

Determinants of Vancomycin Resistance and Mortality Rates in Enterococcal Bacteremia

A Prospective Multicenter Study

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Background: *Enterococcus* species are major nosocomial pathogens and are exhibiting vancomycin resistance with increasing frequency. Previous studies have not resolved whether vancomycin resistance is an independent risk factor for death in patients with invasive disease due to *Enterococcus* species or whether antibiotic therapy alters the outcome of enterococcal bacteremia.

Objective: To determine whether vancomycin resistance is an independent predictor of death in patients with enterococcal bacteremia and whether appropriate antimicrobial therapy influences outcome.

Design: Prospective observational study.

Setting: Four academic medical centers and a community hospital.

Patients: All patients with enterococcal bacteremia.

Measurements: Demographic characteristics; underlying disease; Acute Physiology and Chronic Health Evaluation (APACHE) II scores; antibiotic therapy, immunosuppression, and procedures before onset; and antibiotic therapy during the ensuing 6 weeks. The major end point was 14-day survival.

Results: Of 398 episodes, 60% were caused by *E. faecalis* and 37% were caused by *E. faecium*. Thirty-seven percent of isolates exhibited resistance or intermediate susceptibility to vancomycin.

Twenty-two percent of *E. faecium* isolates showed reduced susceptibility to quinupristin–dalfopristin. Previous vancomycin use (odds ratio [OR], 5.82 [95% CI, 3.20 to 10.58]; $P < 0.001$), previous corticosteroid use (OR, 2.43 [CI, 1.22 to 4.86]; $P = 0.01$), and total APACHE II score (OR, 1.06 per unit change [CI, 1.02 to 1.10 per unit change]; $P = 0.003$) were associated with vancomycin-resistant enterococcal bacteremia. The mortality rate was 19% at 14 days. Hematologic malignancy (OR, 3.83 [CI, 1.56 to 9.39]; $P = 0.003$), vancomycin resistance (OR, 2.10 [CI, 1.14 to 3.88]; $P = 0.02$), and APACHE II score (OR, 1.10 per unit change [CI, 1.05 to 1.14 per unit change]; $P < 0.001$) were associated with 14-day mortality. Among patients with monomicrobial enterococcal bacteremia, receipt of effective antimicrobial therapy within 48 hours independently predicted survival (OR for death, 0.21 [CI, 0.06 to 0.80]; $P = 0.02$).

Conclusions: Vancomycin resistance is an independent predictor of death from enterococcal bacteremia. Early, effective antimicrobial therapy is associated with a significant improvement in survival.

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Enterococcus species have become increasingly prominent as etiologic agents of nosocomial bacteremia (1–9). Enterococcal bacteremia has a mortality rate of 42% to 73% (10, 11) and is common among debilitated patients and those with severe underlying illnesses (5, 6, 12–17). Enterococci have low-level resistance to penicillins, aminoglycosides, and clindamycin and are intrinsically resistant to cephalosporins. Enterococci may acquire resistance to additional antibiotics, including β -lactams, aminoglycosides, and glycopeptides (18). Resistance to multiple antibiotics, in particular vancomycin coupled with high-level ampicillin and aminoglycoside, has been reported with increasing frequency (19). At present, more than 20% of enterococci isolated from intensive care units exhibit vancomycin resistance. The addition of vancomycin resistance to high-level ampicillin and aminoglycoside resistance limits available therapeutic options (20).

To investigate the clinical implications of antibiotic resistance in enterococci, we instituted a prospective, multicenter observational study of outcome in patients with enterococcal bacteremia. We sought to determine 1) factors associated with infection with vancomycin-resistant enterococci (VRE), 2) factors predictive of death in patients with enterococcal bacteremia, 3) the effect of vancomycin resistance on mortality rates, and 4) the effect of antibiotic therapy on outcome.

