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CLINICAL AND LABORATORY FEATURES OF SPONTANEOUS BACTERIAL PERITONITIS
L. Filik, MD, and S. Unal, Cemal Gursel Cad. Erk Apt., No: 52/2, Kurtulus, Ankara, 06520, Turkey

Request for reprints to: Dr. L. Filik, Cemal Gursel Cad. Erk Apt., No: 52/2. Kurtulus, Ankara, 06520, Turkey

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L. FILIK and S. UNAL

ABSTRACT

Background: **Spontaneous Bacterial Peritonitis (SBP) is a complication of cirrhosis. The mortality rate is approximately 30-50%. SBP is defined as an ascitic fluid infection in the absence of any obvious intraabdominal infectious foci. While earlier reports of SBP emphasized high mortality rates, recently lower mortality rates have been reported.**
Objective: **To evaluate the clinical and laboratory features and prognostic indicators of SBP.**
Design: **Retrospective study.**
Setting: **Hacettepe University Hospitals.**
Subjects: **A total of 281 SBP episodes of 214 patients between 3rd march 1981 and 3rd August 1999, in Hacettepe University Hospital were evaluated. Statistical analysis was performed in the group of patients having chronic liver diseases.**
Results: **One hundred and forty nine of the patients 214 (69.6%) were males and 65(30.4%) were females. The mean age of all patients were 49.91±15.01 years (17 to 90 years). All spontaneous ascites infection episodes were symptomatic. In all of the episodes, most common clinical features were as follows: icterus (54.5%), abdominal tenderness (54.5%), hepatic encephalopathy (50.7%), fatigue (46.7%), abdominal pain (44.4%) and fever (38.8%). The culture of the ascitic fluid resulted in isolation of a bacteria in 25.4% of all episodes. The most frequently isolated microorganisms turned out to be gram negative enteric bacterias (76.2%). Sixty seven patients in 179 cases with liver disease passed away (37.4%). The use of cefotaxime and newer cephalosporins seemed to have less mortality (31.7%) as compared with that (42.2%) observed in patients treated with other antibiotic regimens.**
Conclusions: **Of all the factors analysed in patients with chronic liver diseases, being Child-Pugh class C, having fatigue, hepatic encephalopathy, hypotension, higher peripheral blood leukocyte count (≥12000/mm^3), renal dysfunction (serum creatinine level ≥ 2mg/dl), longer prothrombin time (INR ≥2.5), lower ascites protein level (<lgr/dl) and, liver disease for longer time, developing superinfection (an infection other than SBP starting during SBP treatment) were statistically correlated with a higher death rate ($p<0.05$).**

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a severe complication of cirrhosis. SBP is defined as an infection of the ascitic fluid in the absence of any obvious intraabdominal bacterial foci. By definition, a positive ascitic fluid PMNL ≥ 250 cells/mm^3 are required for the diagnosis of SBP. Early diagnosis is crucial and is accomplished by diagnostic paracentesis performed at admission or at the occurence of any symptom or sign suggestive of SBP. A high index of suspicion of SBP and readiness to perform paracentesis are required for early diagnosis of this infection. SBP may present with any non-specific clinical findings (i.e. fever, abdominal pain etc) or as decompensation of liver disease and paracentesis should be performed to rule out this entity in any patient with cirrhotic ascites who is deteriorating(1-3).

SBP is seen in 8-27% of hospitalised cirrhotic patients. While earlier reports of SBP emphasized high mortality rates (90%), in recent years lower mortality rates have been reported (48%-57%). These reports of improved survival and efforts to explain prognostic indicators prompted this retrospective study in our institution(2,3).

Although SBP has been described as occuring in different clinical settings, such as heart failure, nephrotic syndrome, malignancy, it is usually seen as a complication of cirrhosis(2,4,5).

In this study, we investigated the prognostic indicators of all patients admitted to Hacettepe University Hospitals with SBP between 1981 and 1999. The value of identifying risk factors for SBP and its mortality lies not only in

identifying patients likely to benefit from preventive therapy, understanding the pathogenesis of the disease but also to find out the best treatment modality of SBP.

