CLINICAL ARTICLES

Vancomycin-Resistant Enterococcal Bacteremia: Natural History and Attributable Mortality

Michael B. Edmond, Janis F. Ober, Jeffrey D. Dawson, David L. Weinbaum, and Richard P. Wenzel

From the Division of Quality Health Care and Department of Internal Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia; The Western Pennsylvania Hospital, Pittsburgh, Pennsylvania; and the Division of Biostatistics, Department of Preventive Medicine & Environmental Health, The University of Iowa College of Medicine, Iowa City, Iowa

Previous studies have shown that bacteremia due to vancomycin-resistant *Enterococcus* species (VRE) is associated with mortality of 17%–100%, but comorbid conditions may have confounded the estimates. We designed a historical cohort study to determine the mortality attributable to VRE bacteremia. Twenty-seven patients with VRE bacteremia were identified as cases. Within 7 days of the onset of bacteremia, severe sepsis developed in 12 patients (44%) and septic shock developed in 10 (37%). Case patients were closely matched to control patients without VRE bacteremia (1:1) by time of hospitalization, duration of exposure, underlying disease, age, gender, and surgical procedure. The mortality was 67% among cases and 30% among matched controls ($P = .01$). Thus, the mortality attributable to VRE bacteremia was 37% (95% confidence interval [CI], 10%–64%) and the risk ratio for death was 2.3 (CI, 1.2–4.1). We conclude that VRE bacteremia is associated with high rates of severe sepsis and septic shock. The attributable mortality approaches 40%, and patients who have VRE bacteremia are twice as likely to die than closely matched controls.

Nosocomial enterococcal bloodstream infections occur at rates of 3–4 per 10,000 hospital discharges [1] and are responsible for 10% of all infections acquired in hospitals [2]. Enterococcal bacteremia has serious implications; in the era prior to vancomycin resistance, it was associated with a reported crude (total) mortality of 33%–68% [3–7]. Moreover, in the early 1980s, prior to the advent of multiply resistant strains, Landry and colleagues reported that the attributable (direct) mortality due to enterococcal bacteremia was 31% and that enterococcal bacteremia added 39 days to the hospital stay [8].

Since the development of glycopeptide resistance in the late 1980s, isolates of *Enterococcus* resistant to all available antimicrobials have emerged. The rate of vancomycin resistance among enterococcal isolates from the National Nosocomial Infections Surveillance (NNIS) system climbed from 0.3% in 1989 to 7.9% in 1993, a 20-fold increase [9]. Intensive care units (ICUs) have especially high rates, and in 1993, 14% of enterococcal isolates causing infections in ICUs showed resistance to vancomycin [9]. The accelerating problem of vancomycin resistance poses a challenge for clinicians, since no known effective therapy exists for many vancomycin-resistant *Enterococcus* (VRE) strains.

In a recent investigation of an outbreak of VRE bacteremia in patients with hematologic malignancies [10], we observed a crude mortality of 73% (eight of 11 patients died). Four deaths (36%) were thought to be directly attributable to VRE bacteremia, as assessed by the clinicians caring for these patients. Other studies at individual institutions have found crude mortality rates ranging from 17% to 100% [11–16]. In addition, in an evaluation of 1,881 enterococcal primary bloodstream infections at NNIS system hospitals, mortality was significantly higher among those patients whose bloodstream isolates were vancomycin-resistant than among those whose isolates were vancomycin-susceptible (37% vs. 16%; $P < .0001$) [9]. However, many patients with enterococcal bacteremia have significant underlying illnesses, and it is often difficult to determine the relationship between bacteremia and death.

The overall goal of this study was to determine the attributable (direct) mortality and morbidity due to VRE bacteremia. In addition, we delineated the natural history of VRE bacteremia since none of the patients in this study received antimicrobials with in vitro activity against VRE.

Methods

Setting

The study was performed at a 542-bed tertiary-care community teaching hospital in the eastern United States. An outbreak

Received 25 January 1996; revised 7 June 1996.
Grant support: Rhône-Poulenc Rorer.
Reprints or correspondence: Dr. Michael Edmond, Medical College of Virginia, P.O. Box 980509, Richmond, Virginia 23298-0509 (e-mail: MEDMOND@Gems.VCU.EDU).