METHODS

All patients with enterococcal bacteremia were hospitalized at the University of Pittsburgh Medical Center and the Veterans Affairs (VA) Medical Center (Pittsburgh, Pennsylvania), Detroit Medical Center and John D. Dingell VA Medical Center (Detroit, Michigan), Rush-Presbyterian-St. Luke's Medical Center (Chicago, Illinois), New England Medical Center (Boston, Massa-

chusetts), and William Beaumont Hospital (Royal Oak, Michigan). Clinical data were obtained from review of medical records. The institutional review boards of four participating institutions approved the study. At the fifth institution, the study was considered exempt from review because it involved confidential use of existing records and bacterial isolates.

Microbiology

Blood for culture was obtained by venipuncture or through central venous catheters. Enterococcal species were determined by using either VITEK (bioMérieux Vitek, Inc., Hazelwood, Missouri) or MicroScan (MicroScan, Inc., West Sacramento, California) systems according to the manufacturer's recommendations. Identification of species other than *E. faecalis* and *E. faecium* was confirmed as reported elsewhere (21). One of the authors standardized antimicrobial susceptibilities by using Etest strips (AB BIODISK North America, Inc., Piscataway, New Jersey). *Enterococcus faecium* isolates showing resistance or intermediate susceptibility to quinupristin–dalfopristin were tested by broth microdilution and disk diffusion to confirm reduced susceptibility.

If the isolate was unavailable, antimicrobial susceptibilities reported by the submitting microbiology laboratories were used. Minimum inhibitory concentration (MIC) breakpoints from the Ninth National Committee for Clinical Laboratory Standards (NCCLS) were used (22). Because imipenem MIC values for enterococci are not defined, NCCLS breakpoints for Enterobacteriaceae were used (22). Quality control was monitored by using *E. faecalis* American Type Culture Collection (ATCC) 29212. Nine enterococcal isolates displayed intermediate susceptibility to vancomycin (MIC, 8 to 16 $\mu\text{g}/\text{mL}$) but were considered resistant for the purposes of analysis.

Vancomycin resistance genotypes of selected clinical isolates were determined by using polymerase chain reaction (PCR) amplification with primers specific for intragenic sequences of the *vanA* and *vanB* genes (23, 24). Control strains included vancomycin-susceptible *E. faecalis* ATCC 29212, *E. faecium* BM4147 (*vanA*) (25), and *E. faecalis* V583 (*vanB*) (26).

For determination of aminoglycoside resistance genes, genomic DNA for PCR amplification was prepared with the InstaGene Matrix kit (BioRad Laboratories, Hercules, California) and PCR performed as re-

ported elsewhere (27). Aminoglycoside resistance genes detected included *aac(6')-Ie-aph(2'')-Ia* (28), *aph(2'')-Ic* (29), *aph(2'')-Id* (30), and *aph(2'')-Ib* (31).

Definitions

Clinically significant bacteremia was defined as isolation of enterococci in two or more separately obtained blood cultures or from a single blood culture and from a concomitant site of infection in a clinical scenario compatible with bacteremic infection (6). Endocarditis was defined by using the Duke criteria (32). Polymicrobial bacteremia was defined as isolation from blood culture of one or more additional species of bacteria concomitantly with enterococci (same blood culture or another blood culture within 24 hours of the initial blood culture yielding enterococci). A single concomitant isolation of another bacterial species was sufficient, except for isolation of coagulase-negative staphylococci, diphtheroids, α -hemolytic streptococci, and *Bacillus* species that required isolation from two blood cultures.

Length of hospitalization was defined as the time in days from hospital admission to development of clinically significant enterococcal bacteremia. Enterococcal bacteremia occurring 60 days or more from a previous episode in patients already enrolled was counted as a separate episode. The end point was survival at 14 days from the first positive blood culture. Patients discharged from the hospital before 14 days were considered survivors. Medical records were reviewed at entry, at 2 weeks, at 4 weeks, and at 6 weeks (or at time of discharge or death if earlier than 6 weeks). We collected information on patient demographic characteristics, underlying disease, Acute Physiology and Chronic Health Evaluation (APACHE) II scores at bacteremia onset, antibiotic use, use of glucocorticosteroids and other immunosuppressive drugs, and receipt of invasive devices and procedures in the 2 weeks before bacteremia onset. Antibiotic therapy during the 6 weeks after the onset of bacteremia was recorded. Beyond 6 weeks, patients were followed for evidence of relapse of bacteremia and for survival to discharge or death.

