Spontaneous Bacterial Peritonitis in Asymptomatic Outpatients With Cirrhotic Ascites

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The prevalence and natural history of spontaneous bacterial peritonitis in asymptomatic patients with ascites secondary to cirrhosis is unknown. From a prospectively recorded database, we reviewed the clinical and laboratory features of all outpatients with cirrhotic ascites undergoing paracentesis between July 1994 and December 2000. The prevalence of spontaneous bacterial peritonitis in the population of 427 cirrhotic outpatients as defined by neutrocytic ascites (absolute neutrophil count ≥250 cells/mm^3) was 3.5%. Of the 15 patients with neutrocytic ascites, 6 were culture positive (1.4%) and 9 culture negative (2.1%). Eight other patients (1.9%) had bacterascites. The organisms cultured from ascitic fluid in these asymptomatic patients with culture positive neutrocytic ascites and bacterascites were predominantly gram positive. No patient developed hepatorenal syndrome, and 1-year survival of 67% was better than historical data from hospitalized patients with spontaneous bacterial peritonitis. Moreover, patients who did not receive antibiotics for neutrocytic ascites fared no worse than patients who did receive antibiotics. In conclusion, spontaneous bacterial peritonitis in outpatients with cirrhotic ascites is less frequent, occurs in patients with less advanced liver disease, and may have a better outcome than its counterpart in hospitalized patients. In addition, the organisms cultured from ascitic fluid in outpatients are predominantly gram positive. A reassessment of diagnostic criteria for spontaneous bacterial peritonitis in outpatients may be required. (HEPATOLOGY 2003;37:897-901.)

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Spontaneous bacterial peritonitis (SBP) is a potentially life-threatening complication in patients with cirrhosis and has typically been described in hospitalized patients. In this group, SBP may be complicated by renal failure, systemic sepsis, recurrence, and diminished survival.[1-3] The prevalence of SBP in hospitalized patients with cirrhosis and ascites is between 10% and 30%.[4-6] The prevalence and outcome of SBP in asymptomatic outpatients with cirrhotic ascites has been less well studied. A small study of 29 patients with ascites undergoing repeated large volume paracentesis for refractory ascites did not demonstrate any patients with SBP.[7]

In 1998, the American Association for the Study of Liver Disease (AASLD) published guidelines for the initial ascitic fluid analysis in outpatients with cirrhosis.[8] The guidelines recommend determination of total nucleated cell count and a differential cell count on the initial ascitic fluid sample. Routine ascitic fluid bacterial cultures are not recommended unless infection is suspected. The AASLD guidelines recommend that a second paracentesis be carried out to obtain ascitic fluid for bacterial culture and antibiotic susceptibilities if the initial paracentesis shows an absolute neutrophil count of ≥250 cells/mm^3 (neutrocytic ascites). This recommendation, however, is based on data from a small Spanish study of 51 patients published only in abstract form.[9] The International Ascites Club recommends that routine cultures be obtained on ascitic fluid in hospitalized patients; the issue of ascitic fluid cultures in outpatients undergoing paracentesis is not addressed.[10] Thus, it appears that the majority of outpatients with cirrhotic ascites may not have ascitic fluid cultures at the time of paracentesis. Therefore, neither the prevalence of SBP nor the type of organisms cultured from ascitic fluid in this population is clearly known.

Abbreviations: SBP, spontaneous bacterial peritonitis; CNNA, culture-negative neutrocytic ascites; MELD, Model for End-Stage Liver Disease.

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The aim of this study was to determine the prevalence, characteristics, and natural history of SBP among outpatients with cirrhosis and ascites. The study was approved by the Mayo Institutional Review Board.

