% [1, 2, 5, 7, 8, 10, 13–19]. Most studies comparing vancomycin-resistant enterococci with vancomycin-susceptible enterococci revealed a higher crude mortality risk associated with the former [2, 5, 8, 17–19], but 1 study found no difference [20].

Reported estimates of mortality risk associated with vancomycin resistance vary according to study design and analysis, patient population, case definition, control selection, and en-

terococcal species studied [1, 5, 7, 8, 10, 13]. Most published studies have been small, and report only crude mortality rates. Crude mortality does not distinguish between death caused by concurrent comorbid conditions and that due to bacteremia [21]. Few investigators have attempted to assess the independent mortality risk associated with vancomycin resistance while controlling for significant host and environmental factors.

In 3 studies controlling for disease severity in multivariate analyses, vancomycin resistance was not found to be an independent predictor of mortality [17–19]. In another study, when disease severity was not controlled for in the multivariate analysis, vancomycin resistance was an independent predictor of enterococci-associated mortality [5]. In a matched case-cohort study [7] that used an alternative approach, 37% mortality was attributed to bacteremia due to vancomycin-resistant enterococci. A standardized measure of disease severity was not used in the matching procedure.

Our study sought to answer 2 questions. First, what is the association between vancomycin resistance and mortality among patients with *E. faecium* bacteremia, when important host and environmental factors are controlled for? Second, what factors affect the risk of death for patients with *E. faecium* bacteremia?

Patients and Methods

Patients

We conducted a retrospective cohort study of all patients identified as having *E. faecium* bacteremia at Barnes-Jewish Hospital, a tertiary care teaching facility licensed for 1287 beds in St. Louis, Missouri. The first case of vancomycin-resistant *E. faecium* (VREF) bacteremia occurred in 1995, and since then VREF has become endemic within the institution [14, 22, 23]. By means of the hospital's computerized data management system, we identified all patients for whom a blood culture was positive for *E. faecium* from January 1995 through April 1997.

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We defined 2 patient cohorts. The main study cohort was composed of patients with *E. faecium* bacteremia, as defined by the National Nosocomial Infections Surveillance (NNIS) system [24] (see Definitions, below). A second cohort (the full cohort) was composed of all patients for whom at least 1 blood culture was positive for *E. faecium* and included the main study cohort. We compared in-hospital mortality and other secondary outcome measures among patients with bacteremia due to VREF versus those with bacteremia due to vancomycin-susceptible *E. faecium* (VSEF).

Measurement and Analysis

Measurement of host and environmental factors. We did a retrospective chart analysis for all patients, using a standardized data-collection instrument. All drug exposures occurring before the date of the index *E. faecium* blood culture (except for treatment of *E. faecium* bacteremia) were assessed and thus pertain only to the index admission. Complete variable definitions are given in Definitions, below. The following variables were abstracted from each patient's chart: source of admission, lifestyle before morbidity [25], immune status, comorbidities [26], enteral tube feeding, central venous catheterization, mechanical ventilation, Foley catheterization, dialysis, and condition at discharge.

Additional predictor variables were abstracted from the hospital's medical information system. These included age, sex, race, length of stay from admission to the positive index *E. faecium* blood culture, admission and length of stay before index culture in the intensive care unit (ICU), antimicrobial and vasopressor treatment history, and positive microbiology culture results. Antibiotic exposure during the current admission, before performance of the index culture, was assessed and included the total number of iv antibiotics used for at least 24 h, the total number of days of administration of any iv antibiotic, and exposure to specific antibiotics. Because follow-up blood culture specimens are not always drawn, we were unable to reliably measure duration of bacteremia.

Measurement of disease severity. Severity-of-illness measures were assessed for all patients on the day of the index blood culture and included scores for APACHE II [27], the organ system failure index (OSFI) [25], the Chow index [28], and the Systemic Inflammatory Response Syndrome (SIRS) classification scheme [29] (see Definitions). All measures have been validated as predictors of death.

Effective treatment of *E. faecium* bacteremia. Effective treatment of *E. faecium* was defined as initiation of treatment with an antimicrobial agent to which the isolate was known to be susceptible within 3 days of the positive index culture date (see Definitions).

Isolation, identification, and characterization of *E. faecium*. Antibiotic susceptibility of isolates from blood and from normally sterile body fluids was determined by disk-diffusion methods and with reference to standard breakpoints [30]. Vancomycin resistance was defined as an MIC ≥ 16 mg/mL. Isolation, identification, and characterization of VRE from stool and urine samples were done by use of bile-esculin-azide agar (BEAA; Remel, Lenexa, KS) [31].