Immunosuppressive drugs included cyclosporine, cyclophosphamide, azathioprine, tacrolimus, methotrexate, and cytotoxic chemotherapy. Appropriate antibiotic therapy was defined as treatment with at least one antibiotic that had in vitro activity (as defined by Etest) against the enterococcal isolate, initiated within 48

Table 1. Proportion of Enterococcal Isolates Susceptible to Individual Antimicrobial Agents

Antimicrobial Agent	Enterococcus faecalis	Enterococcus faecium
	% (n/n)	
Vancomycin*	91 (218/239)	18 (26/148)
Ampicillin	97 (231/239)	13 (20/148)
High-level gentamicin†	63 (151/239)	40 (59/148)
Quinupristin–dalfopristin‡	–	78 (103/132)
Chloramphenicol	49 (112/229)	75 (106/141)
Doxycycline	36 (82/229)	50 (79/138)

* Of the 118 vancomycin-resistant isolates assayed, 68% (80 of 118) were *vanA*, 31% (37 of 118) were *vanB*, and 1 exhibited both genotypes.

† 168 isolates contained the bifunctional aminoglycoside resistance gene *aac(6′)-Ie-aph(2″)-Ia* (1 isolate had a gentamicin minimum inhibitory concentration [MIC] of 256 μg/mL), 2 contained the *aph(2″)-Ic* gene (gentamicin MIC, 384 μg/mL), 3 contained the *aph(2″)-Id* gene, and 5 contained the *aph(2″)-Ib* gene. Among the remaining isolates, gentamicin MICs were ≤48 μg/mL.

‡ *E. faecium* isolates.

hours of the initial positive enterococcal blood culture and continuing for at least 72 hours. Antibiotics considered potentially active included penicillin, ampicillin, ureidopenicillin, vancomycin, quinupristin–dalfopristin, chloramphenicol, doxycycline, and rifampin.

Statistical Analysis

For categorical variables, proportions were compared by using the Fisher exact test. Continuous variables were analyzed with the Mann–Whitney rank-sum test. Multivariate analysis was done by using logistic regression. Variables with a two-tailed *P* value of 0.05 were included in stepwise logistic regression models for vancomycin resistance and 14-day mortality. The initial bacteremic episode for each patient (*n* = 398) was used for the evaluation of risk factors for bacteremia caused by VRE. Patients who were alive 14 days after the onset of enterococcal bacteremia (*n* = 321) were evaluated for factors associated with microbiological failure. Statistical analysis of the data was performed by using the Prophet system (MarketMiner, Inc., Charlottesville, Virginia) and Epistat (Epistat Services, Richardson, Texas).

RESULTS

Enterococcal Bacteremia

We studied hospitalized patients 16 years of age or older with clinically significant hospital- or community-acquired enterococcal bacteremia. From February 1995 through March 1997, 391 consecutive patients from five participating institutions were entered into the study.

An additional 9 patients from Pittsburgh were entered into the study over a 6-month period (October 1998 through March 1999) to increase the total number of patients to 400. These patients were consecutive and unselected. Two patients younger than 16 years of age were excluded, leaving 398 patients for evaluation.

Eighty-nine patients were from the University of Pittsburgh Medical Center and the VA Medical Center, 97 were from Rush-Presbyterian-St. Luke’s Medical Center, 95 were from the Detroit Medical Center and John D. Dingell VA Medical Center, 61 were from New England Medical Center, and 56 were from the William Beaumont Hospital.

Blood cultures yielded 398 enterococcal isolates. Of these, 60% (239 of 398) were *E. faecalis* and 37% (148 of 398) were *E. faecium*. Three percent (10 of 398) of the isolates belonged to the less common enterococcal species, which include *E. avium*, *E. casseliflavus*, *E. durans*, *E. gallinarum*, and *E. raffinosus*. The species of one isolate could not be identified. Seventeen recurrences were seen at 60 or more days after the initial bacteremia. Of these, 14 were caused by the same enterococcal species as the initial episode. In 12 of these 14 episodes, the pair of isolates had the same susceptibilities to vancomycin.

