

Nosocomial Spontaneous Bacterial Peritonitis and Bacteremia in Cirrhotic Patients: Impact of Isolate Type on Prognosis and Characteristics of Infection

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The characteristics of and prognosis for nosocomial spontaneous bacterial peritonitis (SBP) and bacteremia were examined in a prospective study that included data from 194 consecutive episodes of SBP and 119 episodes of bacteremia, 93.3% of which were nosocomial, in 200 hospitalized cirrhotic patients. Gram-positive pathogens were predominant (70% of the total) among isolates from nosocomial infections; the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was 24.8%. Nosocomial and staphylococcal infections were associated with a higher mortality rate than were community-acquired infections ($P = .0255$) and non-staphylococcal infections ($P < .001$), respectively. In comparison with non-MRSA infections, MRSA infections were more likely to recur and occurred in a greater number of sites other than ascitic fluid and blood ($P = .0004$). Older age ($P = .0048$), higher Child-Pugh score ($P = .0011$), and infection with staphylococci ($P = .0031$) were independently associated with a higher mortality rate. The emergence of MRSA is important because of the recurrence and poor outcome associated with infection with such organisms.

Bacterial infections are a frequent and severe complication of cirrhosis of the liver [1]. Among these, spontaneous bacterial peritonitis (SBP) occurs most frequently, with a prevalence ranging from 10% to 26% [2, 3]. A vast majority of such infections are due to enteric gram-negative bacteria, mainly Enterobacteriaceae. However, these data refer principally to community-acquired infections, and most cirrhotic patients who have end-stage disease have a high risk of nosocomial infection, because they undergo frequent hospitalization and long hospital stays. The etiologies for

nosocomial infections have undergone striking changes, and gram-positive bacteria have emerged as the foremost cause of infection among hospitalized patients [4].

Staphylococcus aureus increasingly is recognized as an important pathogen in cirrhotic patients [5]. It has been shown that this organism is the most common cause of endocarditis among these patients, and *S. aureus* ranked second in frequency among causative agents of bacteremia in patients who have end-stage liver disease and are awaiting transplantation [6, 7]. Moreover, other studies have found a high prevalence of nasal colonization with *S. aureus* among these patients that leads to an increase in the risk of staphylococcal infection [5, 8, 9].

This prospective study was undertaken to analyze the epidemiology of nosocomial SBP and bacteremia in a large population of cirrhotic patients, most of whom had a long hospital stay and end-stage disease. These types of infections are frequent and can be easily bacteriologically documented, and they are associated with

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Table 1. Types of bacteria isolated from cultures of ascitic fluid and blood samples obtained from hospitalized cirrhotic patients with nosocomial spontaneous bacterial peritonitis and/or bacteremia.

| Type of isolate | No. (%) of isolates recovered | | Total |
|--|-------------------------------|------------|-----------|
| | From ascitic fluid | From blood | |
| All Enterobacteriaceae | 45 (24.6) | 26 (21.8) | 71 (23.5) |
| <i>Escherichia coli</i> | 25 (13.7) | 18 (15.1) | 43 (14.2) |
| Enterobacteriaceae other than <i>E. coli</i> | 20 (10.9) | 8 (6.7) | 28 (9.3) |
| Nonfermenting bacilli | 11 (6.0) | 5 (4.2) | 16 (5.3) |
| Streptococci | 43 (23.5) | 20 (16.8) | 63 (20.9) |
| Enterococci | 43 (23.5) | 9 (7.6) | 52 (17.2) |
| Methicillin-resistant <i>Staphylococcus aureus</i> | 34 (18.6) | 41 (34.5) | 75 (24.8) |
| Methicillin-susceptible <i>S. aureus</i> | 2 (1) | 6 (5) | 8 (2.6) |
| Coagulase-negative staphylococci | 2 (1) | 11 (9.2) | 13 (4.3) |
| <i>Bacteroides</i> species | 2 (1) | 1 (1) | 3 (1) |
| <i>Clostridium</i> species | 1 (0.5) | 0 | 1 (0.3) |
| Total | 183 | 119 | 302 |

a high rate of mortality during hospital stay. The second aim of our study was to define the impact of the type of infecting bacteria on the prognosis for and characteristics of infection, taking into account recurrence and association with infection of other sites by the same organism. Because diagnosis of SBP is based principally on the leukocyte and polymorphonuclear leukocyte (PMNL) counts in ascitic fluid, we have analyzed these criteria for the different organisms isolated in our study.