Clinical Infectious Diseases 1996; 23:1234–9

1058–4838/96/2306–0000$02.00

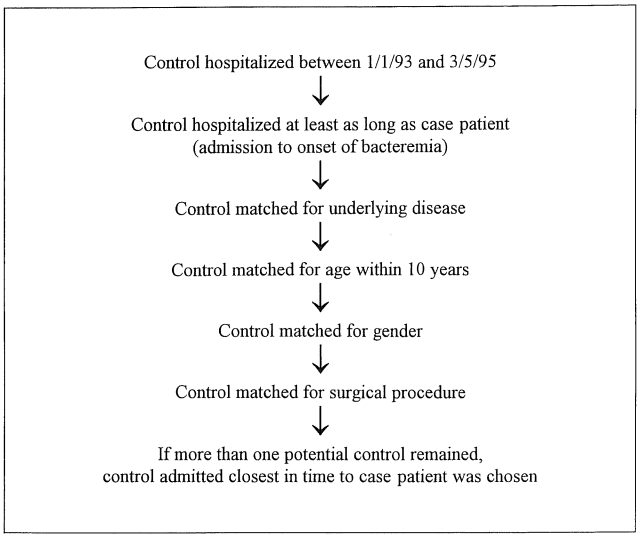

Figure 1. Stepwise procedure for matching best controls to cases.

of VRE bacteremia (11 cases) in the oncology unit of this hospital has been previously reported [10].

Microbiology

Identification of organisms and antimicrobial susceptibility testing were performed via the Vitek automated system (bioMérieux Vitek, Hazelwood, MO). Resistance to vancomycin was defined by an MIC of ≥ 16 μg/mL. Susceptibility to teicoplanin was not routinely determined. All isolates were tested for β-lactamase production with nitrocefin disks.

Study Design

The study was of a matched retrospective (historical) cohort design [17, 18]. In this design, case patients (patients with VRE bacteremia) were very closely matched to controls (patients without VRE bacteremia). Because of the intensity of the matching process, any detectable difference in morbidity or mortality between case patients and controls was considered to be due to VRE bacteremia. Thus, the estimated attributable mortality was determined by subtracting the crude (overall) mortality rate among the controls from the crude mortality rate among the case patients.

A case patient was defined as any patient at least 18 years old for whom one or more blood cultures yielded VRE during the time period of 1 January 1993 to 5 March 1995. Postmortem blood cultures were not included. Patients whose blood cultures yielded VRE that was susceptible to β-lactam agents were excluded. A control was defined as a patient similar to a case patient but without enterococcal bacteremia during hospitalization. Controls were required to have been hospitalized during the same time period as case patients.

Controls were matched to case patients on a 1:1 ratio by means of a stepwise procedure, to ensure the best match (figure 1). For each case patient a list of potential controls with the same underlying primary disease was generated by the hospital information system. From this list, potential controls were chosen for each case patient with use of specific criteria, in the order indicated in figure 1.

Charts of case patients and control patients were reviewed for demographic data, severity of illness indicators, and data concerning outcomes. International Classification of Diseases (ninth revision) codes were used to screen for potential matches with regard to primary underlying disease; charts were then reviewed to confirm that the diagnoses matched. Outcomes determined for case patients and controls were mortality, required ICU care, required mechanical ventilation, and required hemodialysis.

Definitions of Clinical Parameters

To quantify severity of illness due to VRE bacteremia, the definitions for sepsis and organ failure determined by the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine [19] were applied for the 7-day period following any blood-culture isolation of VRE. VRE-induced severe sepsis was defined as VRE bacteremia associated with the systemic inflammatory response syndrome (SIRS) plus end-organ dysfunction, hypoperfusion abnormalities, or hypotension. VRE-induced septic shock was defined as VRE bacteremia–induced SIRS plus hypotension (despite fluid resuscitation) and any hypoperfusion abnormality.

SIRS was defined by two or more of the following criteria: temperature of >38°C or <36°C; heart rate of >90; respiratory rate of >20; and WBC count of $>12.0 \times 10^9$/L or $<4.0 \times 10^9$/L (or $>10\%$ immature forms [bands]). Adult respiratory distress syndrome (ARDS) and acute renal failure were the end-organ dysfunctions detected. ARDS was defined by respiratory insufficiency (partial pressure of O_2 [arterial] fraction of inspired O_2, <175) occurring in the absence of heart failure (if measured, a pulmonary capillary wedge pressure of <18 mm Hg) or primary pulmonary disease.