Overall, 35% of the 398 enterococcal isolates were resistant to vancomycin (MIC ≥ 32 μg/mL), 63% were susceptible to vancomycin (MIC ≤ 4 μg/mL), and 2% displayed intermediate susceptibility (MIC, 8 to 16 μg/mL). **Table 1** shows the susceptibility patterns of the two major *Enterococcus* species. Eight percent of the *E. faecalis* isolates were resistant to vancomycin, 91% were susceptible, and 1% displayed intermediate susceptibility. In contrast, 80% of the *E. faecium* isolates were resistant to vancomycin, 18% were susceptible, and 2% displayed intermediate susceptibility. Of the 11 isolates of other species, none were resistant to vancomycin, 73% (8 of 11) were susceptible to vancomycin, and 27% (3 of 11) displayed intermediate susceptibility to vancomycin.

Three percent of *E. faecalis* isolates were resistant to ampicillin, and 37% were resistant to high-level gentamicin. Among isolates of *E. faecium*, 87% were resistant to ampicillin, 60% were resistant to high-level gentamicin, and 22% showed reduced susceptibility to quinupristin–dalfopristin. Fourteen percent (18 isolates) showed intermediate susceptibility (MIC, 2 μg/mL) and

8% (11 isolates) were resistant ($\text{MIC} \geq 4 \mu\text{g/mL}$) to quinupristin–dalfopristin. Twenty-four of the 29 isolates with reduced susceptibility to quinupristin–dalfopristin were subsequently tested by microbroth dilution and disk diffusion; in each case, the Etest results were confirmed. *Enterococcus faecium* isolates with diminished quinupristin–dalfopristin susceptibility occurred at all five centers. Isolates of *E. faecalis* are almost always resistant to quinupristin–dalfopristin and were therefore not tested in our study.

Polymicrobial bacteremia was demonstrated in 45%

of all patients (179 of 398), 38% (56 of 147) of patients with VRE bacteremia, and 49% (123 of 251) of patients with vancomycin-susceptible enterococcal bacteremia ($P = 0.03$). Fifty percent of patients with *E. faecalis* bacteremia (120 of 239) had polymicrobial bacteremia compared with 36% (54 of 148) of patients with *E. faecium* bacteremia ($P = 0.007$).

Patient Characteristics

Sixty percent of the patients (237 of 398) were men. The mean age ($\pm\text{SD}$) was 57.9 ± 15.4 years among

Table 2. Demographic Features and Characteristics of Patients with Enterococcal Bacteremia*