MATERIALS AND METHODS

Patients: The data was obtained from the files of patients who were admitted to Hacettepe University, Medical Faculty Hospitals between 1981 and 1999. The cases were included in the study, if they satisfied one of following criterias: a) Spontaneous bacterial peritonitis; a combination of a positive ascitic fluid culture, an ascitic neutrophil (PMNL) count ≥250 cells/mm^3 but no evident intra-abdominal source of infection. b) Culture-negative neutrocytic ascites; a PMNL count ≥ 250 cells/mm^3 with negative ascites culture but no evident intra-abdominal source of infection and no other explanation for an elevated ascitic PMNL count (i.e. pancreatitis, intraabdominal haemorrhage). c) Monobacterial non-neutrocytic bacterascites; a PMNL count <250 cells per mm^3 with positive ascitic fluid culture with a history and physical examination suggestive of SBP, but no evident intra-abdominal source of infection.

The cases were excluded from the analysis if the presence or absence of a particular finding was not clearly stated. Thus, denominators may vary according to the number of the cases in which the presence or absence of a finding could be clearly determined.

The mean age was documented in the first episodes of SBP. The prognostic factors regarding mortality in patients with chronic liver disease were based on the last episode of SBP if the case had more than one episode. The clinical features, time interval between starting of symptoms and diagnosis, were documented in all episodes without regarding which episode.

Two hundred and eighty one SBP episodes of 214 patients were reviewed. After a general review regarding symptomatology for all episodes, patients were divided into two major groups: SBP episodes of liver disease (179 patients) and SBP episodes of other diseases i.e. nephrotic syndrome, heart failure etc (35 patients). Statistical analysis of prognostic indicators was done in chronic liver disease group.

Statistical methods: The statistical significance tests between survivors and non-survivors included the Student's t-test for comparison of means in continuous variable and the chi-square test (continuity correction, Pearson, Fisher's exact test) for comparison of rates in categorical variables. The two-sided p-value was calculated for each statistical test. A p-value of ≤ 0.05 was considered significant.

RESULTS

In the study period, the records of 281 SBP episodes of 214 patients were reviewed. One hundred and forty eight of 214 patients (69.6%) were males and 65 patients (30.4%) were females. The mean age of all patients were 49.91 ± 15.01 years with a range of 17 to 90 years. Of 214 patients, 168 had one, 32 had two, 12 had three, one had five and one had eight episodes of ascites infection. The causes of ascites were chronic liver disease in 179 patients and other diseases in 35 patients. Ninety eight of 179 liver disease patients had histopathological diagnosis done. The most frequent liver disease was post hepatitis-B virus infection cirrhosis (51/98) and rest were other causes of chronic liver diseases. All spontaneous ascites infection episodes were symptomatic. The time interval elapsed from the initiation of symptoms and signs to diagnosis was found to be 24 hours in 62.8, 48 hours in 80% of all episodes. In 20% of all episodes, that time interval was longer than 48 hours. In all of the episodes, the most frequent presenting symptoms and findings were icterus, abdominal tenderness and hepatic encephalopathy, noted in 161 of out 274(54.5%), 152 out of 279(54.5%), 142 out in 280(50.7%) patients, respectively.

Tables 1 and 2 list the features of the patients that had been previously reported to have prognostic significance. Of all the factors analysed, being Child-Pugh class C, having fatigue, hepatic encephalopathy, hypotension, higher peripheral blood leukocyte count (≥12000/mm^3), renal dysfunction (serum creatinine level ≥2mg/dl), longer prothrombin time (INR ≥2.5), lower ascites protein level (<lgr/dl), liver disease for longer time, developing superinfection were found to be significantly related with mortality (p≤0.05). Similarly, the serum bilirubin level and duration of liver disease were also significantly related with mortality (Table 2).

The culture of the ascitic fluid gave a positive result in 25.4% of all episodes. The most frequently isolated microorganisms turned out to be gram negative enteric bacterias (76.2%) (Table 3). Blood cultures were positive in 17.5% (Table 4) and urine cultures were in 19.8% of the cases (Table 5). The ascitic fluid gram stain detected bacteria in 32.9% of samples. Sixty seven episodes of patients with liver disease resulted in the patient's death (37.4%). The use of cefotaxime and newer cephalosporins led to a diminished mortality (31.7%) as compared with that (42.2%) observed in patients treated with other antibiotic regimens (Table 6).