Outcome measures. The primary outcome measure was in-hospital mortality. Condition at discharge, length of hospitalization, and duration of admission in an ICU were abstracted from the hospital's medical information system. Since there are no ob-

jective criteria to reliably determine retrospectively whether death was attributable to *E. faecium*, we did not include this outcome measure in our study [21].

Statistical analysis. For the descriptive analysis, we compared patients with VREF with those with VSEF. Statistical significance was assessed by means of the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test or Student's *t* test for continuous variables, depending on variable distribution. All *P* values were based on 2-tailed tests. Reported *P* values are for the χ^2 test or Wilcoxon rank-sum test unless stated otherwise.

We used multivariate logistic regression to determine independent mortality risk factors for both patient cohorts. Significant univariate predictors of the outcome ($P \leq .1$) were eligible for inclusion in the multivariate analysis. When ≥ 2 variables were collinear, we selected the best variable for model entry on the basis of statistical and clinical significance. We used forward stepwise regression with $P \leq .15$ for model entry and $P \geq .2$ for removal from the model. Finally, we eliminated unstable variables from the model by use of forced logistic regression, with $P \geq .05$ as the criterion for variable removal.

To determine the association between vancomycin resistance and death, we again used logistic regression for bivariate and multivariate analyses. We used bivariate analyses to assess the association between vancomycin resistance and death, controlling for each predictor variable in turn. Variables that independently predicted death in the bivariate model were eligible for inclusion in the multivariate analysis. We again used forward stepwise regression analyses, forcing VRE to remain in the model, and finally eliminated unstable variables from the model, using forced logistic regression as above. All statistical analyses were done with STATA statistical software (Release 5.0; Stata, College Station, TX).

Definitions

Clinically significant bacteremia. The positivity of at least 2 blood cultures for *E. faecium* (either VREF or VSEF) or the positivity of a single blood culture and of a concurrently cultured specimen (except for stool) for *E. faecium* (per NNIS system) [24].

Effective treatment medications. If the isolate was susceptible, the following agents were used: for VREF, aminoglycoside with an active cell-wall agent, chloramphenicol, quinupristin/dalfopristin (Synercid; Rhône-Poulenc, Colledgeville, PA), and amikacin; for VSEF, aminoglycoside with an active cell-wall agent, chloramphenicol, ampicillin, quinupristin/dalfopristin (Synercid), imipenem, vancomycin, and mezlocillin.

Other definitions. Polymicrobial infection was defined by isolation of a second bacterial species (including coagulase-negative staphylococci) or fungus in a blood culture on the index date. Nosocomially acquired bacteremia was that occurring >2 days after admission. Chronic renal failure was defined as the requirement of peritoneal dialysis or hemodialysis. Immunocompromised patients included those infected with HIV, those with cancer or hypogammaglobulinemia, transplant recipients, and those treated with systemic steroids or chemotherapy. Fever was a temperature $>38^\circ\text{C}$.

SIRS. Severe sepsis was defined as SIRS syndrome [29] with *E. faecium* bacteremia associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. SIRS shock was defined as SIRS syndrome [29] with *E. faecium* bacteremia and sepsis-

induced hypotension (despite adequate fluid resuscitation [>3 L/d]) and hypoperfusion abnormalities, which we defined as oliguria (<30 mL of urine per h), lactic acidosis (serum lactate concentration, >3 mmol/L), and mental state alterations.

Lifestyle before morbidity. Quantification was as follows: 0, employed; 1, independent, fully ambulatory; 2, restricted activity, able to live alone and get out for necessities, and restricted exercise ability; 3, housebound, not able to live alone (i.e., unassisted); and 4, bed-/chair-bound [25]. A patient with a score ≤ 1 was considered to be independent.

Results

Characteristics of patients. The cohort of patients with NNIS-defined bacteremia (the main cohort) was composed of 69 patients, of whom 46 (67%) had VREF bacteremia and 23 (33%) had VSEF bacteremia. Overall, 48 patients (70%) had primary bacteremia: 28 (61%) were infected with VREF and 20 (87%) infected with VSEF. Twenty-one patients (30%) had secondary bacteremia; the most frequent additional sites were urine (15 patients) and a wound (10). Polymicrobial bacteremia was more common in patients with VSEF bacteremia (VREF, 30%; VSEF, 57%; $P = .036$). The numbers and percentages of cases due to VREF varied over the study period: 10 (2%) in 1995, 46 (67%) in 1996, and 13 (19%) in the first quarter of 1997.

