

## Spontaneous Bacterial Peritonitis among Cirrhotic Patients in Upper Egypt: Clinical and Bacterial Profiles

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### ABSTRACT

**BACKGROUND:** Spontaneous bacterial peritonitis (SBP) and its variants represent fatal and serious complications in cirrhosis patients with ascites. However, few detailed data are available regarding the clinical and bacteriological feature of SBP in our Locality. This work aimed to determine the predictors and variants of SBP, and the

bacterial pathogens.

**METHODS:** We prospectively analyzed clinical characteristics and bacteriological profiles of 150 cirrhotic patients with ascites.

**RESULTS:** 53 (35.3%) patients had SBP. 29 (54.7%) patients found to be classical type, 19 (35.8%) patients found to be CNNA, and 5 (9.4%) patients found to have bacterascites. Patients with SBP have higher bilirubin, CRP, INR, MELD score, Child score, and turbid ascites while those with no SBP had significantly higher serum albumin and total proteins. The predictors for SBP were previous history of SBP (OR = 4.56, 95%CI = 1.22- 3.33;  $p = 0.02$ ) and low albumin in the ascitic fluid (OR= 2.34, 95%CI = 2.01- 4.01;  $p = 0.03$ ). The most frequently isolated organisms in the 34 patients who have positive culture were *E. coli* (41.1%) and *Staph. aureus* (35.3%) followed by *Streptococcus* (11.7%), *Pseudomonas* (5.9%) and *Pneumococci* (5.9%). In the current study, the frequency of gram positive organisms in combination was 52.9% (18/34).

**CONCLUSION:** SBP is a serious complication that occurred in cirrhotic patients with ascites so, early empirical antibiotic is a key strategy in improving the prognosis in these patients. The frequency of gram positive organisms in SBP is increasing. It is essential to perform periodic epidemiological and bacteriological surveillance to adapt treatment recommendations.

**Key words:** SBP; Cirrhosis; Bacterial Profiles

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### INTRODUCTION

Bacterial infections in patients with liver cirrhosis are major complication of cirrhosis where 25%-46% of hospitalizations in cirrhotic patients owe to bacterial infection and so, bacterial infections will be associated with acute decompensation events with high morbidity and mortality in such patients<sup>[1]</sup>.

Spontaneous bacterial peritonitis (SBP) is an acute bacterial

infection of the ascitic fluid with no an obvious surgically-treatable source. SBP is suspected with presence of manifestations as fever, abdominal pain, or disturbed mental status in patients with cirrhosis and ascites<sup>[2]</sup>.

SBP is considered one of most frequent bacterial infection that occurs in patients with cirrhosis. About 7% and 30% of hospitalized patients with cirrhosis and ascites will develop SBP, representing one of their main complications. Cirrhotic patients with ascites had poor prognosis with development of SBP where acute kidney injury, acute-on-chronic liver failure, and death occur in such patients as much as 54%, 60%, and 40% of the patients, respectively<sup>[3]</sup>.

Additionally, recurrence of SBP is a major problem facing those patients where it reaches up to 70% if no prophylaxis is implemented. For this reason universal secondary antibiotic prophylaxis is recommended, since it decreases the probability of recurrence to 20% with survival improvement<sup>[4]</sup>.

The main action to prevent the majority of complications secondary to SBE is prompt and appropriate empirical antibiotic therapy must be received as early as possible on suspicious of SBP to cover the most commonly isolated bacteria. Based on previous studies, gram-negative bacteria, mainly *Enterobacteriaceae*, were major accused organisms of SBP and so, third generation cephalosporin are the first empirical line of antibiotics to treat SBP<sup>[5]</sup>.

However, major changes in the bacteriology of infections in patients with cirrhosis occurred over the last few decades with an increasing prevalence of gram-positive, quinolone-resistant, and multidrug-resistant bacteria<sup>[2]</sup>. A rising prevalence of gram-positive bacteria was reported over the past years in North America, South America, and Europe representing at present 48%-62% of the isolated organisms. The most frequent gram positive isolates are *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus* spp<sup>[6]</sup>.

