MAJOR ARTICLE

Attributable Mortality Rate and Duration of Hospital Stay Associated with Enterococcal Bacteremia

F. J. Caballero-Granado,[1] B. Becerril,[2] L. Cuberos,[2] M. Bernabeu,[1] J. M. Cisneros,[1] and J. Pachón[1]

[1]Servicio de Enfermedades Infecciosas and [2]Servicio de Microbiología, Hospital Universitario "Virgen del Rocío," Seville, Spain

The mortality rate of patients with cases of enterococcal bacteremia is high, although it has often been related to the patients' underlying conditions rather than to the infection itself. To analyze the attributable prognosis of enterococcal bacteremia (assessed by its attributable mortality rate and duration of hospital stay), a prospective, matched case-control study was done. All adults with an episode of enterococcal bacteremia without endocarditis were included. A control patient was randomly selected for every case patient and matched by sex, age and hospital ward. Univariate and multivariate analyses were performed. A total of 122 pairs were included, and incidence of enterococcal bacteremia was 2.3 episodes/1000 discharges. Crude 30-day mortality rates for case patients and control patients were 23% and 17%, respectively ($P = .29$); thus, the estimated attributable mortality rate was 6% (95% confidence interval, −4% to 16%). The mean duration of hospital stay of case patients and control patients were 38 and 17 days, respectively ($P < .001$); thus, the estimated attributable duration of hospital stay was 21 days (95% CI, 7–32 days). Enterococcal bacteremia without endocarditis does not increase risk of death by itself but extends the duration of hospital stay of patients who develop it.

Enterococcus species are expected to cause greater problems for clinicians in the near future. The incidence of enterococcal infections, mainly hospital-acquired, has increased over the past 2 decades [1, 2], and isolates with novel mechanisms of acquired resistance to antimicrobials are more and more frequent [3]. Furthermore, enterococci have a great capacity for transmitting these resistance mechanisms to other species and even other genera [4]. One of the more frequent and more clinically important manifestations of enterococcal infection is bacteremia [2]. Although the clinical features, prognosis, and treatment of enterococcal endocarditis are well established, the morbidity and mortality rates associated with enterococcal bacteremia without endocarditis have roused a strong controversy in recent years. Nearly all studies that have analyzed the mortality rate associated with enterococcal bacteremia have been retrospective cohort studies and have reported very disparate crude mortality rates (13%–68%) [5–12] and related mortality rates (2%–43%) [6, 8–11, 13–15]. Just one comparative study has been done to date [16].

The aim of the present study was to determine the prognosis attributable to enterococcal bacteremia by analysis of its attributable mortality rate and attributable duration of hospital stay.

Received 18 April 2000; revised 12 July 2000; electronically published 7 February 2001.

Reprints or correspondence: Dr. F.J. Caballero-Granado, Servicio de Enfermedades Infecciosas, Hospital Universitario "Virgen del Rocío," Avda. de España No. 4, 9th Floor, 11205 Algeciras, Cádiz, Spain (fjcaba@teleline.es).

Clinical Infectious Diseases 2001; 32:587–94

1058-4838/2001/3204-0010$03.00

PATIENTS AND METHODS

Design of the study. Adults with clinically signif-

icant enterococcal bacteremia (case patients) admitted to "Virgen del Rocío" University Hospital (Seville, Spain) were studied in a prospective, matched, case-control study. This is a tertiary hospital with 1725 beds, 2 adult intensive care units (ICUs), a severe burn unit, and active programs for solid organ transplantation (except for lung transplantation) and bone marrow transplantation.

Only the first episode was analyzed for those patients with >1 episode of bacteremia. Transient episodes and patients with enterococcal endocarditis were excluded. A control patient was randomly selected for each case patient. A control patient was defined as the first patient for whom a blood culture was requested after one was requested for the patient with enterococcal bacteremia, as documented in the Microbiology Laboratory register of entry. The control patient also had to meet the following criteria: negative results of blood culture during hospital stay, age within 1 decade of the patient with enterococcal bacteremia, the same sex as the patient with enterococcal bacteremia, and hospitalization on the same ward as the patient with enterococcal bacteremia (medical wards, surgical wards, and ICUs).

Pairing according to hospitalization wards allowed us to obtain homogeneous case and control groups with respect to type and number of manipulations. This does not imply that case patients and control patients had similar underlying diseases. In fact, we did not pair case patients and control patients by duration of hospital stay before development of enterococcal bacteremia nor by underlying diseases so that we could consider these variables as potential risk factors. Thus, we sought to answer the question about the importance of the underlying diseases and prior hospitalization for the prognosis of patients with enterococcal bacteremia [6, 13, 17].