Patients and Methods

Patients. Since July 1, 1994, a database has been maintained for all patients referred for paracentesis to the Outpatient Procedure Suite of the Mayo Clinic Division of Gastroenterology and Hepatology. From that date to the end of December 2000, when the AASLD guidelines were put in place at our institution, obtaining ascitic fluid cultures on all patients undergoing initial diagnostic paracentesis was the accepted practice. During this period, a total of 513 outpatients with cirrhosis underwent paracentesis. The diagnosis of cirrhosis in these patients was confirmed both by cross matching the patient list against a computer database of diagnoses for each patient and by review of the medical records. The records include a detailed questionnaire filled out by the patient listing the current condition, as well as recent symptoms, medications, procedures, and so forth. To exclude the possibility that any of the patients may have had symptoms of SBP or were at risk for SBP, we excluded patients who had fever >38°C within 2 weeks (n = 29), gastrointestinal bleeding within 3 months (n = 6), significant abdominal pain or tenderness other than could be explained by ascites (n = 15), or worsening of renal function with any increase in serum creatinine to greater than 2.5 mg/dL over the previous 2 weeks (n = 19). None of the patients had hepatic encephalopathy more advanced than stage I because such patients would be hospitalized. Patients with a previous history of SBP (n = 8) and patients on antibiotic prophylaxis against SBP because of low protein ascites (n = 9) were also excluded. At the time of evaluation, no patients were on antibiotics for other reasons. Twelve patients had a serum ascitic fluid-albumin gradient <1.1 gram/dL, but they were already excluded for other reasons (fever n = 6, abdominal pain n = 4, recent gastrointestinal bleed n = 1, and recent worsening in renal function n = 1). Results of only the initial paracentesis carried out at the Mayo Clinic for these patients were analyzed.

Thus, of the 513 patients, 427 fulfilled criteria for inclusion in the analysis. The mean age of the cohort of 427 patients was 58.1 years. Twenty-six percent of the patients were female, and 74% were male. The etiologies of cirrhosis included alcoholic liver disease (n = 132, 31%), viral hepatitis (hepatitis B virus, hepatitis C virus, or a combination of both) with or without alcohol use (n = 162, 38%), cholestatic liver disease including primary biliary cirrhosis and primary sclerosing cholangitis (n = 51, 12%), and other etiologies including autoimmune liver disease, nonalcoholic steatohepatitis, hemochromatosis, cryptogenic, and others (n = 82, 19%). Paracentesis was carried out without ultrasound guidance using a standard sterile technique. Purely diagnostic paracentesis only was carried out in 21 patients; in the others, a therapeutic paracentesis was carried out. Laboratory analysis of the ascitic fluid in all patients included the following: total and differential cell counts, ascitic fluid agarose gel-based protein electrophoresis to determine total protein and albumin levels, and bacterial cultures obtained by bedside inoculation of 10 mL of ascitic fluid into culture bottles processed with the Bactec 9240 system (Becton Dickinson Europe, Meylan, France).[11,12] When indicated, cytology, as well as mycobacterial and other cultures, and more specific biochemical tests were carried out. Serum protein electrophoresis was obtained within 24 hours prior to paracentesis so that the serum-ascitic fluid albumin gradient could be calculated. Blood cultures were not drawn in any of the patients because they had no symptoms to suggest SBP.

Definitions. SBP was diagnosed using standard criteria, namely, an absolute neutrophil count of ≥250 cells/mm^3, that is neutrocytic ascites, in the absence of an intraabdominal source of infection.[10] If ascitic fluid cultures were positive and the neutrophil count was ≥250 cells/mm^3, such patients were diagnosed as having culture-positive neutrocytic ascites. If ascitic fluid cultures were negative in the presence of neutrocytic ascites, these patients were characterized as having culture-negative neutrocytic ascites (CNNA). Patients with positive cultures on ascitic fluid but without neutrocytic ascites were classified as having bacterascites.

Results

Prevalence of SBP Among Outpatients With Cirrhotic Ascites. Of the 427 patients who fulfilled criteria for having cirrhotic ascites without symptoms to suggest SBP, 15 patients fulfilled criteria for SBP with an absolute neutrophil count of ≥250 cells/mm^3. All 15 patients had SBP diagnosed on fluid obtained at therapeutic paracentesis: Mean volume of ascitic fluid obtained was 7.6 ± 5.2 liters. The mean MELD (Model for End-Stage Liver Disease) score[13] in this group was 17.9 (median 17.5, range 7-28). Because of missing values for creatinine in 150 of the patients, MELD scores could not be calculated in the cohort of outpatients without SBP. However, there was no statistically significant difference in the serum bilirubin (5.4 ± 7.5 mg/dL vs. 3.7 ± 4.9 mg/dL), serum albumin (2.9 ± 0.4 g/dL vs. 2.9 ± 0.5 g/dL), and international normalized ratio for prothrombin time