PATIENTS AND METHODS

Study patients. From 1 January 1996 through 31 March 2001, all patients with liver cirrhosis and SBP and/or bacteremia that occurred during a hospital stay were included in the study. Our department (Service de Rééducation Digestive, Hôpital Albert Chenevier, Creteil, France) is a rehabilitation unit specifically devoted to liver disease, and we receive patients from other hospitals in Paris and the surrounding area. All of the patients admitted during the study period required a long hospital stay and rehabilitation because of severe complications of cirrhosis, such as septic complications, gastrointestinal bleeding, refractory ascites, acute alcoholic hepatitis, and severe malnutrition. Because most patients included in the study had been hospitalized for >3 days (average duration, 2–3 weeks) before they were admitted to our department, the episodes of SBP and bacteremia reported in this study had, in the majority of cases, a nosocomial origin.

Diagnostic criteria and testing. The diagnosis of liver cirrhosis was based on the usual clinical, biological, and endoscopic signs (e.g., ascites, jaundice, encephalopathy, liver and spleen enlargement, “vascular spiders,” enlarged abdominal-

wall veins, accelerated prothrombin time, hyperbilirubinemia, hyperglobulinemia, and esophageal varices) and/or examination of liver biopsy specimens. The severity of liver disease was assessed by the Child-Pugh scoring system, in which 5–15 points are assigned and a higher score indicates greater severity of liver failure. Patients in Child-Pugh class A have preserved liver function (5–6 points), patients in class B have mild liver failure (7–9 points), and patients in class C have severe liver failure (10–15 points) [10]. Paracentesis was performed for all patients at admission. The diagnosis of SBP was based on the combination of a positive ascitic fluid culture and a PMNL count of >250 cells/mm³, irrespective of clinical signs of SBP, or a positive ascitic fluid culture with no increase in the PMNL count but with symptoms and signs of infection. The symptomatic form of bacterascites is considered to be a variant of SBP [11]. Patients with secondary peritonitis were excluded from the study.

Samples of blood were also obtained for culture at admission from most patients. The diagnosis of bacteremia was based on a combination of clinical signs (fever, hypothermia, encephalopathy, and/or hypotension) and ≥1 positive blood culture result. Specimens of blood and/or ascitic fluid were placed in blood-culture bottles at the patient’s bedside, incubated at 37°C for 7 days, and examined daily for turbidity. These cultures were subcultured after 2 and 7 days on chocolate-enriched agar plates for aerobic and anaerobic growth. The plates were incubated for 1 or 2 days at 37°C, and organisms were identified.

Treatment regimen. The treatment regimen for SBP and/or bacteremia was empiric antibiotic therapy initiated immediately after the diagnosis of infection was made (day 0). The antibiotics used were a third-generation cephalosporin (cef-

triaxone) or the combination of amoxicillin–clavulanic acid with a fluoroquinolone (ofloxacin). Antibiotic therapy was then adapted to the individual patient, on the basis of the results of the antibiogram for the isolate(s) from that patient. Infections caused by methicillin-resistant *S. aureus* (MRSA) were treated either with vancomycin (for SBP) or with a combination of vancomycin and fosfomycin (for bacteremia). Infections caused by methicillin-susceptible *S. aureus* (MSSA) were treated with oxacillin. Imipenem–cilastatin was used to treat most infections caused by gram-negative bacteria that were resistant to third-generation cephalosporins. Paracentesis was performed 2–3 days and 7–10 days after initiation of antibiotic therapy to determine leukocyte and PMNL counts in ascitic fluid.

Data collection. Analysis was performed for data from each patient with SBP and/or bacteremia and for data from each episode of infection. Data for the following parameters were collected: length of hospital stay; number of episodes of SBP and/or bacteremia; whether death occurred during the hospital stay; time between admission and onset of infection; time between onset of infection and death; and associated infections caused by the same microorganism, including infection of sites other than ascitic fluid and blood and episodes of SBP and/or bacteremia that occurred during the hospital stay and before admission to our unit.