Case patients and control patients were followed until discharge or death. Data were collected from case patients and control patients by a previously designed form. The form gathered epidemiological, microbiological, and clinical data, and information on prognostic features: Epidemiological data included the following: sex, age, hospitalization ward (medical wards, surgical wards, or ICUs), means of acquisition (community or nosocomial), exogenous risk factors for acquiring the bacteremia, underlying diseases and their severity. Microbiological data included the following: mono- or polymicrobial etiology, enterococcal species isolated, its susceptibility to ampicillin, imipenem, ciprofloxacin, vancomycin, and teicoplanin, and the presence or absence of high-level aminoglycoside resistance. Clinical data included the following: source of the bacteremia, severity of illness, and antimicrobial therapy. Information collected about prognostic features included risk of death and duration of hospital stay. Vascular catheter, urinary catheter, nasogastric tube, mechanical ventilation, parenteral nutrition, and prior stay in ICUs were considered to be exogenous risk factors for acquiring enterococcal bacteremia when they were present at the onset of the bacteremia or had been in the previous 72 h. Surgical treatments and prior use of antimicrobials were assessed if they were present in the 14 days before the onset of bacteremia.

The sample size was adjusted so the study was able to detect a difference in mortality rates of $\geqslant$17% between patients with and without enterococcal bacteremia (RR of 1.96). The respective α and β errors selected were 0.05 and 0.2. Thus, a minimum of 116 pairs was needed [18].

Definitions. The requests for blood cultures were made by the physician responsible for each case and control patient. Isolation and identification of *Enterococcus* species were done by customary methods [19]. Definitive identification was done and antimicrobial susceptibility determined by the MicroScan system with PosCombo type 4I panels (Dade International).

An episode of bacteremia was defined as the isolation of $\geqslant$1 organism from $\geqslant$1 culture of blood samples from a patient, under circumstances in which clinical evidence suggested a common source and the times of isolation were not separated by an asymptomatic period when the patient was not receiving antibiotic treatment. When the common source was unknown or multiple sources were evident, any positive blood culture result obtained within 48 h of another positive blood culture results was considered to represent the same bacteremic episode [20].

Clinically significant bacteremia was defined as an episode of bacteremia in a patient in whom clinical evidence of infection existed for $\geqslant$8 h [20]. If signs or symptoms lasted <8 h, this episode was considered to be transient and was excluded.

An episode of bacteremia was considered to be hospital-acquired when the onset occurred 48 h after admission, with no evidence that the infection had been present previously [21]. In any other circumstances, the infection was considered to be community-acquired.

Microbiological and clinical criteria were used to define the source or sources of each case of bacteremia [21]. The microbiological criterion was isolation of the same *Enterococcus* species as was found in results of blood cultures from another site within the time corresponding to the episode of bacteremia; the clinical criteria were symptoms and clinical signs (identified on the basis of interview, physical examination, nonmicrobiological complementary tests made within the time corresponding to the episode of bacteremia, and no contrary evidence) that indicated the site that was the probable source, even if microbiological samples from those sites were absent. When clinical and microbiological criteria did not allow for the determination of the source of the bacteremia, it was considered to be of unknown origin [21].

Severity of the underlying diseases was classified according to the criteria of McCabe and Jackson [22]. A patient was

considered to have diabetes mellitus when a concentration of glucose in plasma of >140 mg/dL was noted on >1 occasion when the patient had an empty stomach. Chronic renal failure was defined as having a creatinine level in plasma of >2 mg/dL and data suggesting that it was a chronic disturbance (i.e., confirmation of its previous existence, normocytic normochromic anemia, renal atrophy, and renal osteodystrophy). A patient was considered to have cirrhosis when that patient had a defined diagnosis (i.e., with diagnostic liver biopsy) or a probable diagnosis (i.e., with clinical and analytical data suggesting chronic liver disease, hepatocellular dysfunction, and portal hypertension). Neutropenia was defined as a polymorphonuclear leukocyte count of <1000/μL.

Severity of illness was classified according to the definitions recommended by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine (sepsis, severe sepsis, and septic shock) [23]. Patients with sepsis (not severely ill or without hemodynamic compromise) were compared with those with severe sepsis or septic shock (with hemodynamic compromise or severely ill).