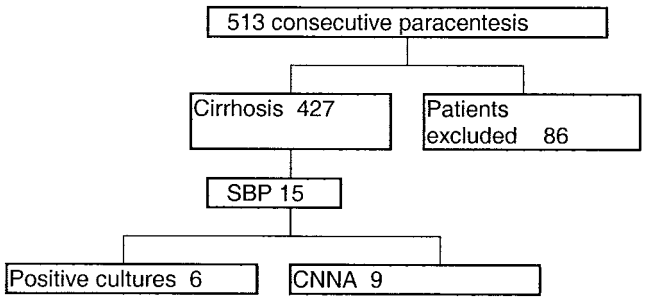

Fig. 1. Study design and results. Five hundred thirteen consecutive outpatients with cirrhotic ascites undergoing paracentesis were studied. Of these, 427 met inclusion criteria for the study. SBP (neutrocytic ascites) was diagnosed in 15 of the patients based on paracentesis results. Six of the patients with SBP had positive ascitic fluid cultures, and 9 had negative cultures. Eight other patients had bacterascites.

(1.5 ± 0.3 vs. 1.4 ± 0.5) between outpatients with and without SBP. The mean total protein in ascitic fluid was significantly lower in the SBP group (0.6 ± 0.04 g/dL) than in patients with bacterascites (0.9 ± 0.3 g/dL, $P = .045$) or with neither neutrocytic ascites nor positive cultures (1.1 ± 0.4 g/dL, $P = .03$). Nine of the 15 patients had CNNA, and 6 had culture-positive neutrocytic ascites. This results in a prevalence of SBP of 3.5% in asymptomatic cirrhotic outpatients undergoing paracentesis (Fig. 1). Details of the patients with SBP are given in Table 1. Eight other patients (1.9%) were diagnosed with bacterascites.

Spectrum of Pathogens. A wide variety of organisms grew from the ascitic fluid cultures. Organisms (number of patients) grown from the ascitic fluid of patients with neutrocytic ascites included the following: *Staphylococcus aureus* (n = 1), *Streptococcus viridans* (n = 3), *Staphylococcus saccharolyticus* (n = 1), and *Bacteriodes fragilis* (n = 1). Organisms isolated from the ascitic fluid of patients diagnosed with bacterascites included the following: *Staphylococcus aureus* (n = 2), *Streptococcus viridans* (n = 1), coagulase-negative *Staphylococcus* (n = 1), *Propionobacterium* (n = 3), and *Pseudomonas luteola* (n = 1).

Outcome of SBP in Outpatients With Cirrhosis. Ten of the 15 patients with neutrocytic ascites (including 6 with CNNA) were hospitalized for antibiotic therapy; intravenous albumin was not administered routinely. One patient with culture-positive neutrocytic ascites was treated with ciprofloxacin as an outpatient. In the 4 other

Table 1. Clinical and Laboratory Features of Patients With Spontaneous Bacterial Peritonitis