**Aim of the work:** This work was designed to assess the frequency of SBP in patients with liver cirrhosis and ascites in our locality, determine its predictors and identify the bacterial pathogens and their sensitivity pattern to find out the optimal antibiotic choice.

## METHODS

### Setting and study design

The current study was prospectively performed on 150 patients in the Department of Tropical Medicine & Gastroenterology at Al-Rajhi Liver Hospital, Assiut University in the period between June 2016 and June 2017. After obtaining institute's Ethics committee approval and valid written informed consent, patients were enrolled in the study.

All patients with liver cirrhosis and ascites admitted during the mentioned period were included in our study. Patients who refused to give consent, patients with a documented evidence of intra-abdominal source of infection or patients with ascites due to non-hepatic causes like nephrotic syndrome and congestive cardiac failure were excluded.

We recorded clinical and demographic data (age, sex, symptoms, signs...etc.), disease manifestations (jaundice, ascites, lower limb edema...etc), and laboratory findings (liver function tests, blood urea nitrogen, serum creatinine, international randomized ration, C-reactive protein and complete count), and disease severity based on Child and MELD scores. Abdominal ultrasonography was performed for all patients with a special focus on the liver, spleen and kidney in terms of size and echogenicity, degree of ascites and nature (clear or turbid), presence or absence of bands of adhesion and the presence or absence of Hepacocellular carcinoma (HCC).

### Ascitic fluid study

Ascitic fluid samples were extracted at the patient's bedside by aseptic manipulation where about 3 ml of ascitic fluid was used in plain tube for measurement of protein and albumin. Another 2 ml of fluid collected in tubes containing EDTA anticoagulant were used for White blood cell count (WBCs) and Polymorphonuclear leucocyte count (PMNL) by automated counter. Ascitic fluid cultured on blood broth (modified culture method and antibiotic sensitivity tests were done in cases of positive growth).

The bacteriologic examination for ascitic fluid was performed using the modified culture method<sup>[7]</sup>. Briefly, inoculation of 10 mL of the ascitic fluid into blood culture bottles was done. The bottles were kept under both anaerobic and aerobic conditions at 37 °C for about 5 days in BACTEC 9050 automatic blood culture system (Becton-Dickinson Diagnostic Systems, MD, USA). Each bottle was tested every 10 min by the BACTEC instrument. Positive bottles for bacteria were removed from the BACTEC system. Gram staining and sub-culture were done to identify the microorganism.

### Diagnosis of SPB

According to ascitic fluid PMNL count and ascitic fluid culture, the following variants were defined<sup>[8]</sup>: (1) Classical spontaneous bacterial peritonitis variant: In which PMNL count in ascitic fluid was equal to or more than 250/mm<sup>3</sup> and ascitic fluid culture was positive; (2) Culture negative neutrocytic ascites variant: In which ascitic fluid culture was negative and diagnosis was based on PMNL count in ascitic fluid was equal to or more than 250/mm<sup>3</sup>; (3) Bacterascites variant: In which ascitic fluid culture was positive but PMNL count in ascitic fluid was less than 250/mm<sup>3</sup>.

### Empirical antibiotic therapy

Cefotaxime was used as an empirical therapy in all patients with ascitic PMN count  $\geq 250$  cells/ $\mu$ L, without waiting results of culture. Also, it was used in bacterascites patients with signs of systemic inflammation. Otherwise, those patients required a second paracentesis and patients in whom the repeat PMN count is  $\geq 250/\mu$ L would be treated for SBP. Based on results of culture and sensitivity, cefotaxime should be changed<sup>[9]</sup>.

### Ethics & Consents

The study was approved by the Faculty's ethics committee and permission was obtained from the ethics committee who was assured that confidentiality would be maintained and ethical principles would be followed. A background about the study and its reason was explained, and the targeted population was encouraged to participate without any undue pressure, and a written consent was taken from each participant.

### Statistical Analysis

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean  $\pm$  SD or median (range) while nominal data were expressed in form of frequency (percentage). *Chi*<sup>2</sup>-test was used to compare the nominal data of different groups in the study while student t-test was used to compare the mean of different groups. Multivariate regression analysis was used to determine the risk factors of SBP in patients with liver cirrhosis and ascites. *P* value was significant if  $< 0.05$ .