Antimicrobial treatment was considered to be appropriate when the patients received at least 48 h of iv doses of an antimicrobial agent active in vitro against the organism isolated in the blood culture. In the case of *Enterococcus* species, these included penicillins, ureidopenicillins, carbapenems, glycopeptides, and quinolones in monotherapy or associated with aminoglycosides. In the remaining circumstances, the antimicrobial therapy was considered to be inappropriate [24].

Crude outcome of the enterococcal bacteremia was considered to be the mortality rate of patients with enterococcal bacteremia during the first 30 days after the onset of the enterococcal bacteremia (30-day mortality rate), regardless of the cause of the death. The overall mortality rate during the whole duration of hospital stay (in-hospital mortality rate) was noted but not analyzed, because deaths occurring >30 days after the onset of enterococcal bacteremia were likely not related to the infection.

The attributable mortality rate of enterococcal bacteremia was defined as the difference between the crude mortality rate of the patients with enterococcal bacteremia and that of the control group [18].

To estimate the attributable duration of hospital stay, the following periods were analyzed: for case patients, the time from the first positive result of blood culture until discharge; for control patients, the period from the date of the blood culture by which each control patient was included in the study until the discharge. Attributable duration of hospital stay was defined as the mean of the differences between these periods of the respective case patients and control patients. Patients who died during the first 30 days after the onset of the enterococcal bacteremia and their matched control patients were excluded for this analysis. Otherwise, attributable duration of hospital stay would be shortened.

Statistical analysis. Relationships among epidemiological, microbiological, and clinical features with respect to 30-day mortality rates were analyzed by a univariate analysis. The χ^2 test was used to compare qualitative variables (or 2-tailed Fisher's exact test when some expected values were <5), and RRs with their respective 95% CIs were estimated. The Mann-Whitney *U* test was used to analyze quantitative variables. Comparisons among case patients and control patients were made by use of the McNemar χ^2 test for dichotomous qualitative variables and the Wilcoxon signed rank test for quantitative ones. A significance level of .05 was used in the statistical calculations [25–27]. A 95% CI for crude mortality rate of the enterococcal bacteremia was estimated [27]. Then, variables related to the crude mortality rate were introduced in a multivariate analysis through a forward stepwise multiple logistic regression model, by means of the Wald test, to determine independent associations. Multicolinearity among variables was assessed. A significance level of .05 was selected [25–27]. EpiInfo (version 5; Centers for Disease Control and Prevention, Atlanta) and SPSS (version 8.0) software were used for all calculations.

RESULTS

Description of the series. Included in the study were 122 consecutive patients who had episodes of clinically significant enterococcal bacteremia during an 18-month period (July 1993 to January 1995) and their matched control patients. The incidence of enterococcal bacteremia at this time was 2.3 cases per 1000 discharges. All pairs fit the matching criteria previously defined. Another 12 patients with enterococcal bacteremia were not included because they had transient episodes. A total of 103 episodes (84%) were hospital-acquired. When comparing case patients and control patients, there were no differences regarding the severity of the underlying conditions ($P = .34$), and only cirrhosis, neutropenia, and organ transplantation were more frequent in case patients than in the control group (table 1).

A total of 99 episodes (81%) of bacteremia were caused by *Enterococcus faecalis,* 19 (16%) by *Enterococcus faecium,* and 4 (3%) by *Enterococcus durans.* Thirty-six of them (30%) were polymicrobial, and gram-negative rods were the more frequently associated organisms (20 episodes [56%]). Gram-positive cocci were associated with 12 episodes (33%), gram-positive cocci and gram-negative rods with 2 episodes (6%), *Candida tropicalis* with 1 episode (2.5%), and *Candida albicans* plus *Escherichia coli* with 1 (2.5%). Antimicrobial susceptibility was determined for 117 isolates (table 2). Susceptibility of another 5 isolates was tested by use of an agar dilution method,

Table 1. Epidemiological features of case patients with enterococcal bacteremia and control patients.