Serial No.	Age (y)	Gender	Etiology of Cirrhosis	Ascitic Fluid Total Nucleated Cell Count/mm³	Ascitic Fluid Absolute Neutrophil Count/mm³	Organism Cultured	Ascitic Fluid Protein g/dL	Hospitalized?	Antibiotic Used	MELD Score	Outcome
1	49	F	Alcohol	540	270	None	0.5	No	None	28	OLT 370 days
2	78	M	HCV	612	275	None	0.6	No	None	17	Alive 2 years
3	50	M	Alcohol	483	305	None	1.1	Yes	Ciprofloxacin	13	Died 240 days
4	69	M	HCV + alcohol	700	352	None	0.8	Yes	Trovafloxacin	24	Died 20 days
5	59	F	PSC	840	356	*Staphylococcus aureus*	0.6	Yes	Cefazolin	11	OLT 391 days
6	79	M	Alcohol	1,040	416	*Streptococcus viridans*	0.4	No	None	15	Alive 14 months
7	37	M	Cryptogenic	680	430	None	0.6	Yes	Cefotaxime	10	Lost to follow-up 29 days
8	50	M	Alpha-a-antitrypsin deficiency	620	434	None	0.5	No	None	18	Lost to follow-up 48 days
9	69	F	NASH	1,122	480	None	0.5	Yes	Cefotaxime	7	Died 6 yrs 7 months
10	74	M	Alcohol	980	594	None	0.7	Yes	Cefotaxime	18	Died 184 days
11	69	M	HCV	1,640	936	None	0.6	Yes	Cefotaxime	27	Lost to follow-up 64 days
12	53	M	HCV	1,562	1,160	*Streptococcus viridans*	0.5	Yes	Cefotaxime	15	Liver Tx 14 months
13	61	M	PSC	3,900	2,528	*Bacteriodes fragilis, Staphylococcus saccharalyticus*	0.5	Yes	Cefotaxime + Metronidazole	23	Died 28 days
14	62	F	HCV	4,800	3,402	*Neisseria meningitidis*	0.6	Yes	Cefotaxime	24	Alive 1 year
15	56	F	Alcohol + HCV	5,600	3,950	*Streptococcus viridans*	0.8	No	Ceftriaxone	18	Died 412 days

Abbreviations: HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation; PSC, primary sclerosing cholangitis.

Table 2. Clinical Outcomes

	Prevalence (%)	Hospitalized (%)	Initiation of Antibiotics (%)	30-Day Mortality (%)	90-Day Mortality (%)	1-Year Mortality (%)
SBP	15/427 (3.5)	10/15 (67)	11/15 (73)	17	17	33
Culture Positive	6/427 (1.4)	4/6 (67)	5/6 (83)	16	16	16
Culture Negative	9/427 (2.1)	6/9 (67)	6/9 (67)	11	11	43
Bacterascites	8/427 (1.9)	0/8 (0)	1/8 (13)	0	0	13

patients (one culture positive and 3 CNNA), the treating clinician determined that a neutrophil count of >500 cells/mm^3 was required before initiating therapy. None of these 4 patients developed symptoms to suggest SBP or had deterioration in either renal or liver function within 30 days. In fact, none of the 15 patients with neutrocytic ascites developed type I hepatorenal syndrome.[14] Follow-up for up to 1 year was available in 12 of these 15 patients (Table 2). Mortality at 1 year was 33% (4 of 12). Mortality at 1 year was 43% in the CNNA subgroup of SBP and 16% in the subgroup of ascitic fluid bacterial culture-positive patients. None of the 8 patients diagnosed with bacterascites were hospitalized, and only one of them was started on ciprofloxacin. Mortality at 30 and 90 days and 1 year in the bacterascites group was 0% and 13% (1 of 8), respectively. Of note, even though antibiotic prophylaxis was not used, there was no recurrence of SBP in any patient.

Discussion

This study supports the clinical suspicion that the prevalence of SBP among outpatients with cirrhosis is markedly low when compared with their hospitalized counterparts. Moreover, only one third of the outpatients diagnosed with SBP died within 1 year of the outpatient paracentesis as compared with a 1-year mortality of 50% to 70% in historically hospitalized patients with SBP.[1] It does appear, however, that SBP in asymptomatic outpatients has distinguishing features from SBP in hospitalized patients and may be a separate entity. The organisms cultured are predominantly gram positive in outpatients as compared with gram negative in hospitalized patients. Survival is better, and type I hepatorenal syndrome as a complication of SBP in outpatients is infrequent, whereas type I hepatorenal syndrome occurs in as many as 30% of inpatients with SBP.[15] Finally, recurrence of SBP is unusual in outpatients even when they are not on antibiotic prophylaxis. Similar to hospitalized patients, the ascitic fluid total protein is low in outpatients with SBP.