## RESULTS

One hundred and fifty patients with liver cirrhosis and ascites were

enrolled in the study, out of them 53 (35.3%) patients developed SBP based on clinical evaluation, and ascitic fluid analysis. We compared both groups with SBP (53) and without (97). It was noticed that the majority of both groups were males. It was noticed that, previous history of SBP, abdominal pain and abdominal tenderness were significantly higher in SBP group. 66% of patients who developed SBP had suspicious of BP a time of admission. Other baseline data are shown in table 1.

Table 2 shows that bilirubin, CRP, INR, MELD score, Child score, and turbid ascites were significantly higher in those patients with SBP while those with no SBP had significantly higher serum albumin and total proteins. By multivariate regression analysis, the current study showed that the predictors for SBP in patients with liver cirrhosis and ascites were previous history of SBP (OR = 4.56, 95% CI = 1.22-3.33;  $p = 0.02$ ) and low albumin in the ascitic fluid (OR = 2.34, 95% CI = 2.01- 4.01;  $p = 0.03$ ) (Table 3).

Out of those patients with SBP, 48 (90.6%) patients had PMNL in the ascitic fluid  $\geq 250 /\text{mm}^3$  while 34 (64%) patients of them had positive growth on culture. The most frequently isolated organisms were *E. coli* (41.1%) and *Staph. aureus* (35.3%) followed by *Streptococcus* (11.7%), *Pseudomonas* (5.9%) and *Pneumococci* (5.9%). The frequency of Gram positive organisms in combination was 52.9% (18/34). As regards sensitivity tests; all isolated organisms were sensitive to Cefotaximie (3<sup>rd</sup> generation cephalosporin). *Staph. aureus* was also sensitive to trimethoprim-sulfamethoxazole, *E.coli* was sensitive to Tazobactam, and *pneumococcus* was sensitive to fluoroquinolones (Figure 1).

The most frequent variant was classical SBP (54.7%) followed by culture-negative neutrocytic ascites (35.9%) and monomicrobial non-neutrocytic bacterascites (9.4%) (Table 4).

## DISCUSSION

We studied 150 patients; 90 males and 60 females. Ascitic fluid samples were obtained from all patients for ascitic fluid analysis, including (PMNL count, total protein and albumin), and bed side culture on blood broth.

Out of them, 53 (35.3%) patients are actually having SBP based on clinical data, and ascitic fluid chemical analysis and culture. In contrast to this result, Bibi *et al*<sup>[10]</sup> (2015) revealed that out of the total 152 patients, 38 (25%) patients had SBP but our results were nearly similar to that obtained by Mohammad *et al*<sup>[11]</sup> (2016) where 54 (31%) patients out of 176 studied patients were diagnosed as SBP.

Riggio *et al*<sup>[12]</sup> (2008) stated that automated cell counter should replace the manual counting for PMNL in the ascitic fluid due to the accuracy and rapid differential counts of leukocytes.

Makhlouf *et al*<sup>[13]</sup> (2018) studied 87 cirrhotic patients with ascites (HCV related) from April 2015 to September 2015, and found that 49 (56.3%) patients were defined as SBP which was higher than in the current study. This may be attributed to early recognition and management of risk factors for SBP.

Prior history of SBP in the current study was significantly higher in those with SBP when compared to those without SBP (35.8% versus 4.1%;  $p = 0.03$ ). Our results were in contrast to the study of Mohammad *et al*<sup>[11]</sup> (2016) which showed that only 14 (26%) patients from 54 SBP cases had previous episodes.

