

# Features and Outcomes of Spontaneous Bacterial Peritonitis in Egypt, Single Center Experience

Khaled A. Gameel<sup>1</sup>, Maha M. Elsabaawy<sup>1</sup>, Mahmoud A. El Tahawy<sup>1</sup>, Azza M. Abd-Elaziz<sup>2</sup>, Imam A. Waked<sup>1</sup>

<sup>1</sup>Department of Hepatology, National Liver Institute, Menofia University, Shebin El Koum, Egypt <sup>2</sup>Department of Microbiology and Immunology, National Liver Institute, Menofia University, Shebin El Koum, Egypt Email: tahawy1000@hotmail.com

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# Abstract

Spontaneous bacterial peritonitis (SBP) is a serious complication of liver cirrhosis, with a recurrence rate up to 70% at 1 yr. Diagnosis of SBP is based on a positive ascitic fluid (AF) culture and/or a polymorph nuclear leukocyte count of >250 cells/µL. Third generation cephalosporins had been viewed as the drug of choice. Aim of the work: to study features, and outcomes of spontaneous bacterial peritonitis in National Liver Institute (Menofia University), a single center study. Methods: This work was conducted on 60 patients had SBP. All patient had AF analysis, bedside AF culture, Blood culture (BC), Serum albumin, Ascitic fluid gradient (SAAG). Results: The more severe the liver disease, as assessed by Child-Turcotte-Pugh (CTP score), the higher the possibility to have positivity of AF culture. Patient who had positive BC had significant rising of Creatinine. The pattern of infection in AF culture is close to that of BC, but Streptococci take the upper hand in BC and Staphylococcus in AF culture. Gram-positive organisms are more common in both AF and BC than gram negative. Mortality rate was higher in culture positive SBP patients 46.2%, and BC positive patients, 62.5%. In all positive cultures patients, Staph Species represents 44.8% with mortality rate of 42% of all mortalities. Most of them were resistant to cephalosporin 62.5%. Strep species represents 31% with mortality rate of 20%. E. coli represents 24.2% with mortality rate of 20%. Conclusion: The microbial pattern of organisms responsible for SBP has changed with predominance of gram-positive organisms. Pattern of microbial infection is similar in both blood and ascetic fluid culture, so BC results can be relied upon to guide therapy, in negative AF culture.

## **Keywords**

SBP, Ascites, Liver Failure, Bacterial Peritonitis

# 1. Introduction

Spontaneous bacterial peritonitis (SBP) is defined as infection of the intra peritoneal fluid without evidence of perforation or an intra abdominal sepsis or potential septic foci [1]. Spontaneous bacterial peritonitis is considered as treatable complication of cirrhosis that has been for long time locked at as lethal condition with mortality rate of 90% [2]. Child-Turcotte-Pugh class C patients having SBP constitute 70%, and usually have poor prognosis [3] [4]. Spontaneous bacterial peritonitis (SBP) reported to have a very high recurrence rate in terminal liver disease population, reaches around 70% at 1 yr. [1]. Regardless of the recent advances in diagnosis, prevention, and treatment of SBP, it has been reported to have a high mortality ranging from 40% to 70% [3]. SBP pathogens are related to the process of bacterial translocation (BT), where viable or non-viable bacteria and bacterial products, cross the intestinal lumen to the regional and extraabdominal lymph nodes [5]. BT to mesenteric lymph nodes (MLN) has widely believed to be responsible for flare of the already present hyper dynamic circulatory state in the cirrhotic patient as well as in the development of spontaneous bacterial peritonitis [6].

There are certain additional factors in favor of BT in cirrhosis; the intestinal bacterial overgrowth, the alterations of the intestinal mucosal barrier and the deficiencies of the local immune response [7].