The criteria for diagnosing SBP in outpatients need to be addressed. There were 4 patients with an absolute neutrophil count of ≥250/mm^3 but less than 500/mm^3 who were not treated with antibiotics, yet none developed worsening of liver or renal function or clinical features of SBP within 30 days. Moreover, there were 8 patients with bacterascites with a favorable outcome, supporting the position that such patients do not require antibiotic therapy. The organisms cultured in these patients with bacterascites had a similar spectrum to those cultured in patients with neutrocytic ascites. Therefore, not only does spontaneous resolution of neutrocytic ascites without renal complications seem to occur in these patients, but, also, spontaneous clearance of bacteria may be taking place. In support of this are previous observations that the presence of neutrophils and bacteria in ascitic fluid are a very rapidly changing phenomenon. As many as 62% of episodes of bacterascites resolve without development of neutrocytic ascites.[16]

The spectrum of bacteria cultured in this study was dissimilar to previous studies in hospitalized patients with cirrhotic ascites. Although the organisms cultured are unusual and did not include *Escherichia coli* and *Klebsiella pneumoniae*, which are usually seen in hospitalized patients with cirrhosis, we believe that these are true infections because they were associated with neutrocytic ascites. The unusual organisms may reflect the nature of our practice in which a majority of patients are referred to us after initial evaluation elsewhere. A study published recently confirms the changing patterns of organisms cultured from patients with SBP.[17] In this study by Fernandez et al.,[17] the gram-positive organisms cultured were explained on the basis of norfloxacin prophylaxis or interventions previously carried out. However, repeated, careful review of the medical records of our patients suggested that they were neither on antibiotics in the weeks prior to the paracentesis nor had they any interventions. Thus, the predominance of gram-positive bacteria requires alternative explanations. Because the present study was carried out at a major referral center, the percentage of patients with asymptomatic SBP may be on the higher side, given the complexity of liver disease in this population. The mean MELD score of 17.9 in the outpatient population with SBP is lower than the mean MELD score (24.8) of a cohort of inpatients with SBP from Barcelona, Spain, and similar to patients with ascites without SBP (19.1) from the same center.[18] This indicates that outpatients with

SBP may have less severe disease as assessed by the MELD score than hospitalized patients with SBP.

The major strength of this study is that it has looked at a large number of cirrhotic patients over several years, minimizing the effect of a sampling error. Furthermore, the paracentesis as well as the ascitic fluid analysis was carried out under a standardized protocol, thus limiting the variability in handling of the ascitic fluid samples. The variation in how patients were treated following the availability of the results of ascitic fluid analysis reflects practice in the "real world" and thus gives an accurate estimate of survival in this group of patients.

Several limitations of the study require further discussion. The observations may be applicable only to patients seen in tertiary care referral centers. Though the database was collected prospectively, the study is limited by the retrospective analysis. For example, it was not possible to completely ascertain paracentesis or exposure to antibiotics within the few weeks prior to entry to the study. Prospective studies are needed to characterize the spectrum of pathogens in outpatients with cirrhotic ascites in the community, but, given the low prevalence of positive cultures in this group of patients, this information is not likely to significantly impact management of such patients. Second, we were not able to determine the Child-Pugh score accurately because of difficulty assessing the severity of ascites and encephalopathy from the medical record. Similarly, serum creatinine values were missing in a large proportion of patients without SBP, making it impossible to gauge the MELD scores in that group. Third, diagnosis and management of SBP was carried out by individual clinicians without a uniform protocol. Finally, the number of outpatients with SBP in our study are too small for us to make recommendations as to whether outpatient antibiotic therapy is preferred to inpatient therapy and to determine which outpatients, other than those with low protein ascites, are at higher risk for developing SBP.

We conclude that the prevalence of SBP in asymptomatic outpatients with cirrhotic ascites is low. The organisms cultured are predominantly gram positive. The 1-year mortality may be as high as 33% but lower than in hospitalized patients. The pathophysiology of spontaneous infection in outpatients with cirrhotic ascites may be more complex than in hospitalized patients because it seems to occur in patients with less advanced cirrhosis. Moreover, the infection may be reversible spontaneously. Thus, the grave prognosis associated with a diagnosis of SBP in inpatients may not be applicable to outpatients with neutrocytic ascites. Consequently, the criteria for diagnosis of SBP in outpatients may need to be reassessed.

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