Frequency of abdominal pain and tenderness, in our study, were significantly higher in those patients with SBP (73.6% and 66% respectively) in comparison to those with no SBP (50.5% and 47.4% respectively) ( $p < 0.05$ ). Also, fever was significantly higher in those with SBP (54.7%) in comparison to those with no SBP (15.5%,  $p = 0.02$ ). Similarly, Makhlouf *et al*<sup>[13]</sup> (2018) found that SBP cases had

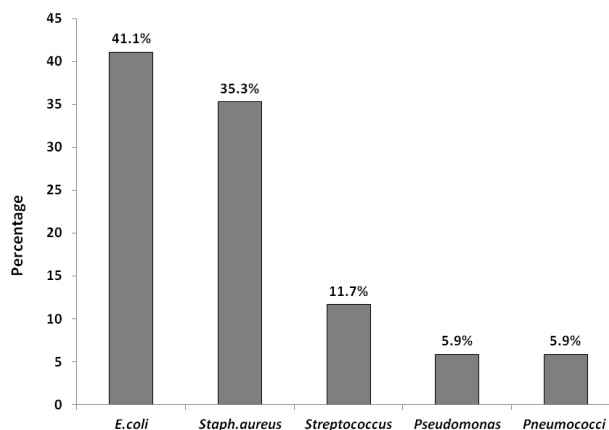


Figure 1 Type of isolated organism in patients with SBP and positive culture.

Table 1 Demographic data of the studied patients.

	SBP (n = 53)	No SBP (n = 97)	P value
Age (years)	57.26 ± 14.15	55.72 ± 14.14	0.52
Sex			
Male	37 (69.8%)	53 (54.6%)	0.3
Female	16 (30.2%)	44 (45.4%)	
Residence			
Rural	41 (77.4%)	70 (72.2%)	0.32
Urban	12 (12.6%)	27 (27.8%)	
Comorbidities			
No.	35 (66%)	68 (70.2%)	0.23
Diabetes mellitus	11 (21%)	15 (15.4%)	
Hypertension	4 (7.5%)	10 (10.3%)	
Cardiac disease	2 (3.7%)	4 (4.1%)	
Chronic kidney disease	1 (1.8%)	0(0%)	
Previous history of SBP	21 (39.6%)	4 (4.1%)	0.03
Abdominal pain	39 (73.6%)	49 (50.5%)	0.01
Abdominal tenderness	35 (66%)	46 (47.4%)	0.04
Fever	29 (54.7%)	15 (15.5%)	0.02
Causes of admission			
Suspected SBP	35 (66%)	0(0%)	0.04
Hematemesis	6 (11.3%)	45 (46.4%)	
Hepatic encephalopathy	2 (3.8%)	30 (30.9%)	
Suspected HRS	10 (18.9%)	22 (22.7%)	

Continuous data were expressed in the form of mean (SD) while nominal data in the form of frequency (percentage). P value was significant if  $< 0.05$ . SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome

higher percentage of abdominal pain (89.9%), fever (65.3%) and abdominal tenderness (55.1%) than non SBP cases.

Many studies either local or international said SBP had wide, highly variable and non-specific presentation and some patients often being asymptomatic and hence diagnostic paracentesis to confirm the diagnosis is recommended<sup>[14]</sup>. It is important to point out that SBP may be asymptomatic, particularly in outpatients<sup>[15]</sup>.

In the current study, patients with SBP had significantly higher bilirubin, C- reactive protein, Child score and MELD score and significantly lower serum albumin and total proteins. These results were consistent to that obtained by Huang *et al*<sup>[16]</sup> (2011) as regarding bilirubin level, Child score and MELD score, but El-Gendy *et al*<sup>[17]</sup> (2014) showed that, there was no significant difference between SBP and non SBP groups as regard to CRP mean value.