The full cohort was composed of 126 patients for whom at least 1 blood culture was positive for *E. faecium*. For 76 patients (60%), the identified organism was VREF, and for 50 (40%) it was VSEF. Patients' characteristics and exposures were similar in both cohorts (table 1). Results of further analyses are presented for the main cohort.

Before developing *E. faecium* bacteremia, patients were severely ill (mean APACHE II score, 18.8), hospitalized for a long time (mean, 15.8 days), often admitted to the ICU (57%), mechanically ventilated (49%), and exposed to multiple antibiotics (mean, 5.2). Effective treatment was administered to the majority of patients (43 [62%] of 69), and there was no statistically significant difference between patient groups in this respect (VREF, 57%; VSEF, 74%; $P = .16$). The mean duration of treatment was 4.6 days (SD = 4.1), the median was 3 days, and the range was 1–19 days. Duration of treatment was not different between groups (mean values: VREF, 5 days; VSEF, 3.9 days; $P = .40$).

Characteristics of patients with VREF and VSEF bacteremia. The incidence of vancomycin resistance increased in association with female sex, prolonged hospitalization and ICU stay before bacteremia, exposure to antimicrobial agents (measured as total number of drugs or duration of treatment, iv vancomycin, or metronidazole) or to agents for gastric acid suppression, year of admission after 1995, enteral feeding, central venous catheterization, and disease severity (table 2).

Risk factors for death of patients with *E. faecium* bacteremia. Factors associated with increased risk of death included

Table 1. Characteristics of patients with *Enterococcus faecium* bacteremia.

Characteristic	Main cohort (n = 69)	Full cohort (n = 126)
Demographics		
Age, y		
Mean (\pm SD)	59.7 (\pm 17.9)	57.7 (\pm 18.4)
Median (range)	61.9 (20–89)	59.9 (15–90)
Male	36 (52)	66 (52)
Nonwhite	24 (35)	47 (37)
Admitted from		
Home	46 (67)	82 (65)
Hospital	14 (20)	29 (23)
Skilled-nursing facility	9 (13)	15 (12)
Disease severity		
APACHE II score, mean (\pm SD)	18.8 (9)	18.0 (9.1)
OSFI score, median (range)	1 (0–6)	1 (0–6)
Chow score, median (range)	3 (0–12)	3 (0–12)
SIRS syndrome	57 (83)	102 (81)
SIRS shock	11 (16)	17 (13)
Comorbidity		
Charlson score, median (range)	2 (0–8)	2 (0–8)
Immunocompromised	32 (46)	57 (45)
Diabetes mellitus	22 (32)	36 (29)
Chronic dialysis	9 (13)	13 (10)
Hospitalized in previous month	45 (65)	79 (63)
Restricted lifestyle score at admission	28 (41)	60 (48)
In-hospital exposure before IC		
Length of stay, d		
Mean (\pm SD)	15.8 (\pm 16.3)	14.1 (\pm 14.9)
Median (range)	12.1 (1–78)	10.0 (1–78)
No. of antibiotics received		
Mean (\pm SD)	5.2 (\pm 4.3)	4.7 (\pm 3.8)
Median (range)	5 (0–15)	4 (0–15)
Stay in ICU	59 (57)	71 (56)
Mechanical ventilation	34 (49)	56 (44)
Effective treatment	43 (62)	81 (64)
Microbiology		
Blood culture sampling site		
Central line	31/42 (74)	50/71 (70)
Peripheral line	11/42 (61)	21/71 (30)
<i>E. faecium</i> isolated ^a before IC	13 (19)	29 (23)
<i>E. faecium</i> isolated ^a after IC	19 (28)	58 (46)
Polymicrobial infection	27 (39)	49 (39)

NOTE. Data are no. (%) unless otherwise stated. IC, index culture; ICU, intensive care unit; OSFI, organ system failure index; SIRS, Systemic Inflammatory Response Syndrome.