The diagnosis of SBP usually fulfilled with either positive ascitic fluid culture, or a polymorph nuclear leukocyte (PMNL) count of >250 cells/ $\mu$ L, or both, in addition to symptoms/signs of spontaneous bacterial peritonitis [8]. Risk Factors of SBP include decompensated cirrhosis and history of SBP [9]. Patients with low complement level have a greatest risk for SBP and those who have low protein levels in the ascitic fluid (<1 g/dL) have a 10-fold higher risk of developing SBP [3]. The association between gastrointestinal bleeding and bacterial infection, that is believed to be related to invasive diagnostic or therapeutic procedures, increase bacterial translocation, depression of the reticuloendothelial system functions caused by hypovolemia and shrinkage of complement levels, that may predispose bleeding patients with cirrhosis to bacteremia [10].

Empirical anti biotic therapy for spontaneous bacterial peritonitis (SBP), consists of third generation cephalosporins [11].

#### Aim of the Work:

The aim of this work is to study features, and outcomes of spontaneous bacterial peritonitis in National Liver Institute (Menofia University), a single center study.

## 2. Material and Methods

This work was carried out in February and July 2010. The study was conducted on 60 patients with liver cirrhosis complicated by ascites, diagnosed as SBP with a polymorph nuclear leukocyte (PMNL) count of >250 cells/ $\mu$ L in the ascetic fluid sample (AF), or positive AF culture. Written consent and National Liver Institute IRB (ethical committee) approval were obtained. Review of medical records showed all patients had HCV related cirrhosis and associated with past history of schistosomiasis. Exclusion criteria: We excluded from this study, Patients with secondary bacterial peritonitis and non-cirrhotic causes of ascites such as tuberculosis or malignancy, patients received systemic antibiotics for any other infection (s) or exposed to paracentesis or endoscopy within 7 days.

All subjects enrolled in the study were subjected to, Full medical history and medical examination, Liver functions tests (total proteins, albumin, AST, ALT, total and direct serum bilirubin, alkaline phosphatase and prothrombin time), Kidney functions tests (serum creatinine, blood urea nitrogen (BUN), Serum electrolytes (serum sodium and potassium), Complete blood count, ascetic fluid analysis (Biochemical, Cytological, gram stain, total and differential cell counts, and modified culture method, or bedside ascetic fluid culture on blood culture medium), Blood culture, Serum albumin, ascitic fluid gradient (SAAG), and Abdominal Ultrasonography.

Following collection of samples for ascetic fluids and blood culture, the patients was treated with third generation cephalosporins (Cefoperazone, or Cefotaxime) according to protocol followed in NLI. Response to treatment was assessed considering clinical improvement, and normal AF analysis, culture, and blood culture.

#### Statistical analysis:

Data was statistically analyzed using SPSS (statistical package for social science) program version 13 for windows and for all the analysis a p value < 0.05was considered statistically significant:

- Data are shown as mean, range or value and 95% confidence interval (95% CI) and frequency and percent.

Chi square test was done for qualitative variable analysis and p-value < 0.05 was considered significant.

Student t-test was done for normally distributed quantitative variables to measure mean and standard deviation and p-value < 0.05 was considered significant.

Mann-Whitney test was done for quantitative variables which are not normally distributed and p-value < 0.05 was considered significant.

All data are tested with Kolmogorov-Smirnov Z test and most of them were found normally distributed and so presented with mean  $\pm$  SD. Parametric testes were used on doing association or correlation.

#### 3. Results

60 patients with SBP were included for analysis. There were 13 (21.7%) patients



who had culture positive SBP while 47 (78.3%) had culture negative SBP. It was observed that most of subjects were males 47 patients 35 of them were culture negative and 12 of them were culture positive. While 13 females were included 12 of them were culture negative and 1 of them was culture positive with a mean age  $53.25 \pm 9.1$  for culture negative and  $56.8 \pm 12.6$  for culture positive.