Statistical analysis. Quantitative variables are given as the mean \pm SD and, for some parameters, the median. Comparison of variables among several groups of patients was done using 1-way analysis of variance (ANOVA) or the nonparametric Kruskal–Wallis test, as appropriate. When ANOVA showed a statistically significant difference, the 2 groups were compared using the Bonferroni–Dunn test. Comparisons of percentages between groups were made with the χ^2 test. Multivariate analysis was done using a stepwise logistic regression model. The threshold for statistical significance was $P < .05$. Data were analyzed with Epi Info VS (Centers for Disease Control and Prevention) and Statview (SAS Institute) software.

RESULTS

The study included 200 cirrhotic patients (128 male subjects and 72 female subjects). One subject was in Child–Pugh class A, 45 subjects were in class B, and 154 subjects were in class C. The cause of cirrhosis was alcoholism in 175 patients, hepatitis C in 16 patients, hepatitis B in 6 patients, and hemochromatosis in 1 patient; the cause was cryptogenetic in 1 patient; and 1 patient had primary biliary cirrhosis. During the study period, 82 episodes of asymptomatic bacterascites (caused by coagulase-negative staphylococci in 84% of episodes) were diagnosed; data from these episodes were excluded from the study. One hundred twenty-two episodes of symptomatic bacterascites and 72 episodes of SBP characterized by an increased

PMNL count in ascitic fluid of >250 cells/mm³ were diagnosed. Data from these 194 episodes of SBP and from 119 episodes of bacteremia were included in the study. One hundred one patients had SBP only, 51 patients had bacteremia only, and 48 patients had SBP and bacteremia; among those patients, SBP and bacteremia were caused simultaneously by the same organism in 31 cases and by 2 different organisms in 2 cases. Twenty-one community-acquired infections (20 episodes of SBP and 1 of bacteremia) occurred in 21 patients. The causative organisms were Enterobacteriaceae in 8 episodes of community-acquired SBP (*Escherichia coli* in 6 cases), streptococci in 10 cases, and enterococci in 2 episodes. *Streptococcus bovis* was isolated from the single patient with community-acquired bacteremia.

The types of organisms isolated from ascitic fluid and blood samples obtained from patients with nosocomial infections are shown in table 1. Among the enterococci, 36 isolates were *Enterococcus faecalis*, 15 were *Enterococcus faecium*, and 1 was *Enterococcus durans*. Nonfermenting bacilli included *Pseudomonas aeruginosa* (9 isolates), *Acinetobacter baumannii* (5 isolates), and *Alcaligenes xylosoxidans* (2 isolates). Aerobic gram-positive pathogens were predominant (70% of the total). Among those, staphylococci were isolated in 32% of cases (96 isolates), and MRSA were predominant among the staphylococci (78%). In 10 episodes of infection (9 episodes of SBP and 1 episode of bacteremia), 2 organisms were isolated. The mortality rate during hospital stay was 49.5% among patients with nosocomial infections and 23.8% among patients with community-acquired infections ($P = .0255$). Patients who died during the hospital stay, compared with surviving patients, tended to be older (mean age \pm SD, 58.2 ± 10.5 vs. 55.4 ± 11.4 years; $P = .0702$), had higher Child–Pugh scores (mean score \pm SD, 11.8 ± 1.8 vs. 10.7 ± 2.0 ; $P = .0008$), and experienced more episodes of SBP and/or bacteremia (mean number of episodes \pm SD, 1.9 ± 1.3 vs. 1.5 ± 1.0 ; $P = .03$). The mortality rates among patients with SBP only, patients with bacteremia only, and patients who had both types of infection were 58.4%, 45.1%, and 52%, respectively (P was NS).

The characteristics of the patients included in the study are shown in table 2. We included patients from whom only 1 type of bacteria was isolated during the hospital stay for ≥ 1 episode of infection and patients from whom >1 type of bacteria was isolated for >1 episode of infection. The number of episodes of SBP and/or bacteremia was higher and the duration of hospital stay was longer among patients from whom >1 type of bacteria was isolated. The mortality rate was higher among patients infected with staphylococci and those infected with >1 type of bacteria than it was in the other groups.