Acute renal failure was defined by (1) an acute increase in serum creatinine level of >2.0 mg/dL, (2) a doubling of the admission creatinine level (in a patient with chronic renal failure), or (3) the requirement for acute dialysis or ultrafiltration. Disseminated intravascular coagulation was not evaluated as an end-organ dysfunction since the majority of patients had an underlying hematologic malignancy, often accompanied by thrombocytopenia and coagulopathy, prior to the development of bacteremia.

Oliguria, lactic acidosis, and mental-status alterations were considered hypoperfusion abnormalities. Oliguria was defined as a urinary output of <0.5 mL/kg per hour for at least 1 hour or <30 mL (total) for 2 hours. Lactic acidosis was defined as a plasma lactate level of >2.0 mmol/L. Daily nursing notes were reviewed for mentions of mental-status alterations. Hypotension was defined by a systolic blood pressure of <90 mm

Hg, a ≥50% drop in systolic blood pressure (in a hypertensive patient), or the requirement for continuous infusion of pressors (for dopamine, the dosage must have been >5 μg/[kg · min]; for other pressors, any dosage qualified).

Statistical Analysis

The mortality attributable to VRE bacteremia was defined as the mortality rate among controls subtracted from that among case patients. The attributable mortality estimate and corresponding 95% confidence interval (95% CI) were calculated in the manner described by Fleiss [20]. An exact McNemar test was performed to assess whether there was a significant difference between the mortality rates for case patients and controls. The risk ratio was estimated by division of the mortality rate for case patients by that for controls. The 95% CI for the risk ratio was calculated by Miettinen's test-based method [21].

In addition to the mortality comparisons, exact McNemar tests were performed to compare the case patients and controls with respect to binary variables, such as neutropenia and ARDS. Exact Wilcoxon's signed-rank tests were used to compare the case patients and controls with respect to continuous variables, such as age and length of stay. For analysis of case patients only, comparisons among categorical variables were made with Fisher's exact test. All exact tests were performed with use of StatXact (Cytel Software, Cambridge, MA; 1992).

Results

Study Population

During the study period, VRE bacteremia developed in 34 adult patients. Five patients were excluded because their enterococcal isolates were susceptible to ampicillin. None of these five isolates were identified to the species level. Two other patients were excluded because they received treatment with quinupristin/dalfopristin, an experimental streptogramin antibiotic with in vitro activity against vancomycin-resistant *Enterococcus faecium.* The study cohort comprised the remaining 27 patients.

Effectiveness of Matching

All of the case patients were matched to controls by date of admission (within a 2-year period). Likewise, all pairs were matched for duration of exposure (i.e., for all pairs, the control was hospitalized at least as long as the interval from admission to onset of bacteremia for the matched case patient). The median age of the case patients was 64 years (range, 24–86 years; mean, 57 years), while the median age of the controls was 58 years (range, 29 to 85 years; mean, 58 years) (P = .40). For 12 pairs (44%), the age difference was ≤5 years, and all but two pairs (93%) were matched within 10 years (table 1). Fifteen (56%) of the case patients and 15 (56%) of the controls were men (P = 1.0). Twenty-five (93%) of the case-control pairs were matched on the basis of gender.

Table 1. Effectiveness of matching cases to controls.

Criterion	Proportion of matched cases/controls (%)
Same date of admission (within a 2-y period)	27/27 (100)
Same duration of exposure to risk	27/27 (100)
Same underlying disease	27/27 (100)
Same age (within 10 y)	25/27 (93)
Same gender	25/27 (93)
Same surgical procedure	9/15 (71)
Total	140/150 (93)

All case patients and controls were concordant with respect to primary underlying-disease diagnosis (table 2). Of the 27 pairs, 74% had an underlying hematologic or neoplastic disorder and 22% had a cardiopulmonary disorder. One-half (48%) of the pairs had acute myelocytic leukemia. Nine case patients underwent a total of 15 surgical procedures, for which nine (60%) were successfully matched (table 3). Three controls underwent a procedure that their respective case patients did not. Overall, the matching process was successful for 140 (93%) of the 150 total variables.