No significant statistical difference between culture negative and culture positive SBP as regard presentation at admission. Abdominal pain was the most frequent presentation as reported by 75% of patients, compared to 30% presented with fever, and 20% of patients presented with HE, 15% presented with hematemesis, and 1.7% by melena, and jaundice (data not tabulated)

Our study revealed that the more severe the degree of liver disease as estimated by the CTP score, the higher the positivity of the culture, however there was no significant statistical difference between culture negative and culture positive (AF culture, and BC) as regard CTP (**Table 4**). Comparing culture negative and culture positive SBP as regards different lab parameters such as Total bilirubin, Direct bilirubin, Albumin, PT, WBCs, BUN and Creatinine, there were no significant statistical difference between them (**Table 1**). In the other hand a significant statistical difference reported between negative and positive blood culture in SBP as regard serum Creatinine, as shown in **Table 2**.

	SI	_		
Studied variables	Culture negative (no. 47) Mean ± <i>SD</i>	Culture positive (no. 13) Mean ± <i>SD</i>	P-Value	
Total bilirubin	6.56 ± 8.18	$6.35 \pm 6.75$	>0.05	
Direct bilirubin	$5.05 \pm 7.26$	$4.18\pm4.13$	>0.05	
Albumin	$2.18\pm0.7$	$1.88\pm0.39$	>0.05	
PT	$20.5\pm7.26$	$22.9\pm8.37$	>0.05	
WBCs	$9893.6 \pm 4995.2$	$9046.9 \pm 4787.6$	>0.05	
BUN	$138.4\pm107.5$	$86.1 \pm 50.3$	>0.05	
Creatinine	$2.1 \pm 1.43$	$1.43 \pm 1.05$	>0.05	

 Table 1. Comparison between all studied lab parameters in culture negative and culture positive SBP.

 Table 2. Comparison between all studied lab parameters in negative blood culture and positive blood culture SBP.

	Blood			
Studied variables	Negative (no. 44) Mean ± <i>SD</i>	Positive (no. 16) Mean ± <i>SD</i>	P-Value	
Total bilirubin	$5.47 \pm 6.42$	9.38 ± 5	>0.05	
Direct bilirubin	3.91 ± 5	$7.5 \pm 9.7$	>0.05	
Albumin	$2.1\pm0.66$	$2.2 \pm 0.67$	>0.05	
PT	$20.12\pm 6.2$	$23.6 \pm 10.12$	>0.05	
WBCs	$9218.41 \pm 4303.1$	$11062.5 \pm 6293.16$	>0.05	
BUN	$111.95 \pm 90.18$	$168.62 \pm 116.25$	>0.05	
Creatinine	$1.73 \pm 1.23$	$2.58 \pm 1.59$	<0.05*	

As regards, AF chemical parameters (LDH, Glucose, Albumin, Total protein and SAAG) there were no significant statistical difference reported between both blood, and AF culture negative and culture positive SBP

It was noticed that the pattern of infection in ascetic fluid culture is near to that of blood culture, but Streptococci take the upper hand in blood culture and Staphylococcus species in ascetic fluid culture. Gram-positive organisms are more common in both ascetic fluid and blood culture than gram-negative organisms as shown in Figure 1.

Figure 2 show that the mortality rate was higher in culture positive SBP patients 46.2% as compared to 29.8% in culture negative group, but the difference was not significant however, the difference was significant in case of blood culture results where, 62.5% versus 22.7% died in culture positive versus culture negative patients, respectively.

Septic shock, Hepato renal syndrome (HRS), Hepatic Encephalopathy (HE)



St epi: Staph epidermis; Gram +ve: Gram positive

Figure 1. Pattern of microbial infection in both ascetic fluid culture and blood culture.



B. culture -ve: Blood culture negative; B. culture +ve: Blood culture positive; Culture -ve AF: Culture negative Ascitic Fluid; Culture +ve AF: Culture positive Ascitic Fluid

Figure 2. Mortality in both Af&blood culture +ve and -ve patients.