^a Except from stool.

increased disease-severity scores—APACHE II (OR, 1.13; $P = .007$ for each point increase), OSFI (OR, 2.04; $P = .001$ for each point increase), Chow (OR, 1.36; $P = .007$ for each point increase), and SIRS shock (see Definitions) (OR, 8.55; $P = .01$); nosocomial acquisition of bacteremia (OR, 5.78; $P = .011$); being in the ICU (OR, 2.82; $P = .043$) or undergoing ventilation (OR, 2.87; $P = .038$) on the date of the index test; and treatment with agents for gastric acid suppression (OR, 3.75; $P = .036$). Polymicrobial infection, invasive procedures (central venous catheterization, total parenteral nutrition, dialysis, or urinary catheterization), and recent hospitalization were not associated with mortality.

Administration of effective treatment within 3 days of the positive blood culture finding did not affect mortality risk (OR, 2.15; 95% CI, 0.77–5.99; $P = .144$). Treatment with an appro-

Table 2. Descriptive analysis comparing patients with bacteremia due to vancomycin-resistant or -susceptible *Enterococcus faecium* (VREF or VSEF) in the main cohort ($n = 69$).

Variable	VREF ($n = 46$)	VSEF ($n = 23$)	<i>P</i>
Length of stay before IC, d	20.6 (16.5)	6.3 (11.1)	.0001
Antibiotic treatment, d	61.1 (59.4)	17.9 (31.7)	.0001
Enteral feeding	28 (61)	1 (4)	.0001 ^a
Received iv vancomycin before IC	33 (72)	6 (26)	.0001
Nosocomially acquired <i>E. faecium</i> bacteremia	41 (89)	9 (39)	.0001
ICU length of stay before IC, d	9.2 (9.9)	2.1 (4.6)	.0004
No. of antibiotics received	6.5 (4.1)	2.7 (3.9)	.0005
Gastric acid suppressants	39 (85)	11 (48)	.0010
Total length of stay, d	39.7 (25.5)	21 (16.3)	.0019
In ICU before IC	32 (70)	7 (30)	.0020
Metronidazole use before IC	24 (52)	4 (17)	.0090 ^a
Ventilator use before IC	28 (61)	6 (26)	.0060
SIRS shock	11 (24)	0 (0)	.0120 ^a
Central venous line	40 (87)	14 (61)	.0130
Polymicrobial bacteremia	14 (30)	13 (57)	.0360
Male	20 (44)	16 (70)	.0410
APACHE II score	20.4 (9.6)	15.8 (7)	.0491 ^b
Chow score	3.5 (2.4)	2.7 (2.9)	.0730
Nonwhite	19 (41)	5 (22)	.1080 ^a
No. of <i>E. faecium</i> -positive blood cultures	2.8 (3.2)	3 (2.5)	.1305
Effective treatment (within 3 d)	26 (57)	17 (74)	.160
In ICU on date of IC	20 (43)	6 (26)	.160
Diabetes	17 (37)	5 (23)	.201

NOTE. Data are mean value (\pm SD) or no. (%) of patients. IC, index culture; ICU, intensive care unit; SIRS, Systemic Inflammatory Response Syndrome.

^a Fisher's exact test.

^b Per Student's *t* test.

priate antibiotic was initiated within 1 day for the majority of patients (36 [84%] of 43). The OR associated with administration of appropriate treatment on the day of the index test was 0.74 (95% CI, 0.25–2.20; $P = .59$); within 1 day, 1.33 (95% CI, 0.48–3.68; $P = .58$); within 2 days, 1.2 (95% CI, 0.35–4.13; $P = .77$). Of the 26 patients who did not receive an appropriate antibiotic within 3 days, 18 (69%) survived.

The multivariate analysis identified the APACHE II score, the OSFI score, and SIRS shock as significant independent predictors of death (table 3). About 25% of the variation in mortality status in the study cohort is due to the 3 variables in the model.

Association between vancomycin resistance and death. Crude mortality rates were 42% (29/69) overall, 48% (22/46) for VREF bacteremia, and 30% (7/23) for VSEF bacteremia (OR, 2.10; 95% CI, 0.73–6.04; $P = .17$). Vancomycin resistance failed to reach significance as a predictor of death in any of the bivariate analyses, in which each variable was controlled for in turn. When effective treatment was controlled for, VREF achieved borderline statistical significance (VREF OR, 2.54; $P = .099$).

Multivariate analysis. When we controlled for underlying severity of illness with the APACHE II score and OSFI score, resistance to vancomycin was not associated with mortality (OR, 1.74; $P = .39$; table 4). These variables explained about one-fifth of the variance.