Clinical Features of Case Patients

The median duration of hospitalization from time of admission to the time of the first blood-culture isolation of VRE (onset of VRE bacteremia) was 21 days (range, 0–118 days; mean, 30 days). *E. faecium* was the species responsible for bacteremia in 24 patients (89%); the enterococcal isolate from three patients (11%) was not speciated. For all enterococcal isolates the MIC of vancomycin was ≥32 μg/mL, except for one patient's isolate, for which the MIC was 16 μg/mL. None of the isolates produced β-lactamase.

In 21 patients (78%) the bacteremia was unimicrobial. Five patients' VRE-positive blood cultures yielded one other organism (*Lactobacillus* species, *Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus aureus,* or α-hemolytic streptococci). One patient had *Escherichia coli* and vancomycin-sensitive *Enterococcus faecalis* isolated concomitantly with vancomycin-resistant *E. faecium.*

Of the 27 patients with VRE bacteremia, 24 (89%) had VRE colonization or infection at another site. Eighteen (67%) had VRE stool colonization, 9 (33%) had VRE isolated from the urine, and 5 (19%) had VRE isolated from the sputum. Fifteen patients (56%) were found to be colonized or infected prior to the development of bloodstream infection; thirteen (48%) of these had gastrointestinal colonization.

Table 2. Underlying diseases in the study population.

Disease category, underlying disease	No. of matched case/control pairs
Hematologic and neoplastic disorders	20
Acute lymphocytic leukemia	1
Acute myelocytic leukemia	13
Chronic myelocytic leukemia	3
Myelodysplastic syndrome	1
Lymphoma, AIDS-related	1
Breast carcinoma	1
Cardiopulmonary disorders	6
Acute myocardial infarction	1
Aortic valve disorder	1
Aspiration pneumonia	1
Staphylococcal pneumonia	1
Posttraumatic pulmonary insufficiency	1
Chronic obstructive pulmonary disease with respiratory failure	1
Chronic renal insufficiency	1
Total	27

Only one control patient had VRE isolated from the stool, and the remaining control patients had no sites of VRE infection or colonization. There was no significant difference in the proportion of case patients and controls with neutropenia (absolute neutrophil count, $<500/mm^3$) at the time of bacteremia (52% and 33%, respectively; $P = .13$).

VRE bacteremia was highly associated with the development of hypoperfusion abnormalities and end-organ dysfunction within 7 days of onset of bacteremia (22 [81%] of 27 patients; table 4). The most common hypoperfusion abnormality noted was mental-status alteration, which occurred in 21 (78%) of the patients. Twelve patients (44%) met the criteria for severe sepsis, and septic shock developed in an additional 10 (37%). Crude mortality was strongly correlated with the development of these two conditions: none of the 5 patients who had neither severe sepsis nor septic shock died, 8 of 12 (67%) who had severe sepsis died, and all 10 patients who had septic shock died ($P = .0002$).

Table 3. Surgical procedures in the study population.

Procedure	Cases:control (*n*:*n*)
Ethmoidectomy	1:0
Tracheostomy	5:4
Lung biopsy	1:0
Cardiac valve replacement	2:2
Coronary artery bypass grafting	2:2
Exploratory laparotomy	1:0
Cholecystectomy	1:0
Partial small-bowel resection	1:0
Liver biopsy	1:1
Total	15:9

Table 4. Hypoperfusion abnormalities and end-organ dysfunctions developing within 7 days of the onset of vancomycin-resistant enterococcal bacteremia ($n = 27$).

Condition	No. (%) of bacteremic patients
Mental status alteration(s)	21 (78)
Hypotension	10 (37)
Refractory hypotension	10 (37)
Oliguria	10 (37)
Acute renal failure	10 (37)
Lactic acidosis	3 (11)
Adult respiratory distress syndrome	4 (15)
Any hypoperfusion abnormality or end-organ dysfunction	22 (81)

There were no significant differences in the proportions of case patients vs. controls with regard to the development of ARDS (15% of cases vs. 4% of controls; $P = .38$), acute renal failure (37% vs. 19%; $P = .23$), or hypotension (52% vs. 26%; $P = .065$). There was a strong trend for required mechanical ventilation among case patients, although this finding was not statistically significant (52% vs. 22%; $P = .06$). There was no difference between the two groups in the need for hemodialysis (15% vs. 0%; $P = .13$). However, patients with VRE bacteremia were significantly more likely to require care in an ICU (56% of cases vs. 22% of controls; $P = .035$).