Variable	Patients with Vancomycin-Resistant Bacteremia (n = 147)†	Patients with Vancomycin-Susceptible Bacteremia (n = 251)	P Value	Odds Ratio (95% CI)
Demographic characteristics				
Men, %	59	60	NS	0.98 (0.63–1.51)
Mean age \pm SD, y	57.9 \pm 15.4	61.1 \pm 17.7	0.03	
Comorbid illness, %				
Solid cancer	20	27	NS	0.98 (0.41–1.15)
Hematologic malignancy	20	5	<0.001	4.96 (2.32–10.7)
Solid organ transplant	23	8	<0.001	4.10 (2.22–7.56)
Bone marrow transplant	4	2	NS	1.76 (0.56–5.55)
Diabetes mellitus	32	24	NS	1.50 (0.95–2.37)
Cirrhosis	21	8	<0.001	3.31 (1.79–6.10)
Chronic obstructive pulmonary disease	18	23	NS	0.73 (0.45–1.24)
Atherosclerotic heart disease	29	28	NS	1.02 (0.65–1.61)
Valvular heart disease	7	8	NS	0.99 (0.46–2.18)
Kidney disease	42	29	0.006	1.85 (1.20–2.83)
Kidney disease requiring dialysis	27	16	0.006	2.00 (1.23–3.29)
HIV infection	3	5	NS	0.57 (0.18–1.79)
Ethanol abuse	18	16	NS	1.20 (0.70–2.06)
Intravenous drug use	4	6	NS	0.67 (0.26–1.58)
Neurologic disease	35	37	NS	0.94 (0.61–1.44)
Pressure ulcer	20	12	0.035	1.91 (1.08–3.38)
Immunosuppressive therapy, %				
Corticosteroids	50	18	<0.001	4.73 (2.98–7.48)
Other agents‡	39	12	<0.001	4.88 (2.94–8.08)
Invasive devices or procedures within 2 weeks of bacteremia, %				
Vascular catheter	92	80	0.002	2.76 (1.42–5.38)
Urinary catheter	67	56	0.04	1.61 (1.05–2.46)
Mechanical ventilation	48	33	0.003	1.96 (1.29–2.98)
Bronchoscopy	8	4	NS	1.95 (0.83–4.53)
Endoscopy	14	14	NS	1.01 (0.56–1.80)
Cystoscopy	1	3	NS	0.49 (0.10–2.37)
Abdominal drain	27	18	0.056	1.62 (0.99–2.64)
Gastric tube	49	40	0.059	1.50 (0.99–2.27)
Abdominal or biliary surgery	24	18	NS	1.51 (0.92–2.47)
Other				
Previous antibiotic use, %	89	62	<0.001	5.0 (2.80–8.91)
Intensive care unit, %	52	34	<0.001	2.01 (1.36–3.12)
Previous hospitalization, %	49	34	0.004	1.88 (1.24–2.87)
Median length of hospitalization, d	17	3	<0.001	
Median APACHE II score	20.5	16	<0.001	

* APACHE = Acute Physiology and Chronic Health Evaluation; NS = not significant.

† Includes isolates displaying intermediate susceptibility to vancomycin.

‡ Includes tacrolimus, cyclosporine, azathioprine, methotrexate, cytotoxic chemotherapeutic agents.

Table 3. Antibiotic Treatment within 14 Days before Onset of the Initial Episode of Enterococcal Bacteremia

Antibiotic	Patients with Vancomycin-Resistant Bacteremia (n = 147), %*	Patients with Vancomycin-Susceptible Bacteremia (n = 251), %	P Value	Odds Ratio (95% CI)
Penicillins	38	24	0.003	1.96 (1.23–3.12)
Vancomycin	63	16	<0.001	9.08 (5.42–15.07)
Aminoglycosides	39	17	<0.001	3.06 (1.87–5.02)
Cephalosporins	29	18	0.012	1.89 (1.14–3.18)
Imipenem	18	6	<0.001	3.38 (1.65–6.99)
Quinolones	35	18	<0.001	2.43 (1.48–3.99)
Metronidazole	27	10	<0.001	3.37 (1.98–6.08)
Chloramphenicol	5	0	<0.001	Not calculable
Quinupristin–dalfopristin	1	0.4	Not significant	0.16 (0.03–1.27)

* Includes isolates displaying intermediate susceptibility to vancomycin.

patients with VRE bacteremia and 61.1 ± 17.7 years among patients with vancomycin-susceptible enterococcal bacteremia ($P = 0.03$). Ages ranged from 17 to 98 years (median, 61 years). In addition, patients with VRE bacteremia were significantly more likely to be immunosuppressed because of receipt of glucocorticosteroids or other medications, which included tacrolimus (formerly FK-506), cyclosporine, and azathioprine (Table 2). Patients with VRE bacteremia were more likely to have underlying comorbid illnesses, to have had invasive procedures in the previous 2 weeks, and to have been admitted to intensive care units. The median length of hospitalization for patients with VRE bacteremia was 17 days at the time of onset of initial enterococcal bacteremia, compared with 3 days for patients with vancomycin-susceptible disease ($P < 0.001$). Patients with VRE bacteremia had a median APACHE II score of 20.5, compared with a median score of 16 for patients with vancomycin-susceptible disease ($P < 0.001$). Patients with VRE bacteremia were significantly more likely to

have received antibiotics within 14 days of onset of initial enterococcal bacteremia (Table 3).