Type of variable, characteristic	Case patients	Control patients	*P*	OR (95% CI)
Matched variables				
Age, years, mean ± SD	56.6 ± 18.7	56.3 ± 17.9	.25[a]	
Sex				
Male	71 (58)	71 (58)	1	
Female	51 (42)	51 (42)		
Hospitalization ward				
Medical	64 (52.5)	64 (52.5)		
Surgical	15 (12.3)	15 (12.3)	1	
ICU	43 (35.2)	43 (35.2)		
Unmatched variables				
McCabe classification of underlying disease				
Nonfatal	69 (56.6)	77 (63.1)		
Ultimately fatal	50 (41)	43 (35.2)	.34[b]	
Rapidly fatal	3 (2.4)	2 (1.6)		
Underlying disease				
None	41 (33.6)	51 (41.8)	.22	
Diabetes mellitus	26 (21.3)	21 (17.2)	.51	
Renal failure	21 (17.2)	14 (11.5)	.25	
Hemodialysis	11 (9)	10 (8.2)	1	
Cirrhosis of the liver	15 (12.3)	3 (2.5)	<.01	5 (1.5–17.3)
Solid organ cancer	23 (18.9)	26 (21.3)	.72	
Hematologic malignancy	10 (8.2)	6 (5)	.42	
AIDS	6 (5)	7 (5.7)	1	
Other conditions				
Neutropenia	13 (10.7)	3 (2.5)	.01	6 (1.3–26.8)
Organ transplantation	15 (12.3)	4 (3.2)	.02	3.8 (1.2–11.3)
Valvular heart disease	5 (4.1)	3 (2.5)	.72	
Exogenous risk factors for bacteremia				
Prior duration of hospital stay, median d (IR)	12 (5–22)	4.5 (1–15)	<.01[a]	
Intravascular catheter	105 (86)	88 (72)	.01	2.4 (1.2–4.7)
Urinary catheter	71 (58)	38 (31)	<.01	4.3 (2.2–8.6)
Nasogastric tube	42 (34)	28 (23)	.03	2.3 (1.1–4.6)
Surgery	29 (24)	28 (23)	1	
Prior ICU stay	44 (36)	39 (32)	.3	
Mechanical ventilation	25 (21)	19 (16)	.3	
Parenteral nutrition	18 (15)	3 (3)	.002	6 (1.8–20.4)
Prior use of antimicrobials	83 (68)	58 (48)	.001	2.7 (1.5–4.8)

NOTE. Data are no. of patients (%), except as indicated. ICU, intensive care unit; IR, interquartile range.

[a] Wilcoxon test. All other comparisons were by McNemar χ^2 test.

[b] Ultimately and rapidly fatal underlying diseases were combined to perform the McNemar χ^2 test.

but these results were not included in the analysis. Sixty-eight isolates (58%) did not present synergy between penicillins and aminoglycosides because of high-level resistance to one or both antimicrobial groups.

Clinical features. Sources of enterococcal bacteremia were as follows: intra-abdominal (30 patients [25%]), intravascular catheter (21 patients [17%]), urinary tract (18 patients [15%]), soft tissues (4 patients), respiratory tract (3 patients), and CNS (1 patient). Three patients had a multiple source. Forty-eight patients (39%) had bacteremia of unknown origin. A total of 118 patients (97%) had fever, and 4 (3%) had hypothermia, 23 (19%) alteration of mental status, 23 (19%) oliguria, and 20 (16%) hypotension. No patients had disseminated intravascular coagulation nor septic metastasis. Eighty-four patients (69%) had sepsis and 38 (31%) had severe sepsis or septic shock (i.e., hemodynamic compromise was present).

Table 2. Susceptibilities of 117 enterococcal strains causing bacteremia in hospitalized patients.

Antimicrobial, MIC (μg/mL)	*E. faecalis* (n = 95)	*E. faecium* (n = 19)	*E. durans* (n = 3)
Amp (resistant, ⩾16)	2 (2)	10 (53)	0
Imp (intermediate, 8; resistant, ⩾16)	1 (1)	15 (79)	0
Cpfx (intermediate, 2; resistant, ⩾4)	43 (45)	4 (21)	0
Vm (intermediate, 8–16; resistant, ⩾32)	0	2 (11)	0
Gm (high-level, >500)	40 (42)	1 (5)	0

NOTE. Data are no. of strains (%). There were no strains resistant to teicoplanin. Amp, ampicillin; Cpfx, ciprofloxacin; Gm, gentamicin; Imp, imipenem; Vm, vancomycin.

Appropriate antimicrobial therapy was given to 104 patients (85%). The more frequently used antimicrobials were a β-lactam antibiotic, either alone (38 patients [36.5%]) or with an aminoglycoside (24 patients [23%]). Other treatments used were a glycopeptide alone (12.5%) or associated with an aminoglycoside (5%), a quinolone alone (10.5%) or associated with an aminoglycoside (1%), and sequential treatments because of other isolates (11.5%) (β-lactam antibiotics and glycopeptides, β-lactam antibiotics and quinolones, quinolones and glycopeptides). Mean duration of therapy was 11 days.