We determined whether the risk ratio for death associated

with VREF status was homogeneous across disease severity scores in stratified analyses with the Mantel-Haenszel test for homogeneity [32]. We used an APACHE II score of 18 (the median) and an OSFI score of 3 [25] to dichotomize the continuous scores. The risk ratio for death associated with vancomycin resistance was not significant and was homogeneous across the disease severity strata in both cohorts.

The full cohort. Our findings were similar for the full cohort. Crude mortality rates were 40% (51/126) overall, 43% (33/76) for VREF bacteremia, and 36% (18/50) for VSEF bacteremia ($P = .41$). Vancomycin resistance was not a significant predictor of death in the univariate analysis (OR, 1.36; 95% CI, 0.65–2.84; $P = .41$) or the multivariate analysis, in which disease severity was controlled for (OR, 1.28; 95% CI, 0.47–3.51; $P = .81$).

Other outcomes. Infection with a vancomycin-resistant organism was associated with prolonged hospitalization (means: VREF, 39.7 days; VSEF, 20.9 days; $P = .0019$). Patients with VREF bacteremia were hospitalized longer before the development of bacteremia (VREF, 20.6 days; VSEF, 6.3 days; $P = .0001$). Length of hospitalization after diagnosis was about 4 days longer for patients with VREF bacteremia, but this failed to achieve statistical significance (19.1 days vs. 14.7 days; $P = .51$). Similarly, total length of stay in the ICU was longer for patients with VREF bacteremia, by an average of 9 days (VREF, 15.2 days; VSEF, 6.4 days; $P = .0075$). However, ICU length of stay after diagnosis was not significantly different between the 2 patient groups (VREF, 5.9 days; VSEF, 4.3 days; $P = .23$). Exclusion of patients who died did not significantly alter these conclusions.

Discussion

We have demonstrated that vancomycin resistance is not independently associated with increased mortality among patients with *E. faecium* bacteremia. We found this to be true in the bivariate and multivariate analyses, controlling for significant host and environmental factors separately or simultaneously. These results persist whether bacteremia is defined by NNIS criteria (the main cohort) or simply by the finding of a positive blood culture (the full cohort). We did detect an absolute difference of 18% in crude mortality rates between patients with

Table 3. ORs from multivariate analysis for independent predictors of death among 69 patients with *Enterococcus faecium* bacteremia defined according to the National Nosocomial Infections Surveillance system.

Variable	OR (95% CI)	<i>P</i>
OSFI score (per point)	1.87 (1.04–3.35)	.036
APACHE II score (per point)	1.09 (1.00–1.18)	.040
SIRS shock	7.01 (1.06–46.40)	.043

NOTE. Model $\chi^2 = 23.47$; pseudo R^2 , 0.25; area under receiver operating characteristic curve, 0.82. OSFI, organ system failure index; SIRS, Systemic Inflammatory Response Syndrome.

Table 4. ORs from multivariate analysis for independent predictors of death, controlling for vancomycin resistance, among 69 patients with *Enterococcus faecium* bacteremia defined according to the National Nosocomial Infections Surveillance system.

Variable	OR (95% CI)	P
Vancomycin-resistant <i>E. faecium</i>	1.74 (0.50–6.12)	.39
APACHE II score (per point)	1.10 (1.02–1.19)	.013
OSFI score (per point)	1.71 (0.99–2.93)	.052

NOTE. Model $\chi^2 = 19.62$; pseudo R^2 , 0.21; area under receiver operating characteristic curve, 0.81. OSFI, organ system failure index.

VREF and VSEF bacteremia, which was not statistically significant. This apparent effect vanished when we controlled for important host and environmental factors, suggesting that differences in crude mortality rates are misleading in determining mortality risk associated with vancomycin resistance in cases of *E. faecium* bacteremia.

A larger sample size probably would have allowed us to detect a statistically significant association between vancomycin resistance and death in the univariate analysis. However, we had adequate power to report 3 independent predictors of death in the multivariate analyses [33] and have demonstrated that when severity of illness is controlled for by use of 2 variables, there is no increase in mortality associated with vancomycin resistance.

Conflicting conclusions from other studies seeking to elucidate the mortality risk associated with vancomycin resistance in enterococcal bacteremia may be a result of the use of different comparators. Control populations have included patients with no bacteremia [7, 15], patients with bacteremia due to different enterococcal species [13], and patients infected with varied enterococcal species [2, 9, 17–19]. Interspecies differences may confound estimates of mortality risk attributable to vancomycin resistance. We avoided this effect by including only patients with *E. faecium* bacteremia in our study cohort.