Makhlouf *et al*<sup>[13]</sup> (2018) found significant difference between

**Table 2** Baseline Laboratory and Sonographic Data in both Groups.

Data	SBP (n = 53)	No SBP (n = 97)	p value
<b>Liver function tests</b>			
Bilirubin (μmol/l)	81.24 ± 21.87	41.06 ± 10.98	0.02
Direct bilirubin (μmol/l)	57.5 ± 12.13	26.98 ± 8.99	0.01
Serum albumin (mg/dl)	21.20 ± 7.35	25.10 ± 5.70	0.03
Alanine transaminase (U/l)	52.09 ± 10.11	54.68 ± 13.22	0.46
Aspartate transaminase (U/L)	63.01 ± 17.13	66.01 ± 12.67	0.99
Total protein (mg/dl)	65.70 ± 12.48	71.96 ± 10.68	0.03
<b>Kidney function tests</b>			
Blood urea nitrogen (mg/dl)	15.16 ± 4.09	9.98 ± 3.02	0.09
Serum creatinine (mg/dl)	1.51 ± 0.54	1.34 ± 0.65	0.07
<b>Complete blood picture</b>			
Total leucocytic count (x10 <sup>6</sup> /ml)	9.53 ± 2.70	8.39 ± 1.73	0.13
Hemoglobin (g/dl)	9.63 ± 1.83	9.93 ± 1.71	0.59
Platelets (x10 <sup>6</sup> /ml)	120.64 ± 35.21	113.11 ± 22.98	0.21
International normalization ratio	2.01 ± 0.79	1.46 ± 0.29	0.03
<b>Serum electrolytes</b>			
Sodium (μmol/l)	132.1 ± 5.04	136.33 ± 6.65	0.09
Potassium (μmol/l)	4.03 ± 0.95	3.87 ± 0.63	0.45
C- reactive protein (mg/dl)	45.87 ± 11.08	32.10 ± 12.86	0.03
MELD score	17.24 ± 1.36	15.11 ± 1.03	0.03
<b>Grades of ascites</b>			
Mild	12 (22.6%)	24 (24.7%)	0.9
Moderate	30 (56.6%)	55 (56.7%)	
Marked	11 (20.8%)	18 (18.6%)	
<b>Characteristics of ascites</b>			
Clear	25 (47.2%)	61 (62.9%)	0.02
Turbid	28 (52.8%)	36 (37.1%)	
<b>Child classification</b>			
B	7 (13.2%)	46 (47.4%)	0.01
C	46 (86.8%)	51 (52.6%)	
Child score	11.98 ± 2.24	9.80 ± 1.87	0.01

Continuous data were expressed in the form of mean (SD) while nominal data in form of frequency (percentage). *p* value was significant if < 0.05. SBP: spontaneous bacterial peritonitis; MELD: model for end stage liver disease

both groups regarding total serum bilirubin, and CRP where these values were higher in SBP cases (*p* value = 0.037, *p* value = 0.001) respectively. In the current study, frequency of Child C class was significantly higher in patients with SBP which was consistent with the results obtained from the study of Schwabl *et al.*<sup>[18]</sup> (2015).

We found that ascitic fluid proteins and albumin were significantly lower in those patients with SBP in comparison to those with no SBP. Similarly, Novella *et al.*<sup>[19]</sup> (1997) found ascitic fluid protein was significantly lower in SBP patients. Also, our study showed similar result to that obtained by Verma *et al.*<sup>[20]</sup> (2017) who reported that patients with spontaneous bacterial peritonitis were found to have significantly lower ascitic fluid albumin in comparison to patients with sterile cirrhotic ascites.

Out of 53 patients who diagnosed as SBP in this work: 48 (90.6%) patients had ascitic fluid PMNL ≥ 250 cell/ml and in remaining 5 (9.4%) patients had ascitic fluid PMNL < 250 cell/ml. In the present study, from 53 patients who were diagnosed as SBP, there were 29 (54.7%) patients found to be classical type, 19 (35.8%) patients found to be CNNA, and 5(9.4%) patients found to have bacterascites.

Bibi *et al.*<sup>[10]</sup> (2015) found out of the 38 patients who developed SBP, classical type was present in 8 (21%) patients, CNNA was found in 20 (52.6%), and 10 (21.3%) patients were found to have

**Table 3** Predictors of SBP in patients with LC and ascites.

Variables	Odd's ratio	95% confidence interval	p value
Abdominal pain	1.98	0.40- 1.20	0.35
Fever	1.02	0.04- 0.18	0.21
Previous SBP	4.56	1.22- 3.22	0.02
Suspected SBP at admission	1.34	0.09- 1.22	0.52
Total bilirubin	3.02	2.11- 2.23	0.21
Total proteins	1.22	1.22- 2.33	0.67
Prothrombin time	1.23	0.98- 1.23	0.36
High C reactive protein	0.99	1.02- 2.01	0.45
Low albumin in the ascitic fluid	2.34	2.01- 4.01	0.03
Child C class	1.23	0.34- 0.99	0.56
MELD score	1.94	1.01- 2.09	0.33

*P* value was significant if < 0.05. MELD: model for end stage liver disease; LC: liver cirrhosis.