Mortality rates. The in-hospital mortality rate of the group of patients with enterococcal bacteremia was 29%, and the 30-day mortality rate was 23%. The crude mortality rate was higher among patients in the ICU (36%) than among those in surgical (7%) or medical wards (19%; $P = .02$). The crude mortality rate was not related to age, sex, underlying diseases or their severity, nor to duration of hospital stay before onset of bacteremia. Four patients with community-acquired bacteremia (21%) and 31 with nosocomial bacteremia (30%) died ($P = .4$). Exogenous risk factors associated with a higher crude mortality rate were placement of a urinary catheter (presence vs. absence of risk factors, 32% vs. 10%, respectively; $P = .007$; RR, 4.4; 95% CI, 1.5–12.6) or nasogastric tube (43% vs. 13%; $P < .001$; RR. 5.3; 95% CI. 2.1–12.9), mechanical ventilation (56% vs. 14%; $P < .001$; RR, 7.5; 95% CI, 2.8–20), prior stay in an ICU (mean ± SD, 8.8 ± 10.8 days vs. 4.4 ± 11.8 days; $P < .002$), and parenteral nutrition (50% vs. 18%; $P = .003$; RR, 4.5; 95% CI, 1.6–18.8). Infection with an organism resistant to ampicillin was also associated with a higher crude mortality rate (50% vs. 20%; $P = .04$; RR, 4; 95% CI, 1.2–13.6). Species and polymicrobial etiology (overall and stratified by gram-positive and gram-negative organisms associated) did not modify the crude mortality rate. Figure 1 shows cumulative crude mortality rate for 30 days after the onset of the enterococcal bacteremia for monomicrobial and polymicrobial bacteremia. The shapes of the curves are similar; the mortality rate is higher during the first 10 days and tails off thereafter, flattening the curves.

Patients with hemodynamic compromise had a higher crude mortality rate than did those with sepsis (50% vs. 11%; $P < .001$; RR, 8.3; 95% CI, 3.3–21.3), and those patients who received inappropriate antimicrobial therapies also had a higher crude mortality rate (61% vs. 16%; RR, 8; 95% CI, 2.7–23.7). Crude mortality rate was not higher among patients who were treated with monotherapy (β-lactam antibiotics or glycopeptides) than among those who were treated with combined therapy (including an aminoglycoside; 23% vs. 16%; $P = .4$). No source of infection was associated with a higher crude mortality rate.

Variables as independent risk factors for crude mortality rate selected by a multiple logistic regression model are shown in table 3. Crude mortality rate of patients with enterococcal bacteremia (23%) was not higher than that of the control group (17%; $P = .29$). Thus, the estimated attributable mortality rate due to enterococcal bacteremia was 6% in the present study (95% CI, −4% to 16%), a percentage that was not significant. Nevertheless, a stratified analysis was done to find whether the mortality rate of any group of patients with enterococcal bacteremia was really attributable to enterococcal bacteremia. This did occur for those patients who received inappropriate antimicrobial therapy (attributable mortality rate, 50%; 95% CI, 49%–50%; $P = .012$), those who developed hemodynamic compromise (attributable mortality rate, 26%; 95% CI, 18%–34%; $P = .031$). No other epidemiological, microbiological (monomicrobial or polymicrobial etiology included), or clinical factors increased crude mortality rate of patients with enterococcal bacteremia above that of their matched control patients.

Duration of hospital stay. A total of 94 patients who did not die during the first 30 days after the onset of the enterococcal bacteremia and their respective control patients were

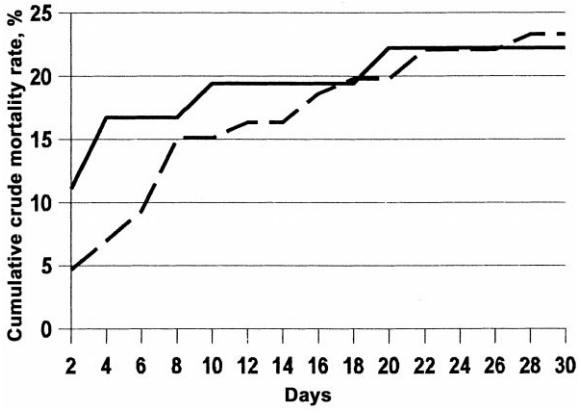

Figure 1. Cumulative crude mortality rates during first 30 days after onset of enterococcal bacteremia: comparison of monomicrobial *(dashed line)* and polymicrobial *(solid line)* cases of bacteremia.