Mortality

The crude mortality among case patients was 67% (18 of 27), and among controls it was 30% (8 of 27) ($P = .01$; table 5). Thus, the attributable mortality (crude mortality among case patients minus crude mortality among controls) was 37% (95% CI, 10%–64%). The estimated risk ratio for death was 2.3 (95% CI, 1.2–4.1). Outcome was concordant for 13 of the matched pairs (11 lived and two died). The remaining 14 pairs had a discordant outcome (in six of these pairs, the case patient died).

The median interval from the first blood-culture isolation of VRE to death ($n = 18$) was 8.5 days (mean, 14 days; range, 0–77 days). The crude mortality among the patients with po-

Table 5. Crude mortality, attributable mortality, and relative risk of death associated with vancomycin-resistant enterococcal bacteremia.

Variable	Value	95% CI
Mortality rate: % (proportion) of patients		
Crude, among cases	66.7 (18/27)	...
Crude, among controls	29.6 (8/27)	...
Attributable*	37.1 (10/27)	10–64
Risk ratio	2.3	1.2–4.1

*$P = .01$, per McNemar test.

lymicrobial bacteremia was 67% (4 of 6), whereas only 1 of 6 matched controls (17%) died ($P = .25$).

There was no significant difference in length of stay between case patients and controls. Median length of stay was 31 days for case patients and 36 days for controls ($P = .47$). For the seven pairs of patients who both survived, median length of stay was 55 days (range, 20–75 days) for case patients and 36 days (range, 24–66 days) for controls ($P = .08$). There was no significant difference between the median length of stay of case patients and controls who had underlying hematologic or neoplastic diseases (30.5 days vs. 34.5 days; $P = .54$).

Discussion

Although enterococci are generally considered to be relatively nonvirulent pathogens, this study highlights the significant morbidity and mortality attributable to VRE bacteremia. Severe sepsis or septic shock, the most advanced stages of the inflammatory response to infection, developed in >80% of patients with VRE bacteremia. Moreover, mortality rates for these patients were extremely high. The 67% crude mortality rate for VRE-induced severe sepsis and the 100% crude mortality rate for VRE-induced septic shock are markedly higher than the rates reported by Rangel-Frausto et al. [22] for bloodstream infections in general (20% for severe sepsis and 46% for septic shock). However, most patients in the present study had underlying neoplastic diseases, and the rates of development of severe sepsis and septic shock with a high attendant crude mortality may not be generalizable to other populations.

With a historical cohort study design, we estimated that over one-third of patients in whom VRE bacteremia develops will die as a direct consequence of their bloodstream infection. Moreover, patients with VRE bacteremia are twice as likely as closely matched controls without VRE bacteremia to die during their hospitalization. In this study design the intensity of matching between case patients and controls eliminates to the greatest extent possible the influence of comorbid conditions.

The major weakness of this study is that case patients and control patients were not matched for severity of illness with a standardized tool (e.g., APACHE score) prior to the development of bacteremia. It is likely that the intensity of the matching process helped to crudely control for severity of illness, particularly the matching with regard to duration of hospitalization, surgical procedures, and specific clinical diagnosis. Although the overall success of the matching process was 93%, it was most difficult to match case patients and controls for surgical procedures (71% of the pairs were matched).

To place the mortality attributable to VRE bacteremia into perspective, it is useful to review the mortality attributable to other organism-specific bloodstream infections studied via a similar study design. Three such studies were described in the literature in the late 1980s. Landry and co-workers determined the mortality attributable to vancomycin-susceptible enterococcal bacteremia to be 31% [8]. The mortality attributable to coagulase-negative staphylococcal bacteremia was determined by Martin et al. to be 14% [23], and that to candidemia was found by Wey and colleagues to be 38% [24]. Thus, the mortality attributable to VRE bacteremia and candidemia is similar.