By multivariate analysis, bacteremia with a VRE isolate was significantly associated with previous receipt of vancomycin within 14 days of bacteremia (OR, 5.82 [95% CI, 3.20 to 10.58]; $P < 0.001$), previous receipt of glucocorticosteroids within 14 days of bacteremia (OR, 2.43 [CI, 1.22 to 4.86]; $P = 0.01$), and severity of illness as assessed by total APACHE II score (OR, 1.06 per unit change [CI, 1.02 to 1.10 per unit change]; $P = 0.003$).

Primary Site of Infection

Vascular catheters were the most common site of infection among patients with VRE bacteremia and the second most common site of infection among patients with vancomycin-susceptible enterococcal bacteremia, although the difference was not statistically significant. Twenty percent of patients with VRE bacteremia (29 of

Table 4. Factors Associated with 14-Day Mortality in Patients with Enterococcal Bacteremia*

Variable	Patients Who Survived	Patients Who Died	P Value	Odds Ratio (95% CI)
Previous hospitalization, % (n/n)	34 (109/321)	60 (46/77)	<0.001	2.93 (1.76–4.88)
Intensive care unit, % (n/n)	36 (114/321)	62 (48/77)	<0.001	2.96 (1.77–4.96)
Hematologic malignancy, % (n/n)	8 (25/321)	21 (16/77)	0.003	3.10 (1.56–6.16)
Immunosuppressive therapy, % (n/n)	20 (64/321)	32 (25/77)	0.021	1.97 (1.13–3.42)
Vascular catheter, % (n/n)	82 (264/321)	94 (72/77)	0.014	3.11 (1.20–8.05)
Urinary catheter, % (n/n)	55 (178/321)	79 (61/77)	<0.001	3.06 (1.69–5.54)
Mechanical ventilation, % (n/n)	32 (104/321)	64 (49/77)	<0.001	3.65 (2.17–6.14)
Gastric tube, % (n/n)	39 (125/321)	61 (47/77)	<0.001	2.49 (1.49–4.15)
Previous vancomycin, % (n/n)	28 (91/321)	55 (42/77)	<0.001	3.03 (1.82–5.05)
Vancomycin resistance, % (n/n)	31 (98/321)	64 (49/77)	<0.001	4.04 (2.40–6.81)
Median length of hospitalization, d	6	18	<0.001	
Median APACHE II score	16	23	<0.001	

* APACHE = Acute Physiology and Chronic Health Evaluation.

Table 5. Factors Associated with 14-Day Mortality in Patients Alive 48 Hours after Onset of Monomicrobial Enterococcal Bacteremia

Variable	Patients Who Survived	Patients Who Died	P Value	Odds Ratio (95% CI)
Previous hospitalization, % (n/n)	34 (59/174)	65 (22/34)	0.001	3.57 (1.56–8.30)
Intensive care unit, % (n/n)	30 (53/174)	71 (24/34)	<0.001	5.48 (2.30–13.29)
Hematologic malignancy, % (n/n)	10 (18/174)	26 (9/34)	0.02	3.12 (1.15–8.39)
Cirrhosis, % (n/n)	13 (23/174)	29 (10/34)	0.04	2.74 (1.06–6.97)
Vascular catheter, % (n/n)	80 (139/174)	94 (32/34)	0.05	4.03 (0.88–16.00)
Urinary catheter, % (n/n)	49 (84/174)	79 (27/34)	0.001	4.13 (1.61–11.06)
Mechanical ventilation, % (n/n)	30 (52/174)	68 (23/34)	<0.001	4.91 (2.09–11.65)
Gastric tube, % (n/n)	32 (56/174)	62 (21/34)	0.002	3.40 (1.49–7.82)
Previous vancomycin, % (n/n)	30 (52/174)	62 (21/34)	0.001	3.79 (1.66–8.73)
Previous imipenem, % (n/n)	7 (12/174)	26 (9/34)	0.002	4.86 (1.68–14.03)
Vancomycin resistance, % (n/n)	32 (56/174)	76 (26/34)	<0.001	6.84 (2.74–17.66)
High-level gentamicin resistance, % (n/n)	46 (80/174)	68 (23/34)	0.02	2.46 (1.06–5.76)
Appropriate antibiotic therapy, % (n/n)	55 (96/174)	18 (6/34)	<0.001	0.174 (0.06–0.47)
Median length of hospitalization, d	6	13	0.002	
Median APACHE II score	16	22	<0.001	

* APACHE = Acute Physiology and Chronic Health Evaluation.