Table 1

Prognostic factors in patients with SBP

Variable	Mortality No. (%)	Statistical analysis (p-value)
Child Score b	6 (18.2)	0.018
Child Score c	42 (43.3)	
Abdominal pain present	27 (35.5)	0.601
Abdominal pain absent	39 (39.4)	
Fatigue present	36 (46.2)	0.050
Fatigue absent	30 (31.6)	
Gl Haemorrhage present	11 (52.4)	0.222
Gl Haemorrhage absent	56 (35.9)	
Hepatic encephalopathy present	49 (49.0)	0.000
Hepatic encephalopathy absent	17 (22.1)	
Hypotension present	22 (62.9)	0.002
Hypotension absent	45 (32.1)	
Hypothermia present	4 (80.0)	0.059
Hypothermia absent	43 (34.7)	
Fever present	16 (27.1)	0.058
Fever absent	50 (43.1)	
Episode no = 1	46 (33.8)	0.095
Episodes no > 1	20 (50.0)	
Leukocyte (mm^3) >12000	27 (52.9)	0.013
Leukocyte (mm^3) <12000	38 (31.4)	
Thrombocyte (mm^3) >98000	24 (31.2)	0.580
Thrombocyte (mm^3) <98000	23 (37.1)	
Creatinine (mg/dl) <2	39 (30.0)	0.000
Creatinine (mg/dl) ≥2	26 (66.7)	
Total Bilirubin (mg/dl) <2.5	11 (28.2)	0.282
Total Bilirubin (mg/dl) ≥2.5	50 (39.4)	
Prothrombin time (INR) <2.5	10 (23.3)	0.022
Prothrombin time (INR) ≥2.5	49 (45.0)	
Ascites protein (g/dl) <1	30 (42.9)	0.049
Ascites protein (g/dl) ≥1	14 (24.6)	
Superinfection present	11 (73.3)	0.005
Superinfection absent	37 (32.5)	

Table 2

Prognostic factors in patients with SBP

	Mean±SD (death)	Mean ± SD (cure)	Statistical analysis (p-value)
T. Bilirubin (mg/dl)	12.060±14.224	5.572±7.807	0.000
Chronic liver disease duration (month)	33.62±33.99	25.41±38.11	0.039
Thrombocyte (mm^3)	137394±113064	141598.21±106107.16	0.548

Table 3

Ascitic fluid culture results

Bacteria (n=232)	No.	(%)
E. coli	29	12.5
Enterobacter	8	3.4
Klebsiella	6	2.6
S. pneumoniae	6	2.6
Acinetobacter	3	1.3
Pseudomonas	2	0.9
Enterococcus	2	0.9
MRSA	2	0.9
S. maltophilia	1	0.4
No microorganisms	173	74.6

Table 4

Blood culture results

Bacteria (n=143)	No.	(%)
E. coli	15	10.5
Enterobacter	3	2.1
Pseudomonas	3	2.1
Klebsiella	2	1.4
Enterococcus	1	0.7
Acinetobacter	1	0.7
No microorganisms	118	82.5

Table 5

Urinary culture results

Bacteria (n=207)	No.	(%)
E. coli	15	7.2
Enterobacter	7	3.4
Klebsiella	4	1.9
Pseudomonas	3	1.4
Enterococcus	3	1.4
MSSE	2	0.9
Acinetobacter	1	0.5
Proteus	1	0.5
Candida	5	2.4
No bacteria	166	80.2

Table 6

Mortality in chronic liver disease patients with respect to antibiotic used

Treatment	Mortality	
	No.	(%)
Cefotaxime	39/123	31.7
SAM/CAM	11/16	68.8
Ofloxacine / Ciprofloxacine	7/15	46.7
Pen G+Gentamycine	9/15	37.5
Imipenem	1/1	100
Total number of deaths	67/179	

DISCUSSION

This retrospective study documents 214 patients of SBP, but 179 with liver cirrhosis. In general, the clinical features, laboratory findings and prognostic indicators found in this study are compatible with those in previous reports (9-14).