The characteristics of episodes of SBP and bacteremia are shown in table 3. Time between admission and onset of infection was the shortest for infections caused by MSSA and

Table 2. Characteristics of hospitalized cirrhotic patients with nosocomial spontaneous bacterial peritonitis (SBP) and/or bacteremia, by type of infecting bacteria.

| Variable | Staphylococci | Streptococci | Enterococci | Enterobacteriaceae | Nonfermenting bacilli | Multiple bacterial strains | P ^a |
|---|----------------------------|------------------------------|------------------------------|------------------------------|----------------------------|------------------------------------|----------------|
| No. of patients | 49 | 46 | 28 | 45 | 6 | 26 | — |
| Type of infection, no. of patients | | | | | | | |
| SBP | 10 | 31 | 23 | 24 | 4 | 9 | — |
| Bacteremia | 30 | 6 | 3 | 12 | 0 | 0 | — |
| SBP and bacteremia | 9 | 9 | 2 | 9 | 2 | 17 | — |
| Sex, no. male/female | 29/20 | 29/17 | 19/9 | 29/16 | 4/2 | 18/8 | — |
| Age, mean years \pm SD | 56.9 \pm 12.3 | 56.7 \pm 10.9 | 56.9 \pm 11.8 | 57.2 \pm 10.7 | 59.8 \pm 6.6 | 56.5 \pm 9.6 | NS |
| Child-Pugh score, mean \pm SD | 11.0 \pm 1.8 | 11.0 \pm 1.6 | 11.3 \pm 1.7 | 11.1 \pm 2.1 | 10.2 \pm 2.4 | 11.3 \pm 1.8 | NS |
| Duration of hospital stay, days | | | | | | | |
| Mean \pm SD | 70.9 \pm 53.2 | 48.0 \pm 37.7 ^b | 52.6 \pm 42.2 ^c | 56.6 \pm 37.0 ^d | 40.2 \pm 14.3 | 101.1 \pm 85.3 ^{b,c,d} | .0003 |
| Median | 55 | 41 | 36 | 46 | 41 | 71 | — |
| No. of septic episodes per patient, mean \pm SD | 1.4 \pm 0.8 ^e | 1.4 \pm 0.5 ^f | 1.2 \pm 0.5 ^g | 1.3 \pm 0.6 ^h | 1.5 \pm 0.8 ⁱ | 3.4 \pm 1.5 ^{e,f,g,h,i} | <.0001 |
| Mortality rate, no. (%) of patients | 32 (65.3) | 12 (26.1) | 14 (50.0) | 12 (26.7) | 3 (50.0) | 18 (69.2) | <.0001 |

^a Comparisons among groups were performed using 1-way analysis of variance, except for mortality rate, for which the χ^2 test was used. When a statistically significant difference was seen, the Bonferroni-Dunn test was used to compare the 2 groups.

^b For streptococci vs. multiple bacterial strains, $P < .0001$.

^c For enterococci vs. multiple bacterial strains, $P < .0003$.

^d For enterobacteriaceae vs. multiple bacterial strains, $P < .0001$.

^e For staphylococci vs. multiple bacterial strains, $P < .0001$.

^f For streptococci vs. multiple bacterial strains, $P < .0001$.

^g For enterococci vs. multiple bacterial strains, $P < .0001$.

^h For enterobacteriaceae vs. multiple bacterial strains, $P < .0001$.

ⁱ For nonfermenting bacilli vs. multiple bacterial strains, $P < .0001$.

Table 3. Characteristics of episodes of spontaneous bacterial peritonitis (SBP) and bacteremia in hospitalized cirrhotic patients, by type of infecting bacteria.