Table 3. Independent risk factors associated with 30-day mortality in patients with enterococcal bacteremia.

Variable	Regression coefficient	SE	*P*	OR	95% CI
Inappropriate therapy	3.42	0.88	<.01	30.8	5.4–175.6
Severity of illness	2.49	0.68	<.01	12.2	3.2–46.6
Mechanical ventilation	2.25	0.7	<.01	9.6	2.4–38
Ampicillin resistance	1.9	0.9	<.04	6.8	1.11–41
Constant	−3.88	0.7	<.01	—	—

NOTE. Model: χ^2, 52.68; *df*, 4; $P < .001$. Correlation matrix did not demonstrate colinearity among variables.

included in this analysis. The mean duration of hospital stay after acquiring the enterococcal bacteremia was 38.4 days (median, 21 days; SD, 59.5 days), compared with 17.5 days for control patients (median, 13 days; SD, 17 days) ($P < .001$). Thus, duration of hospital stay attributable to enterococcal bacteremia was 21 days (95% CI, 7–32 days). Considering the cost of 1 day of hospital stay in "Virgen del Rocío" Teaching Hospital ($360US/day in the ICU and $216/day in medical and surgical wards) and the cost of ampicillin therapy for 10 days ($320), the mean cost of the excess of duration of hospital stay attributed to enterococcal bacteremia is at least $7880/episode in the ICU and $4856/episode in medical and surgical wards.

DISCUSSION

In this study, patients with enterococcal bacteremia were compared with patients with fever but without any bacteremia. Both groups of patients were matched by age, sex, and hospitalization wards. They were homogeneous in type, severity of underlying diseases, and length of prior hospital stay, so the morbidity of the enterococcal bacteremia depended on other factors.

The crude and related mortality rates among patients with enterococcal bacteremia are similar to the rates among patients with bacteremia caused by other gram-positive cocci (crude mortality rate, ⩽44%, depending on the staphylococcal species; related mortality rate, 14%–24%) and lower than the rates among patients with bacteremia caused by gram-negative rods (crude mortality rate, 20%–50%; related mortality rate, 25%; attributable mortality rate, 25%) and yeasts (crude mortality rate, 90%; attributable mortality rate, 38%) [2, 12, 28–39]. The in-hospital mortality rate was intermediate in the present series (29%) compared with that reported by other authors (13%–68%) [5–8, 10–16, 33–35, 40]. The 30-day mortality rate (23%) was also in the range of that reported in other studies as related mortality rate (2%–43%) [8, 11, 13, 16, 33–35].

A number of poor prognosis factors have been described, although designs of most studies from which they were inferred did not consider bias and interactions that exist among the different factors as a consequence of the characteristics of patients in whom enterococcal bacteremia occurs. Some of those described are advanced age [6, 12], severe underlying diseases and immunodeficiencies [6, 10, 12, 16], nosocomial acquisition [10, 12], polymicrobial etiology [12, 13, 33], multiple or intra-abdominal sources or surgical wound infection [12], prior surgery [12], hemodialysis [16], prior use of antimicrobials [6, 12], severe infection [24, 41], and inappropriate antimicrobial therapy [6, 8, 12, 13, 24, 42]. It is evident that all of these factors could be related to each other in hospitalized patients. Thus, a multivariate analysis is needed to clarify which factors are really important for prognosis.

Our results show that the crude mortality rate among patients with enterococcal bacteremia is not higher than that among patients without enterococcal bacteremia, when sex, age, and hospitalization ward are the same. Only one prior study has analyzed the mortality rate attributed to enterococcal bacteremia, which was estimated to be 31% [16]. This difference could be explained in part by differences in design. The study of Landry et al. [16] was retrospective, included patients with endocarditis, used noncontemporary controls, matched case patients and control patients by underlying diseases (so how much underlying diseases conditioned the death of patients with enterococcal bacteremia is not known), and included control patients who might have had community-acquired bacteremias.

Independent risk factors associated with 30-day crude mortality rate among patients with enterococcal bacteremia in the present study were infection with an organism resistant to ampicillin, inappropriate antimicrobial therapy, hemodynamic compromise, and prior need for mechanical ventilation. In a retrospective analysis of 81 enterococcal bacteremias, 41 of them clinically significant, independent risk factors associated with a fatal outcome of clinically significant bacteremias were inappropriate antimicrobial therapy (OR, 17), prior use of antimicrobials (OR, 14), and the presence of severe underlying diseases (OR, 10) [6].