HE: Hepatic encephalopath; HRS: Hepatorenal syndrom

Figure 3. Causes of death in studied group.

and hypovolemia were the causes of death in the present study (50%, 35%, 15%, and 15% respectively) (**Figure 3**).

The total number of positive cultures was 29 cases (16 positive blood culture and 13 positive ascitic fluid culture), Staph Species represents 44.8% (13/29) with mortality rate of 61.5% (8/13) of all staph Infection, 27.6% (8/29) of all positive culture and 42% (8/20) of all mortalities in this study. Most of staph mortalities are resistant to cephalosporins 62.5% (5/8). Strept species represents 31% (9/29) with mortality rate of 44.4% (4/9) of all strept infection, 13.8% (4/29) of all positive culture and 20% (4/20) of all mortalities in this study. E.coli represents 24.2% (7/29) with mortality rate of 57.1% (4/7) of all E.coli infection, 13.8% (4/29) of all positive culture and 20% (4/20) of all mortalities in this study (**Table 3**). Shifting to another antimicrobial drug (ampicillin/sulbactam, Ciprofloxacin or Levofloxacin) was noticed in about 36.7% of cases (22/60).

# 4. Discussion

Cirrhosis is widely considered as the commonest etiology for immunodeficiency status, proceeding AIDS. Infectious complications in cirrhosis could be associated with high morbidity and mortality [12]. Spontaneous bacterial peritonitis is one of the severe and common sequels of cirrhosis with a significant mortality. Spontaneous bacterial peritonitis might be related to deterioration of reticuloendothelial system phagocytic function, leukocyte dysfunction, and depletion of serum complement level, or function [13]. The overall incidence of SBP in different studies around 8% - 30% while the mean rate of the hospital mortality rate as high as 78% [14].

The results of the present study showed that when comparing between culture negative and culture positive SBP as regards different lab parameters such as Total bilirubin, Direct bilirubin, Albumin, PT, WBCs, BUN and Creatinine. There was no significant statistical difference between them. But there was a significant statistical difference between negative blood culture and positive blood culture in SBP as regard serum Creatinine. However, no significant statistical

Organism n = 29	Ascitic culture	Blood culture	Death	Recovery	Resistance to 3rd generation cephalosporin	Sensitivity to other antibiotics
Staph 13 cases	7 24.1%	6 20.7%	8 27.6%	5 17%	5 17%	Vancomyc. Quinolone. Imepenems
Strept. 9 cases	2 6.9%	7 24.1%	4 13.8%	5 17%	0 00%	Piperacillin tazobactam
<i>E. coli</i> 7 cases	4 13.8%	3 10.4%	4 13.8%	3 10.4%	0 00%	Imepenems Augmenti. Azithromy.

Table 3. Outcome of patients with positive cultures in relation to microorganisms.

N.B: The all percentages in this table are from all positive cultures from either ascetic fluid or blood = 29 cases, 13 cases of which are positive ascetic culture and 16 cases are positive blood culture.

Table 4. Comparison between patient child class and score in culture negative & culture positive SBP, and in positive & negative blood culture (BC).

SBP					Blood Culture			
Child class	Culture positive (no. 13) n %	Culture negative (no. 47) n %	<i>Total</i> n %	P-Value	Positive (no. 16) n %	Negative (no. 44) n %	<i>Total</i> n %	P-Value
Child A	12.1	00.0	11.7	>0.05	12.3	00.0	11.7	>0.05
Child B	1225.5	17.7	1321.7	>0.05	1022.7	318.75	1321.7	>0.05
Child C	3472.4	1292.3	4676.7	>0.05	3375	1381.25	4676.7	>0.05
Child score	$10.96\pm2.04$	$11.54 \pm 1.05$	$11.03 \pm 1.92$	>0.05	$10.93 \pm 1.87$	$11.5 \pm 1.9$	$11.03 \pm 1.92$	>0.05

difference between them as regards other lab. Parameters (Total bilirubin, Direct bilirubin, Albumin, PT, WBCs and BUN).