| Variable | MRSA | MSSA | Coagulase-negative staphylococci | Streptococci | Enterococci | Enterobacteriaceae | Nonfermenting bacilli | P ^a |
|--|--------------------------|--------------------------|------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|----------------|
| No. of episodes | | | | | | | | |
| SBP | 28 | 2 | 0 | 41 | 43 | 45 | 10 | — |
| Bacteremia | 35 | 6 | 9 | 9 | 7 | 18 | 4 | — |
| SBP and bacteremia | 6 | 0 | 2 | 12 | 2 | 8 | 1 | — |
| Total | 75 | 8 | 13 | 74 | 54 | 79 | 16 | — |
| Time between admission and onset of infection, days | | | | | | | | |
| Mean ± SD | 41.5 ± 35.6 ^b | 21.0 ± 21.9 ^c | 78.8 ± 58.3 ^{b,c,d,e,f,g} | 29.1 ± 47.7 ^e | 38.6 ± 46.6 ^f | 29.3 ± 33.8 ^g | 37.4 ± 35.4 ^d | .0019 |
| Median | 30.5 | 12.0 | 55.0 | 14.0 | 19.5 | 21.0 | 37.0 | — |
| No. of associated infections caused by the same microorganism, mean ± SD | 1.8 ± 1.5 ^{h,i} | 0 | 1.1 ± 1.0 | 0.8 ± 1.0 | 0.5 ± 0.7 ^h | 0.7 ± 1.0 ⁱ | 1.4 ± 1.5 | .0004 |
| Mortality rate, no. (%) of episodes resulting in death | 45 (60.0) | 6 (75.0) | 12 (92.3) | 23 (31.0) | 32 (59.3) | 30 (38.0) | 12 (75.0) | <.001 |
| Time between onset of infection and death, days | | | | | | | | |
| Mean ± SD | 28.0 ± 39.5 | 14.5 ± 19 | 37.4 ± 36.0 | 30.0 ± 46.7 | 23.5 ± 23.8 | 36.3 ± 44.1 | 18.8 ± 26.8 | NS |
| Median | 10 | 5.5 | 16.5 | 6.5 | 12 | 14 | 3 | — |

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

^a Comparisons among groups were performed using 1-way analysis of variance, except for mortality rate, for which the χ^2 test was used. When a statistically significant difference was seen, the Bonferroni-Dunn test was used to compare the 2 groups.

^b For MRSA vs. coagulase-negative staphylococci, $P < .001$.

^c For MSSA vs. coagulase-negative staphylococci, $P < .01$.

^d For nonfermenting bacilli vs. coagulase-negative staphylococci, $P < .01$.

^e For streptococci vs. coagulase-negative staphylococci, $P < .001$.

^f For enterococci vs. coagulase-negative staphylococci, $P < .001$.

^g For Enterobacteriaceae vs. coagulase-negative staphylococci, $P < .001$.

^h For MRSA vs. enterococci, $P < .01$.

ⁱ For MRSA vs. enterobacteriae, $P < .01$.

those caused by streptococci. MRSA was the predominant type associated with infections at multiple sites caused by the same microorganism in a single patient. MRSA infections at sites other than ascitic fluid and blood included urinary tract infections (6 episodes), skin infections (7 episodes), arthritis (2 episodes), acute diarrhea (5 episodes), lung infections (1 episode), parotiditis (1 episode), and infection of a central venous catheter (1 episode). In comparison, infections of sites other than ascitic fluid and blood included, for enterococci, urinary tract infections (1 episode); for Enterobacteriaceae, urinary tract infections (11 episodes) and skin infections (1 episode); and for nonfermenting bacilli, skin infections (1 episode).

Analysis of lethality for different types of infecting bacteria showed that staphylococcal isolates and nonfermenting bacilli were associated with the highest mortality rates, whereas Enterobacteriaceae and streptococci were predominant among surviving patients. The time between onset of infection and death did not differ significantly for episodes of infection with different strains; the median time period was the lowest for episodes of infection with nonfermenting bacilli.

Leukocyte and PMNL counts in ascitic fluid for episodes of SBP are shown in table 4. Leukocyte and PMNL counts were lower at day 0 and day 2–3 in patients infected with gram-positive pathogens than in patients infected with gram-negative bacteria, and these cell counts decreased between day 0 and day 2–3 in patients infected with any type of bacteria other than staphylococci. At day 0, the PMNL count was <250 cells/mm³ in 92.1% of patients infected with staphylococci, in 73.6% of patients infected with streptococci, in 64.4% of patients infected with enterococci, in 39.6% of patients infected with Enterobacteriaceae, and in 15.4% of patients infected with nonfermenting bacilli. In the entire population of patients with SBP, the mortality rate was in the same range among patients

with symptomatic bacterascites as it was among patients with increased PMNL counts in ascitic fluid (48.4% vs. 45.0%, respectively; *P* was NS).