In the present series, overall, the group of patients with enterococcal bacteremia did not have a significant attributable mortality rate; however, some groups of patients did have a significant attributable mortality rate (i.e., patients who did not receive appropriate antimicrobial therapy and those with a

worse clinical status). This finding should be stressed. Other authors have also reported better prognosis for patients with enterococcal bacteremia and appropriate antimicrobial therapy [6, 13]. Furthermore, this is the only independent risk factor that can be easily modified by clinicians. We have not found a different prognosis for patients treated with monotherapy or combined therapy. Although this study was not designed to assess different antimicrobial regimens, this finding supports the idea that monotherapy with a penicillin or glycopeptide is sufficient for treating enterococcal bacteremias without endocarditis, regardless of the severity of the infection [8, 12, 13].

Mean duration of hospital stay after acquiring the enterococcal bacteremia was >5 weeks, and the estimated attributable duration of hospital stay was 21 days. This point is of great interest for prognosis and has never been previously analyzed for enterococcal bacteremia. Whereas severity of illness and mortality rate are indexes of human cost, attributable duration of hospital stay is an index of cost in resources, both in personnel and in supplies. Although Landry et al. [16] studied the duration of hospital stay of patients with enterococcal bacteremia and compared it with that of their matched control patients, these authors analyzed the complete duration of hospital stay. In contrast, in our study, only the stay after acquiring the enterococcal bacteremia of survivors was considered because that period is susceptible to being directly extended by an episode of bacteremia.

We conclude that enterococcal bacteremia without endocarditis does not increase mortality rate but does extend the duration of hospital stay of the patients who contract it, compared with febrile nonbacteremic patients.