This was partially matching with Saleh MA et al., [15] who found that only total bilirubin was significantly higher in the positive ascitic fluid culture group. This was nearly matching with Pelletier *et al.*, [16] who found that the only significant difference was the level of serum creatinine that was higher in the positive ascitic fluid culture group.

When comparing between culture negative and culture positive SBP as regards different AF chemical parameters (LDH, Glucose, Albumin, Total protein and SAAG) there was no significant statistical difference between them in the present study.

Although abdominal pain and fever are the cardinal features of peritonitis, SBP could be presented in cirrhotic patients with different clinical manifestation as HE, upper GI bleeding, increasing jaundice and renal function derangement or without symptoms [17].

Abdominal pain and fever represented 75% (45/60) and 30% (18/60) respectively in this study, Although no significant difference in clinical presentations was observed in culture positive and culture negative SBP, the incidence was higher in culture positive than culture negative SBP, 84.6% versus 72.3% for abdominal pain and 53.8% versus 23.4% for fever, reflecting a more immunocompromised state in culture positive SBP patients.



This is similar to the conclusion reached by Pelletier G *et al.*, [16], who found that there were no differences in clinical signs and symptoms and CTP grading between culture negative and culture positive SBP.

The incidence of culture positive SBP was 21.7% (13/60) more or less near to 23% reported by Lubna Kamani *et al.*, [18], other studies by Saleh MA *et al.*, 1994 and Pelletier G *et al.*, 1990 [15] [16], reported higher yield ranging from 50 to 71%. This could be attributed to the larger amount of ascetic fluid (10 cc) inoculated into blood culture bottles as reported by this studies. Although, the amount inoculated in this study was less than 10 cc, it could not alone explain this difference in culture yield and other unexplained factors could have participated. The incidence of culture positive SBP increases with increasing severity of liver disease reflected by CTP score; it was noticed that the more the CTP score the higher the positivity of the culture, but there was no significant statistical difference between culture negative (10.96  $\pm$  2.04) and culture positive SBP (11.54  $\pm$  1.05) as regard CTP score, also no significant statistical difference between blood culture negative (10.93  $\pm$  1.87) and blood culture positive SBP (11.55  $\pm$  1.9) as regard CTP score. This could be attributed to increasing immunodeficiency with increasing the severity of liver disease [6].

The interesting feature noted in this study is the predominance - in culture positive SBP as well as positive blood culture in SBP of gram positive organisms 69.2% (9/13) and 81.25 (13/16) respectively as compared to gram negative organisms 30.8% (4/13) and 18.75% (3/16) respectively. Even if Staph epidermis was excluded—considered to be contaminants—still gram-positive organisms exceed gram-negative organisms. Lubna Kamani *et al.*, [18] reported increased incidence of gram negative SBP 72.7% (32/44) of which 61.3% (27/44) were caused by *E. coli*. They also reported the same pattern of infection in blood culture, 60.7% gram-negative organisms with *E. coli* representing 53.5% alone. Also Saleh MA *et al.*, [15] reported prevalence of monomicrobial gram negative organisms with *E. coli* representing 2/3 of cases alone.

The results of this study have been supported by the published reports by Cholongitas E *et al.*, [19] which shows a greater predominance of gram-positive organisms in ascetic fluid culture.

Oliviero Riggio and Stefania Angeloni [20] reported that, in clinical practice, switch from Cefotaxime to another antibiotic was necessary in more than 40% of SBP cases; this is supporting the possibility that microbial etiology of SBP, as well as sensitivity to antibiotic therapy is changing. In our institute the same situation has been encountered as shifting to another antimicrobial or given a combination as (ampicillin/sulbactam, ciprofloxacin or Levofloxacin) was noticed in about 36.7% of cases (22/60). The clinical implication of this data is to start a combination of antimicrobial therapy covering both gram positive and gram-negative organisms till culture results become available.