**Table 4** Variants of ascitic fluid infection in the current study.

Variants	Ascitic fluid analysis	N = 53
Classical SBP	Positive culture with PMNL ≥ 250 cell/mm <sup>3</sup>	29 (54.7%)
CNNA	Negative culture with PMNL ≥ 250 cell/mm <sup>3</sup>	19 (35.9%)
MNB	Positive culture with PMNL < 250 cell/mm <sup>3</sup>	5 (9.4%)

Data was expressed in the form of frequency (percentage). SBP, spontaneous bacterial peritonitis; CNNA, culture-negative neutrocytic ascites; MNB, monomicrobial non-neutrocytic bacterascites.

bacterascites.

The difference between the current study and previous studies could be attributed to the different culture techniques as Pawar *et al.*<sup>[21]</sup> (1994) has reported a significant association between the culture technique and culture positivity ratio. Also, we used the modified culture method through enrichment in blood culture bottles by immediately placing up to 10 mL of the peritoneal fluid into each blood culture bottle (10 mL/bottle maximum) which may be responsible for the increased detection rate of the causative organism<sup>[7]</sup>.

The most frequent accused organism in the 34 patient who have positive culture in the present study was *Escherichia coli* where it occurred in 14 (41.1%) patients and was sensitive to Cefotaxime and Tazobactam, followed by *Staph.aureus* that occurred in 12 (35.3%) patients and was sensitive to Cefotaxime and Septrin followed by *Streptococcus* (11.7%), *Pseudomonas* (5.9%) and *Pneumococci* (5.9%). The other cases that had negative culture, their diagnosis was according to ascitic fluids PMNL count which was equal to or above 250 cell/mm<sup>3</sup> where 19 (35.8%) patient, met this criteria and this called culture negative neutrocytic ascites (CNNA) and they were given Cefotaxime.

In the study of Kawale & his co-workers (2017)<sup>[22]</sup>, the ascitic fluid culture was positive in 27 (54%), CNNA was seen in 23 (46%). *E. coli* (40%) was the most commonly found organism in ascitic fluid, followed by *streptococcus pneumoniae* (8%), *Klebsiella* (4%), and anaerobe was seen in 2% cases. Mohammad & colleagues (2010)<sup>[23]</sup> reported that *E-coli* were isolated from (61.55%) and *Streptococci* in (15.38%).

In a study done by Tsung & co-workers (2013)<sup>[24]</sup>, they reported that *Escherichia coli* were detected in (12 of the 47 cases, 25.5%), *Klebsiella* species (9 cases, 19.1%) and *Streptococcus* species (9 cases, 19.1%) and the remaining were CNNA.

High rates of resistance against Cephalosporins and Fluoroquinolones were reported from previous studies but international data still suggests a higher sensitivity to these drugs<sup>[25]</sup>.

In the current study, the frequency of gram positive organisms



in combination was 52.9% (18/34). Similarly, Alexopoulou *et al*<sup>[26]</sup> (2013) reported that gram-positive cocci (GPC) were found to be the most frequent cause in culture-positive SBP in (55%) and a variety of drug - resistant microorganisms have emerged.

In conclusion, SBP is one of the most serious complications that occurred in cirrhotic patients with ascites so, early empirical antibiotic therapy is a key strategy in improving the prognosis in these patients. Primary and secondary spontaneous bacterial peritonitis prophylaxis have proven to be effective, but should be used with caution to reduce the risk of bacterial resistance development. The frequency of gram positive organisms in SBP is increasing. It is essential to perform periodic epidemiological and bacteriological surveillance to adapt treatment recommendations.

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