We performed a multivariate analysis in which mortality rate (episodes of infection resulting in death) was the dependent variable and independent variables included age, Child-Pugh score for each episode of infection, type of isolate (staphylococci, enterococci, or nonfermenting bacilli), number of episodes of SBP and/or bacteremia during the hospital stay, and type of infection (community acquired or nosocomial). Older age (OR, 1.045; 95% CI, 1.013–1.078; *P* = .0048), higher Child-Pugh score (OR, 1.372; 95% CI, 1.134–1.659; *P* = .0011), and infection with staphylococci (OR, 2.845; 95% CI, 1.421–5.695; *P* = .0031) were found to be independently associated with a higher mortality rate.

The resistance to antibiotics of the gram-negative bacteria most commonly found in our study and among streptococcal and enterococcal isolates is shown in table 5. Among the Enterobacteriaceae, the highest levels of resistance were seen in *Enterobacter cloacae*, *Serratia marcescens*, and *Citrobacter freundii* isolates. The mortality rate among patients infected with resistant Enterobacteriaceae was comparable to that among patients infected with susceptible Enterobacteriaceae (45.5% vs. 35.8%, respectively; *P* was NS). All streptococci and almost all *E. faecalis* were susceptible to amoxicillin, whereas most *E. faecium* were resistant to this antibiotic. The mortality rate among patients with infections caused by *E. faecalis* was similar to that among patients infected with *E. faecium* (64% vs. 47%, respectively; *P* was NS). Among coagulase-negative staphylococci, 92% were resistant to methicillin.

We have studied the relationship between the use of norfloxacin as prophylaxis for SBP and the type of isolates causing SBP or bacteremia. Among the 63 episodes of SBP and bac-

Table 4. Leukocyte and polymorphonuclear leukocyte (PMNL) counts in ascitic fluid samples obtained from hospitalized cirrhotic patients with spontaneous bacterial peritonitis, by type of infecting bacteria.

| Variable | Staphylococci | Streptococci | Enterococci | Enterobacteriaceae | Nonfermenting bacilli | <i>P</i> ^a |
|--|---------------|--------------|-------------|--------------------|-----------------------|-----------------------|
| No. of patients | 38 | 53 | 45 | 53 | 11 | — |
| Leukocyte count, mean cells/mm ³ ± SD | | | | | | |
| D0 | 207 ± 291 | 924 ± 1705 | 1003 ± 1883 | 3563 ± 8568 | 4169 ± 4469 | <.0001 |
| D2–D3 | 933 ± 2518 | 585 ± 671 | 782 ± 1227 | 1771 ± 2636 | 2764 ± 3156 | .0012 |
| D7–D10 | 493 ± 1320 | 304 ± 813 | 177 ± 305 | 159 ± 138 | 554 ± 652 | NS |
| PMNL count, mean cells/mm ³ ± SD | | | | | | |
| D0 | 87 ± 200 | 650 ± 1359 | 771 ± 1686 | 3275 ± 8342 | 3391 ± 3977 | <.0001 |
| D2–D3 | 757 ± 2396 | 371 ± 571 | 558 ± 1012 | 1520 ± 3528 | 1855 ± 2287 | .0022 |
| D7–D10 | 316 ± 1122 | 155 ± 762 | 48 ± 140 | 31 ± 60 | 350 ± 529 | NS |

NOTE. D, day after diagnosis of spontaneous bacterial peritonitis and initiation of treatment (D0, day of diagnosis).

^a Comparisons among groups were performed using the Kruskal-Wallis test.

Table 5. Resistance to antibiotics among the principal gram-negative bacterial, streptococcal, and enterococcal isolates from hospitalized cirrhotic patients with spontaneous bacterial peritonitis and/or bacteremia.