147) had infection at an abdominal site other than the biliary tract, compared with 4% (10 of 251) of patients with vancomycin-susceptible enterococcal bacteremia ($P < 0.001$). Patients with VRE bacteremia were as likely to have definitive evidence of infective endocarditis (3% [4 of 147]) as were patients with vancomycin-susceptible enterococcal bacteremia (3% [8 of 251]). Patients with endocarditis were more likely to have prosthetic heart valves (17% [2 of 12] vs. 1.3% [5 of 386]; $P = 0.016$) and were less likely to have indwelling intravascular lines (25% [3 of 12] vs. 52% [202 of 386]; $P = 0.062$) than were the remaining patients. No significant differences were seen with regard to skin, wound, or pulmonary sites of infection between patients with VRE bacteremia and vancomycin-susceptible enterococcal bacteremia. The source of bacteremia was unknown in 74 cases (22 in the group with VRE infection and 52 in the group with vancomycin-susceptible enterococcal infection).

Outcome

The overall mortality rate was 19% (77 of 398) at 14 days; the 117 patients discharged alive by day 14 were considered survivors. Factors significantly associated with 14-day mortality by univariate analysis are shown in Table 4. By multivariate analysis, the significant independent risk factors of 14-day mortality were underlying hematologic malignancy (OR, 3.83 [CI, 1.56 to 9.39]; $P = 0.003$), vancomycin-resistant isolates (OR, 2.10 [CI, 1.14 to 3.88]; $P = 0.02$), and severity of

illness as assessed by APACHE II score (OR, 1.10 per unit change [CI, 1.05 to 1.14 per unit change]; $P < 0.001$). The mortality rate in patients with endocarditis (17% [2 of 12]) was similar to that of all patients; however, 6 patients (2 with VRE infection) died before discharge. Bacteriologic failure, defined as enterococcal bacteremia recurring 5 to 60 days after the initial episode, occurred in 16 patients. Seventy-five percent of the isolates (12 of 16) were vancomycin resistant, and 25% (4 of 16) were vancomycin susceptible ($P = 0.001$).

Clinical Outcome: Effect of Appropriate Therapy

To specifically examine the effects of treatment of enterococcal bacteremia, we performed a separate analysis that excluded patients with polymicrobial bacteremia. Monomicrobial enterococcal bacteremia was identified in 219 patients. Of these, 11 died or were discharged within 48 hours of bacteremia onset, leaving 208 patients for evaluation. The 14-day mortality rate was 16%. Factors significantly associated with 14-day mortality in this subgroup of patients are presented in Table 5. Of the patients surviving 14 days, 55% (96 of 174) received appropriate antimicrobial therapy. In contrast, among those patients who died, only 18% (6 of 34) received appropriate therapy ($P < 0.001$). By multivariate analysis, APACHE II score was independently associated with mortality (OR, 1.10 per unit change [CI, 1.03 to 1.17]; $P = 0.003$). Receipt of appropriate antibiotic therapy had a protective effect (OR, 0.21 [CI, 0.06 to 0.80]; $P = 0.02$).

DISCUSSION

In our prospective, multicenter observational study, enterococcal bacteremia with a vancomycin-resistant strain was an independent predictor of death. Appropriate antibiotic therapy initiated within 48 hours was a significant independent predictor of survival. Thus, our results are compatible with the hypotheses that vancomycin resistance is an independent contributor to death in patients with enterococcal bacteremia and that timely administration of an active antimicrobial agent improves survival.