While the earlier studies reported high mortality in SBP to be as high as 80%, more recent reports note mortality rates of 20-40%. However, overall patient mortality remains much higher (80%) despite successful treatment of peritonitis (2,6,7). In this study, the in-hospital mortality was found to be 37.4% for unselected group of cirrhotic patients. The mortality rate observed in this study was consistent with the mortality reported in some recent series. But, Hacettepe University Hospital is a tertiary care center, that's why the rate may not reflect the true mortality of SBP in the community.

In our study, of all the factors analysed, being Child-Pugh class C, having fatigue, hepatic encephalopathy, hypotension, higher peripheral blood leukocyte count ($\geq 12000/mm^3$), renal dysfunction (creatinine ≥ 2 mg/dl), longer prothrombin time (INR≥ 2.5), lower ascites protein level (<1 gr/dl) and, liver disease for longer time, developing super infection were independently correlated with a higher death rate ($p<0.05$). It is predicted so, because being Child-Pugh class C, having hepatic encephalopathy, renal dysfunction (creatinine ≥ 2mg/dl), longer prothrombin time (INR≥ 2.5), and, liver disease for longer time are some of the indicators reflecting the severity of loss liver functions which is the principal determinant of survival (15,16). Lower ascites protein levels (<lgr/dl) have been demonstrated to correlate with ascites opsonic activity as well as with concentrations of other local defense substances such as complement, immunoglobulins, and

fibronectin in several studies(17). When the total bilirubin level was accepted as 2.5 mg/dl, it didn't seem to be an independent risk factor for mortality, but the total bilirubin levels were statistically different between patients cured and those who died. Then, we could accept the total bilirubin level higher than 2.5 mg/dl - for example 3.2 mg/dl as Guarner *et al* defined as a risk factor increasing mortality(18).

The previous studies showed that variceal haemorrhage increased risk of development and mortality of SBP, but in our study we didn't see any survival difference between the patients with and without variceal haemorrhage(1,2,19).

Another important observation was that all the cases were symptomatic. It has been known that around 10% of cases of spontaneous ascites infection are asymptomatic(1-4). Some degree of underestimation and delay in the diagnosis might have caused that result. Thrombocyte level wasn't found to be an independent risk factor and also the mean of thrombocyte levels were not statistically different between patients recovered and those who died. Whereas Guarner *et al.* stated that thombocytopenia was one of the risk factors for development of SBP(18).

Superinfection is more common in compromised patients, then the increased mortality is expected in patients with SBP developing superinfection. It has been suggested that survival is expected to improve further if SBP is treated with non-nephrotoxic antibiotics like cefotaxime(20-23). Our findings corroborate this data since the use of cefotaxime and newer cephalosporins led to a diminished mortality (31.7%) as compared with that observed in patients treated with other antibiotic regimens (42.2%). Our study would appear to support the empirical use of cefotaxime in suspected SBP.

Fever, abdominal pain and hypothermia had no adverse effect on outcome regardless of the mechanism.

The mortality rates were not significantly different related with the episode number of SBP (=1 or >1). That finding contradicts the previous studies in which because those patients survive an episode of SBP are at high risk of recurrence: 43% at six months, 69% at one year, 74% at two years and recurrent episodes increase the mortality as a reflection of worsening of liver functions(2).

The culture of the ascitic fluid gave positive results in 25.4% of all episodes. The most frequently isolated microorganisms turned out to be gram negative enteric bacterias (76.2%). The 25.4% positivity rate in our cases was lower than quoted by other studies(24-30). Blood cultures were positive in 17.5% and urine cultures were in 19.8% of the cases which were slightly lower than previous reports(2,4,31,32). The diagnostic usefulness of gram stain has varied widely in previous reports, in our study the ascitic fluid gram stain detected bacteria in 32.9% of samples, our rate of positive stains is consistent with the previous reports(33,34).

Sixty seven episodes of patients with liver disease resulted in the patient's death (37.4%). The use of cefotaxime and newer cephalosporins led to a diminished mortality (31.7%) as compared with that (42.2%) observed in patients treated with other antibiotic regimens. Our findings corroborate that if SBP is treated with non-nephrotoxic antibiotics like newer cephalosporins (35-40).

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