| Antibiotic | Prevalence of resistance among isolates, % | | | | | | | | | |
|--------------------------|--|--|--|---------------------------------------|--|--|---|---------------------------------|--|---|
| | <i>Escherichia coli</i> (n = 43) | <i>Klebsiella pneumoniae</i> (n = 11) | <i>Enterobacter cloacae</i> (n = 4) | <i>Serratia marcescens</i> (n = 4) | <i>Citrobacter freundii</i> (n = 3) | <i>Pseudomonas aeruginosa</i> (n = 9) | <i>Acinetobacter baumannii</i> (n = 5) | <i>Streptococci</i> (n = 63) | <i>Enterococcus faecalis</i> (n = 37) | <i>Enterococcus faecium</i> (n = 15) |
| Amoxicillin | 55 | — | — | — | — | — | — | 0 | 3 | 93 |
| Amox-CA | 19 | 10 | — | — | — | — | — | — | — | — |
| Ticarcillin | 55 | 100 | 100 | 50 | 33 | 33 | 20 | — | — | — |
| 3GC | 2 | 0 | 100 | 50 | 33 | — | — | — | — | — |
| Ceftazidime ^a | 1 | 0 | 100 | 50 | 33 | 0 | 60 | — | — | — |
| Imipenem | 0 | 0 | 0 | 0 | 0 | 10 | 0 | — | — | — |
| Fluoroquinolone | 19 | 0 | 50 | 50 | 33 | — | — | — | — | — |
| Amikacin | 1 | 0 | 50 | 50 | 0 | 10 | 60 | — | — | — |
| Vancomycin | — | — | — | — | — | — | — | — | 0 | 0 |

NOTE. Amox-CA, amoxicillin–clavulanic acid; 3GC, third-generation cephalosporin.

^a Ceftazidime is a 3GC used specifically against *P. aeruginosa*.

teremia that occurred in 51 patients who were receiving norfloxacin or who had stopped taking norfloxacin ≤ 10 days before the onset of infection, 22 episodes were caused by staphylococci (34.9%), 32 episodes by streptococci and enterococci (50.8%), 7 episodes by Enterobacteriaceae (11.1%), and 2 episodes by nonfermenting bacilli (3.2%). The difference between the prevalence rates for these organisms was statistically significant ($P < .05$).

DISCUSSION

In the present study, we showed the epidemiology of nosocomial SBP and bacteremia in a population of hospitalized patients with cirrhosis characterized by severe liver failure, long hospital stays, and a high mortality rate. Nosocomial infections are associated with emergence of resistant bacteria in a broad spectrum of pathological conditions; however, little is known about nosocomial infections in cirrhotic patients. In a previous study, we demonstrated changes in the type and antibiotic-resistance levels of bacteria that caused SBP during a 20-year period (the 1980s and 1990s), including the emergence of strains of Enterobacteriaceae that were resistant to amoxicillin, β -lactamase inhibitors, and third-generation cephalosporins and the emergence of MRSA strains and resistant strains of *Enterococcus* in the last 10 years [12]. Whereas Enterobacteriaceae are usually predominant among organisms causing community-acquired SBP and bacteremia, these organisms were isolated in only 23.5% of episodes of nosocomial infection in the present study. Instead, gram-positive pathogens were predominant. Of these isolates, 32% were staphylococci, and there was a high prevalence of the methicillin-resistant phenotype. Frequent use of antibiotic therapy among cirrhotic patients, who are subject to recurrent infection, likely leads to selection of resistant bacteria.

In comparison with infections caused by other organisms, staphylococcal infections are characterized by a higher degree of recurrence and occurrence of a greater number of infections in sites other than blood and ascitic fluid, such as the skin, digestive tract, urinary tract, lungs, and joints. In the present study, SBP and/or bacteremia caused by Enterobacteriaceae were principally associated with urinary tract infections, a result that is in agreement with the findings of a previous study that showed an association between community-acquired SBP and asymptomatic bacteriuria [13]. Nasal carriage of *S. aureus* appears to play a key role in the epidemiology and pathogenesis of infection and may account for the recurrence of infections at multiple sites [14, 15]. We have shown elsewhere that the prevalence of carriage of MRSA among cirrhotic patients who had long hospital stays is high; moreover, carrier patients were exposed to a risk of infection with MRSA that was 10-fold higher than that for noncarrier patients [9]. Other investigators

also have shown an increased prevalence of carriage of *S. aureus*, in particular of MRSA, among cirrhotic patients [5, 16]. Furthermore, the high prevalence rate of MRSA carriage among patients with end-stage liver disease likely is related to the increase in MRSA infections among patients who have received liver transplants [4].