Two other retrospective cohort studies have compared patients with clinically significant bacteremia due to VREF and VSEF [5, 8]. Both found vancomycin resistance to be a significant univariate predictor of death. In addition, Linden et al. [5] did a multivariate analysis and found vancomycin resistance to be an independent predictor of enterococci-associated death among patients with severe liver disease. Their analysis was limited, however, because they used subjective assessment of cause of death as the primary outcome measure [21], did not control for disease severity, and investigated a limited patient population.

E. faecium bacteremia is associated with a high overall crude mortality rate. The 40%–42% crude mortality rates measured in our study cohorts are comparable with those in other studies of patients with enterococcal bacteremia [3, 7, 18, 19] and with overall mortality estimates for nosocomial bacteremia [34]. We identified 3 independent predictors of death for patients with NNIS-defined *E. faecium* bacteremia, all pertaining to underlying disease severity: high APACHE II scores, high OSFI

scores, and the presence of SIRS shock. Others have reported increased disease severity as an independent risk factor for death among patients with enterococcal bacteremia [17–19].

We were uncertain about which disease-severity measure to use and elected to use 4 instruments in this study, to identify the best metric for future work. It is most interesting that 3 measures of disease severity remained in our final model as independent predictors of death. This suggests that each captures a different aspect of severity and that >1 measure should be included in future studies.

In our study cohort, prompt initiation of treatment with an antimicrobial agent to which the isolate was known to be susceptible offered no survival benefit. This effect was independent of the susceptibility profile of *E. faecium* and the time to administration of treatment. Although the lack of treatment benefit is striking, it may be due to the unexplained brief duration of treatment (mean, 4.6 days) or inappropriate dosing, which we did not evaluate. However, we also found a high rate of spontaneous resolution among untreated patients (~70% in both cohorts), which suggests that at least in some patients, untreated *E. faecium* bacteremia is transient and has no impact on survival.

These findings suggest that criteria to initiate antibiotic treatment and current treatment protocols for *E. faecium* bacteremia need to be carefully evaluated to assess both benefit and cost, including the risk of inducing resistance in pathogens. Use of proven alternative maneuvers, such as central venous line removal [35], should be considered.

There are several limitations to our study. First, the retrospective design limits the measurement of risk factor and outcome data. We were unable to include data about surgical interventions, percutaneous drainage, and central venous line removal, which are difficult to assess from retrospective chart review, and are not captured reliably in the ICD-9-CM (International Classification of Diseases [ninth revision]–Clinical Modification) system. However, since it is unlikely that these practices occurred differentially in the patient groups, omission of these data probably is not a threat to the validity of our results.

Second, use of hospital mortality as the primary outcome measure may introduce ascertainment bias for death if there was differential discharge. It is possible that patients infected with VSEF were more readily discharged than patients infected with VREF, given the complexity of the treatment regimens, which could lead to underestimation of mortality for VSEF-infected patients. The effect of this potential bias would be to lower the apparent death rate among VSEF-infected patients and increase the OR for vancomycin resistance as a predictor of death. Since we did not find an association between vancomycin resistance and death, we do not believe this phenomenon threatens our conclusion.

Third, we included ICU and non-ICU patients in our study population, although it has been suggested that different mor-

tality risks may apply to these 2 patient groups [36]. Although presence in the ICU on the index test day increased mortality risk in the univariate analysis, it was not significant in the multivariate analysis. In the main cohort, 44 (64%) of the patients were in the ICU at some point during their hospitalization, and this exposure did not increase mortality risk (RR, 1.26; 95% CI, 0.68–2.33; $P = .44$). This suggests that inclusion of ICU and non-ICU patients in the study cohort does not introduce significant selection bias.

In summary, we have shown that vancomycin resistance (vs. vancomycin susceptibility) does not independently increase mortality risk, postdiagnosis duration of hospitalization, or ICU admission for patients with bacteremia due to *E. faecium*. Similar to the finding among bacteremic patients infected with *Staphylococcus aureus* [37], enterococci with genes that confer antimicrobial resistance appear to be no more virulent than those susceptible to drugs, as long as suitable treatment is administered. The public health risks associated with vancomycin resistance, particularly that of transmission of resistant genes to more virulent gram-positive pathogens such as *S. aureus*, may be more significant than the mortality and morbidity risk of VREF for individual patients.

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