Previous studies have failed to demonstrate that vancomycin resistance in enterococci is an independent predictor of outcome (14, 16, 33, 34). One study showed that vancomycin resistance was an independent predictor of death in liver transplant recipients, but these results might not be applicable to a heterogeneous patient population such as ours (35). The benefit of appropriate antibiotic therapy for enterococcal bacteremia has been widely disputed in the literature. Several investigators have shown that therapy for enterococcal bacteremia with bacteriostatic antibiotics either alone or in combination results in lower mortality rates than treatment with inappropriate drugs (5, 9, 36). Others, however, have not demonstrated any advantage (2, 4, 7, 8, 12, 37, 38).

These previous studies were retrospective, did not uniformly adjust for severity of illness, and did not always differentiate between clinically significant bacteremia and transient bacteremia or blood culture contamination. To our knowledge, our study is the largest prospective study of enterococcal bacteremia reported to date. It is multi-institutional and reflects a broad spectrum of patients. Major hypotheses and clinical end points were defined a priori. We used a predetermined, uniform end point of survival at 14 days. This method of determining outcome eliminates potential bias in assignment of cause of death, which is particularly problematic in patients with many comorbid conditions. Our method of determining outcome has been validated in previous prospective studies of bacteremia (39–41). Furthermore, our definition of significant bacteremia ensured that the patients studied had true infection rather than transient bacteremia or blood culture contamination (6, 36, 42).

At present, the optimal therapy for VRE bacteremia

is uncertain (34, 43–45). The streptogramin quinupristin–dalfopristin is a promising agent (45). Twenty-one of the patients included in our study received quinupristin–dalfopristin for treatment of VRE bacteremia. During the period of the study, however, this combination was available only through investigational use protocols. As a consequence, it was administered relatively late in the course, a mean of 6.2 days after the onset of bacteremia. Thus, its efficacy could not be assessed according to our definition of appropriate antimicrobial therapy. It is notable that 22% of *E. faecium* isolates in our study were resistant or displayed intermediate susceptibility to quinupristin–dalfopristin on initial testing, indicating that resistance to this agent may be a significant limiting factor in treatment of VRE bacteremia. Emergence of increased resistance to quinupristin–dalfopristin during therapy has been observed (35, 46).

Most VRE isolates are susceptible to linezolid (47), a recently approved agent. To date, the reported clinical experience with linezolid in the treatment of enterococcal bacteremia is limited, but it may prove to be useful in cases of quinupristin–dalfopristin resistance or failure. Other potentially useful agents, such as daptomycin, are available only through clinical protocols or compassionate use programs.

Our results have important implications for clinical practice. Bacteremia with VRE predicts a poor outcome. However, we note that the occurrence of VRE infection may be reduced by 1) reducing inappropriate vancomycin use to limit the selection of glycopeptide-resistant strains and 2) following appropriate infection control practices to prevent VRE dissemination (48).

Because delayed or inappropriate therapy is associated with death in enterococcal bacteremia, early therapy with one of the newer agents, such as quinupristin–dalfopristin or linezolid, may improve survival in patients with VRE bacteremia. We have identified clinical factors associated with an increased risk for VRE infection, including previous receipt of vancomycin, previous receipt of glucocorticoids, and relatively high acute severity of illness (median APACHE II score, 20.5). Patients at high risk for VRE infection may benefit by inclusion of an agent active against VRE in the antimicrobial regimen as soon as gram-positive cocci morphologically compatible with enterococci are identified in blood culture. The regimen should then be modified as soon as identification and susceptibility testing

are completed. This would permit agents active against VRE to be administered 24 to 48 hours earlier than with the alternate strategy of waiting until culture and susceptibility results are finalized. Whether this strategy will in fact reduce death due to VRE bacteremia should be the subject of future controlled trials.

In conclusion, we found that vancomycin resistance is an independent predictor of death in patients with enterococcal bacteremia. Timely administration of an antimicrobial agent active in vitro against the infecting strain is associated with survival. Therefore, control of spread of VRE and availability of effective therapeutic agents may decrease death from enterococcal bacteremia.

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