Our study shows, for the first time, that the type of the infecting bacteria has an effect on the outcome of infection for cirrhotic patients. A previous study failed to show that the type of bacteria had an effect on mortality; however, few gram-positive pathogens were included in that study, and it was not possible to analyze the role of different organisms, such as staphylococci, streptococci, and enterococci [17]. In the present study, the mortality rate among patients with infections caused by Enterobacteriaceae was 26.7%, resulting in a survival rate close to that reported in previous studies [18–20]. In contrast, the mortality rate found in the present study among patients infected with staphylococcal isolates was higher than the rate reported by other studies for this group of patients [18–20]. The majority of infections caused by staphylococci were bacteremia, which may explain the higher mortality rate in the group of patients with such infections—the prognosis for cirrhotic patients with bacteremia is poor [21, 22]. In the present study, we report only a few cases of MSSA infection; however, the high mortality rate found among patients infected with MSSA in the present study, like data published elsewhere [23], does not support the hypothesis that methicillin resistance has greater significance among patients with *S. aureus* bacteremia or SBP. Our results suggest that a high level of resistance to antibiotics is not the main factor involved in poor prognosis, because infection with resistant Enterobacteriaceae or *E. faecium* was not associated with a mortality rate higher than that seen among patient infected with more-susceptible Enterobacteriaceae or *E. faecalis*. Only the presence of staphylococci, among the bacteria isolated in our study, was independently associated with a higher mortality rate. This result highlights the significance of staphylococcal SBP and/or bacteremia for the prognosis for infection among hospitalized cirrhotic patients.

Of the episodes of SBP included in our study, 63% were symptomatic bacterascites. We found comparable high mortality rates among patients with symptomatic bacterascites and those with SBP characterized by an increased PMNL count in ascitic fluid, which is in agreement with the findings of previous studies showing that this form of bacterascites is a variant of SBP [11]. With regard to the cellular reaction to infection in ascitic fluid, we report a significant difference between the reaction to infection with gram-negative bacteria and the reaction to infection with gram-positive pathogens. Leukocyte and PMNL counts were higher in patients with SBP caused by gram-negative bacteria. Most patients with SBP caused by gram-

positive cocci (mainly staphylococci) had PMNL counts that were lower than the threshold of 250 cells/mm³. Leukocytes and PMNL counts decreased after initiation of treatment in patients with gram-negative bacterial, streptococcal, or enterococcal SBP. In contrast, these counts increased in the first 48–72 h after the diagnosis of infection in patients with staphylococcal SBP. Lack of efficiency of initial antibiotic therapy may account for this result, but differences in the mechanisms involved in local recruitment and migration of leukocytes cannot be excluded.

In our unit, administration of norfloxacin prophylaxis to cirrhotic patients is stopped soon after admission because of the relationship between receipt of norfloxacin and nasal and stool carriage of MRSA and the onset of MRSA SBP and bacteremia that we have described elsewhere [9, 24]. As might be expected, few Enterobacteriaceae, in comparison with gram-positive pathogens, were isolated from patients who were taking norfloxacin or who had stopped taking norfloxacin a few days before the onset of infection. All of the Enterobacteriaceae strains seen in the present study were resistant to norfloxacin. Despite cessation of norfloxacin prophylaxis, Enterobacteriaceae were a minority among isolated organisms; this may be the result of frequent and widespread use of antibiotics, including quinolones, to treat symptomatic infections in hospitalized cirrhotic patients.

In conclusion, the epidemiology of nosocomial SBP and bacteremia in hospitalized cirrhotic patients is characterized by a decreased prevalence of Enterobacteriaceae and a predominance of gram-positive cocci. The usual cytologic criterion in the diagnosis of SBP, a PMNL count >250 cells/mm³, does not seem valid for infection caused by gram-positive cocci, because most episodes of SBP that are caused by these organisms are symptomatic bacterascites and are associated with a PMNL count in ascitic fluid that is lower than this cutoff point. The emergence of staphylococci, in particular methicillin-resistant isolates, is of concern, because staphylococcal infections commonly recur, occur in multiple sites, and are associated with a poor outcome. Our study shows that vancomycin must be used to a greater extent to treat septic complications in cirrhotic patients. Indications for vancomycin treatment should be sought before the results of ascitic fluid and blood cultures are available (i.e., within 48 h after initiation of standard empiric antibiotic therapy) when standard therapy is not effective. Moreover, strategies are needed to limit transmission of these organisms and to prevent staphylococcal infections in units that admit patients who have end-stage liver cirrhosis.

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