It is interesting that the finding of 37% mortality attributable to VRE bacteremia is similar to that previously observed for vancomycin-susceptible enterococcal bacteremia (31%) [8]. However, the crude mortality for both case patients and controls in that previous study was markedly lower (43% and 12%, respectively). It is noteworthy that ~75% of patients in the present study had an underlying malignancy, whereas only 16% of the patients in the prior study had a malignant condition.

The similarity in attributable mortality rates for vancomycin-resistant and vancomycin-susceptible bacteremia lends credence to the impression that strains of enterococci that are vancomycin-resistant are not inherently more virulent. Recall that the patients with bacteremia due to vancomycin-susceptible enterococci were treated and the patients with VRE bacteremia were not. Overall, no difference was observed in the median length of stay between those with and without VRE bacteremia. This may be because the length of stay was shorter for those who died of VRE bacteremia.

In conclusion, this study demonstrates the high crude and attributable mortality rates associated with VRE bacteremia and the intensity of the inflammatory response induced by this infection. These findings underscore the urgent need for a better understanding of the risk factors associated with these infections and the need for antimicrobial agents with potent activity against these pathogens.

References

1. Banerjee SN, Emori TG, Culver DH, et al. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. Am J Med **1991**;91(suppl 3B):86S–9S.
2. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev **1993**;6:428–42.
3. Garrison RN, Fry DE, Berberich S, Polk HC Jr. Enterococcal bacteremia: clinical implications and determinants of death. Ann Surg **1982**;196:43–7.
4. Klimek JJ, Ajemian E, Gracewski J, et al. Enterococcal infections in a large community hospital, with emphasis on bacteremia. Am J Infect Control **1980**;8:58–61.
5. Dougherty SH, Flohr AB, Simmons RL. ''Breakthrough'' enterococcal septicemia in surgical patients: 19 cases and a review of the literature. Arch Surg **1983**;118:232–8.
6. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore) **1988**;67:248–69.
7. Holm SE. Gram-positive microorganisms in sepsis. Scand J Infect Dis Suppl **1982**;31:68–77.
8. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to nosocomial enterococcal bacteremia: a controlled study. Am J Infect Control **1989**;17:323–9.
9. Centers for Disease Control and Prevention. Nosocomial enterococci resistant to vancomycin—United States, 1989–1993. MMWR Morb Mortal Wkly Rep **1993**;42:597–9.

10. Edmond MB, Ober JF, Weinbaum DL, et al. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis **1995**;20:1126–33.
11. 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.
12. Vasquez A, Lutfey M, Ticci L, Serrell F, Kreiswirth B, Simberkoff M. Clinical, microbiologic, and epidemiologic evaluation of vancomycin-resistant *Enterococcus faecium* [abstract no 852]. In: Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1993**:275.
13. Jones R, Forman W, O'Donnell J, Suh B. High mortality associated with vancomycin-resistant *Enterococcus* bacteremia [abstract no 846]. In: Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1993**:274.
14. Lam S, Singer C, Tucci V, Morthland VH, Pfaller MA, Isenberg HD. The challenge of vancomycin-resistant enterococci: a clinical and epidemiologic study. Am J Infect Control **1995**;23:170–80.
15. 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.
16. Wells CL, Juni BA, Cameron SB, et al. Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. Clin Infect Dis **1995**; 21:45–50.
17. Wakefield DS, Pfaller M, Ludke RL, Wenzel RP. Methods for estimating days of hospitalization due to nosocomial infections. Med Care **1992**; 30:373–6.
18. Spengler RF, Greenough WB III. Hospital costs and mortality attributed to nosocomial bacteremias. JAMA **1978**;240:2455–8.
19. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med **1992**;20:864–74.
20. Fleiss JL. The analysis of data from matched samples. In: Statistical methods for rates and proportions. 2nd ed. New York: John Wiley and Sons, **1981**:113–9.
21. Kleinbaum DG, Kupper L, Morgenstern H. Epidemiologic research: principles and quantitative methods. Belmont, California: Lifetime Learning Publications, **1982**:296–301, 388–9.
22. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. JAMA **1995**;273:117–23.
23. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia: mortality and hospital stay. Ann Intern Med **1989**;110: 9–16.
24. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: the attributable mortality and excess length of stay. Arch Intern Med **1988**;148:2642–5.