References

1. Korten V, Murray BE. The nosocomial transmission of enterococci. Curr Opin Infect Dis **1993**; 6:498–505.
2. Pittet D. Nosocomial bloodstream infections. In: Wenzel RP, eds. Prevention and control of nosocomial infections. 2d ed. Baltimore: Williams & Wilkins, **1993**:512–55.
3. Eliopoulos GM. Increasing problems in the therapy of enterococcal infections. Eur J Clin Microbiol Infect Dis **1993**; 12:409–12.
4. Jett BD, Huycke MM, Gilmore MS. Virulence of enterococci. Clin Microbiol Rev **1994**; 7:462–78.
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. Hoge CW, Adams J, Buchanan B, Sears SD. Enterococcal bacteremia: to treat or not to treat, a reappraisal. Rev Infect Dis **1991**; 13:600–5.
7. Malone DA, Wagner RA, Myers JP, Watanakunakorn C. Enterococcal bacteremia in two large community teaching hospital. Am J Med **1986**; 81:601–6.
8. Gullberg RM, Homann SR, Phair JP. Enterococcal bacteremia: analysis of 75 episodes. Rev Infect Dis **1989**; 2:74–85.
9. Bryan CS, Reynolds KL, Brown JJ. Mortality associated with enterococcal bacteremia. Surg Gynecol Obstet **1985**; 160:557–61.
10. Shlaes DM, Levy J, Wolinsky E. Enterococcal bacteremia without endocarditis. Arch Intern Med **1981**; 141:578–81.
11. Carton JA, Maradona JA, Asensi V, et al. Infección hospitalaria por enterococos. El uso previo de antibióticos como factor de riesgo a través de un estudio de casos y controles. Med Clin (Barc) **1993**; 101: 769–73.
12. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore) **1988**; 67: 248–69.
13. Graninger W, Ragette R. Nosocomial bacteremia due to *Enterococcus faecalis* without endocarditis. Clin Infect Dis **1992**; 15:49–57.
14. Garrison RN, Fry DE, Berberich S, Polk HC Jr. Enterococcal bacteremia: clinical implications and determinants of death. Ann Surg **1982**; 196:43–7.
15. Barrall DT, Kenney PR, Slotman GJ, Burchard KW. Enterococcal bacteremia in surgical patients. Arch Surg **1985**; 120:57–63.
16. 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.
17. Murray BE. The life and times of the *Enterococcus.* Clin Microbiol Rev **1990**; 3:46–65.
18. Fleiss JL. Statistical methods for rates and proportions. 2d ed. New York: John Wiley & Sons, **1981**.
19. Facklam RR, Sahm DF. *Enterococcus.* In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of clinical microbiology. 6th ed. Washington: American Society for Microbiology, **1995**:308–14.
20. Roberts FJ, Geere IW, Coldman A. A three year study of positive blood cultures, with emphasis on prognosis. Rev Infect Dis **1991**; 13:34–46.
21. Garner JS, Jarvis WR, Emori TG, Horan TG, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control **1988**; 16: 128–40.
22. McCabe WR, Jackson GG. Gram-negative bacteremia. I. Etiology and ecology. Arch Intern Med **1962**; 110:847–55.
23. American College of Chest Physicians and Society of Critical Care Medicine consensus conference committee. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest **1992**; 101:1644–55.
24. Caballero-Granado FJ, Cisneros JM, Luque R, et al. Comparative study of bacteremias caused by *Enterococcus* species with and without high-level resistance to gentamicin. J Clin Microbiol **1998**; 36:520–5.
25. Carrasco JL, Hernán MA, eds. Estadística multivariante en las ciencias de la vida. Madrid: Editorial Ciencia 3, **1993**.
26. Kleinbaum DG, Kupper LL, Morgenstern H, eds. Epidemiologic research. Principles and quantitative methods. New York: Van Nostrand Reinhold, **1982**.
27. Kramer MS, ed. Clinical epidemiology and biostatistics. A primer for clinical investigators and decision-makers. New York: Springer-Verlag, **1988**.
28. López-Dupla M, García-Tobaruela A, Lavilla Uriol P. Candidiasis diseminada. In: Gil Aguado A, Lavilla Uriol P, Pintado García V, eds. Micosis sistémicas. Actualización. Madrid: Grupo Aula Médica, **1997**: 1–23.
29. Martin MA. Epidemiology and clinical impact of gram-negative sepsis. Infect Dis Clin North Am **1991**; 5:739–52.
30. Waldvogel FA. *Staphylococcus aureus* (including toxic shock syndrome). In: Mandell GL, Douglas, RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 3d ed. New York: Churchill Livingstone, **1990**: 1489–510.
31. Dahmash NS, Chowdhury MN, Fayed DF. Coagulase-negative staphylococcal bacteraemia with special reference to septic shock: experience in an intensive care unit. J Infect **1994**; 29:295–303.
32. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. Ann Intern Med **1989**; 110: 9–16.
33. Celis G, Pallarés R, Ariza J, Cisnal M, Martín R, Gudiol F. Características clínicas y epidemiológicas de la bacteriemia por *Enterococcus faecalis:* estudio prospectivo de 80 episodios. Enferm Infecc Microbiol Clin **1988**; 6:454–9.
34. Nicolás JM, Mariscal D, Moreno A, Mensa J. Bacteriemia por *Enterococcus faecalis.* Estudio de 113 casos. Med Clin (Barc) **1991**; 96:717–8.

35. Noskin GA, Peterson LR, Warren JR. *Enterococcus faecium* and *Enterococcus faecalis* bacteremia: acquisition and outcome. Clin Infect Dis **1995**; 20:296–301.
36. Mylotte JM, Beam TR Jr, Allen JC. *Staphylococcus aureus* bacteremia: a prospective study. South Med J **1983**; 76:1131–5.
37. Mylotte JM, McDermott C, Spooner JA. Prospective study of 114 consecutive episodes of *Staphylococcus aureus* bacteremia. Rev Infect Dis **1987**; 9:891–907.
38. Sheagren JN. *Staphylococcus aureus.* The persistent pathogen. Part I. N Engl J Med **1984**; 310:1368–73.
39. Topeli A, Unal S, Hayran M, Akalin HE. Septic shock as a predictor of mortality in bacteremia caused by coagulase-negative staphylococci. Eur J Clin Microbiol Infect Dis **1997**; 16:411–6.
40. Gray J, Marsh PJ, Stewart D, Pedler SJ. Enterococcal bacteraemia: a prospective study of 125 episodes. J Hosp Infect **1994**; 27:179–86.
41. Wells VD, Wong ES, Murray BE, Coudron PE, Williams DS, Markowitz SM. Infections due to β-lactamase–producing, high-level gentamicin-resistant *Enterococcus faecalis.* Ann Intern Med **1992**; 116:285–92.
42. Moellering RC Jr. Emergence of *Enterococcus* as a significant pathogen. Clin Infect Dis **1992**; 14:1173–8.