Blood culture represents the gold standard for diagnosis and treatment of

bacterial infection. The incidence of positive blood culture in this study was 26.7% (16/60) and all had culture negative SBP. The explanation of this result is difficult but it could be related to early performance of blood culture before the circulating organism increase in the ascitic fluid, the established theory of ascetic fluid infection is that portal hypertension increases bacterial translocation to the lymphatic system, portal vein and then to the systemic circulation causing bacteremia which in turn infects ascitic fluid [21], interestingly, all culture positive SBP has negative blood culture. Other than technical factors, this could be attributed to the episodic nature of bacteremia.

This study shows that microbial pattern in either culture positive SBP or positive blood culture is nearly the same with predominance of gram-positive pathogens. Considering, the prognostic significance of early appropriate antibiotic treatment in patients with SBP, it would be important to take into consideration the results of blood culture to guide therapy of SBP with negative ascitic fluid culture.

The total number of positive cultures is 29 cases (16 positive blood culture and 13 positive ascitic fluid culture. Staph. Species represents 44.8% (13/29) with mortality rate of 61.5% (8/13) of all staph infection and 42% (8/20) of all over mortalities. Most of staph Mortalities are resistant to cephalosporins 62.5% (5/8). This highlights our concept of starting combination therapy in the treatment of SBP.

The overall mortality in this study was 33.3% (20/60). This is a high incidence of mortality as compared to Lubna Kamani et al. [18] who reported that overall 23/187 (12.2%) patients with SBP were died. Other studies by Sette et al. 1996 [22], Hurwich et al. 1993 [23], Mattos 1994 [24], Jeffries et al. 1999 [25], Thuluvath et al. 2001 [26] and Fernandez et al. 2002 [27], reported a hospital mortality up to 30% in regardless aseptic precautions; mortality was related to complications such as sudden variceal bleeding, hepatorenal syndrome, or progressive liver failure. Also Sheer TA and Runyon BA 2005 [28], reported that mortality rate of SBP is around 30%. This might be due to the changing pattern of pathogen with predominance of gram-positive organisms and the high resistance to first line antimicrobial (3rd generation cephalosporins) in the setting of advanced liver disease as illustrated by the high mortality in culture positive SBP and blood culture in CTP C patients.

The mortality was higher in culture positive SBP patients 46.2% (6/13) as compared to 29.8% (14/47) in culture negative group, but the difference was not significant. On the other hand, the difference was significant in case of blood culture results where, 62.5% (10/16) versus 22.7% (10/44) died in culture positive versus culture negative patients, respectively.

Renal impairment is a well known prognostic factor for poor survival in patients with culture positive SBP as reported by Lubna Kamani et al., 2008 [18] and Follo A *et al.*, 1994 [29]. In this study, the mortality was significant in patients with positive blood culture than in those with negative blood culture where, serum creatinine is significantly higher in the first group. Serum creatinine is not significantly different in culture positive and culture negative SBP.

Septic shock, HRS, HE and hypovolemia were the causes of death in the present study. Septic shock represents 50% (10/20) of total mortality, while HRS 35% (7/20) which may be related to uncontrolled sepsis as mentioned previously. Predominance of gram-positive pathogens (especially drug resistant staph Species) was beyond this grave outcome in patients with SBP and strongly mandates alternative policy for management of patients with this potentially fatal complication.

## **5. Recommendations**

The microbial pattern of organisms responsible for SBP has changed with predominance of gram-positive organisms. This shift, in addition to resistance to 3<sup>rd</sup> generation cephalosporins necessitates culture of ascetic fluid and blood before starting antimicrobial drugs. We recommend starting empirical treatment with a combination of antimicrobials covering both Gram negative and Gram-positive organisms.

As long as the pattern of microbial infection is similar for both blood and ascetic fluid culture, blood culture results can be relied upon to guide therapy, in cases of negative ascetic fluid culture.

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