

THE PREDICTIVE VALUE OF SOME RECENT PARAMETERS FOR DIAGNOSIS OF SPONTANEOUS BACTERIAL PERITONITIS

By

AIDA MOHAMMED IBRAHIM¹, NAGLAA GAMAL ABOUL-AZAYM¹,
MEDHAT ALI SALAH¹, SAYED MOHAMED MOHII-ELDIN²,

and ABDALLAH MAHMOUD ABDALLAH³

Departments of Clinical Pathology¹, Tropical Medicine² and Internal Medicine³,
Faculty of Medicine, Al Azhar University's Hospitals, Cairo, Egypt

Abstract

Spontaneous Bacterial Peritonitis (SBP) is a frequent and severe complication in patient with cirrhosis and ascites due to CLD with high mortality rate (20%-40%). SBP causes an inflammatory reaction resulting in an increased number of PMNs in ascitic fluid. It was reported that diagnosis of SBP is established when the ascitic fluid PMN count is greater than 250 cells/mm³. Lysis of the PMNs during transport to the laboratory, may occur which may lead to false negative results. This study evaluated the usefulness of some recent parameters for diagnosis of SBP that can be used for future development of a rapid bedside test. Identifying a sensitive marker that can be used for rapid diagnosis of SBP in cirrhotic patients will have important clinical and economic consequences for this group of patients and also for clinicians involved in their cares. This study was conducted on 100 patients with ascites admitted to Tropical Medicine department, Al-Azhar University Hospitals in the period from January 2015 to August 2015. The results showed that there was a highly significant positive correlation between ascetic fluid LAF level and neutrophils in ascitic fluid in cases of SBP, Also there was positive correlation between ascetic fluid LAF and ascetic fluid LDH (p value<0.001).

Key words: Egypt, Spontaneous Bacterial Peritonitis,

Introduction

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication of decompensated cirrhosis and ascites (Navasa, 1999). It probably originates with the passage of bacteria from the intestinal lumen to the systemic circulation and then to the ascitic fluid (Llovet *et al*, 1998). Although the concentration of bacteria in ascitic fluid is low, the inflammatory response, as estimated by the concentration of polymorphonuclear leukocytes and cytokines (tumor necrosis factor α and interleukin-6) in ascitic fluid and blood, is very intense (Navasa *et al*, 1998). Since its first description in the 1970s, when the mortality rate exceeded 80%, a significant and substantial improvement in the prognosis of SBP has been noted. In more recent prospective studies the mortality rate was reported to be around 20%. On the other hand the percentage of SBP in hospitalized cirrhotic patients with ascites ranges between 10% & 30%, whereas the prevalence of SBP among outpatients with cirrhosis is markedly lower about 3.5%

(Wallerstedt *et al*, 2007).

The key pathogenic mechanism that starts SBP is bacterial translocation (BT), a process by which both viable and non-viable enteric bacteria, as well as their products (endotoxins, DNA), cross the intestinal mucosal barrier to infect mesenteric lymph nodes, whence they enter the bloodstream and then ascitic fluid (AF). Patients with a reduced defensive capacity in their AF have been shown to be more susceptible to peritonitis development. All three major defense mechanisms preventing BT in normal subjects are impaired during cirrhosis: intestinal flora stability, intestinal epithelium integrity, and host's immune defense (Wiest, 2011).

A broad range of signs and symptoms are seen in spontaneous bacterial peritonitis (Dănulescu *et al*, 2015). A high index of suspicion must be maintained when caring for patients with ascites, particularly those with acute clinical deterioration. The completely asymptomatic cases have been reported in as many as 30% of patients. Fever and chills occur in as many as 80% of patients. Ab-

dominal pain or discomfort is found in as many as 70% of patients. Abdominal tenderness is found in more than 50% of patients with spontaneous bacterial peritonitis. Findings can range from mild tenderness to overt rebound and guarding. In some cases, the abdominal examination findings mimic an acute intra-abdominal catastrophe requiring emergency surgical evaluation. Physical examination may also disclose hypotension (5-14% of patients) or signs of hepatic failure such as jaundice and angiomata (Chi *et al*, 2015).

The diagnosis of SBP is primarily based on polymorphonuclear (PMN) count in AF as obtained using diagnostic paracentesis. SBP is established when PMN numbers are equal to or greater than 250/ μ l in absence of a surgically amenable intra-abdominal infectious site. In addition to cell counts, AF samples should be always obtained for culture. A positive culture is not necessary for diagnosis given its low sensitivity because of low bacterial levels in AF. Other infection markers such as serum procalcitonin and ascitic lactoferrin have proven useful for diagnosis of SBP, but more studies were needed before its use might be recommended (Runyon, 2013).

The aim of the study was to determine the prevalence of eosinophilic esophagitis in patients with upper gastrointestinal symptoms.

Materials and Methods

A prospective study involving 100 patients with ascites who were admitted to Tropical Medicine department, Al-Azhar University Hospitals; Al-Hussein and Sayed Galal Hospitals.

The patients were divided into two groups. GI (Patients): included 60 patients suffering from End stage liver disease (ESLD) with ascites secondary to chronic HCV and diagnosed as SBP and GII (Controls): included 40 patients suffering from ESLD with ascites secondary to chronic HCV but without SBP. Generally speaking, diagnosis of peri-

tonitis as a complication of cirrhosis is an important clinical problem

Inclusion criteria: Patients who agreed to participate in the study by informed written consent. All patients are affected by decompensated liver cirrhosis and have hepatic ascites and presenting by picture suggesting of SBP like fever, generalized abdominal pain and tenderness.

Exclusion Criteria: These were as follows: 1- Receiving antibiotics during the past week or outside the hospital for any reason; 2- History of abdominal surgery in the past month; 3- Renal dysfunction; 4- Secondary bacterial peritonitis; 5- Peritonitis carcinomatosis; 6- Pancreatic peritonitis; 7- Malignancy, or 8- Tuberculosis.

Diagnosis of SBP was first by eliciting the ascites, then by looking for signs and symptoms consistent with peritoneal irritation, and finally by confirmation with peritoneal fluid testing: 1- Clinical presentation: Ascites, fever, generalized abdominal pain and tenderness, and 2-Laboratory investigation: (PMNL in ascetic fluid > 250/ mL).

All the patients were subjected to the following: 1- Full medical history and physical examination. The presence of any of fever, abdominal pain, rebound tenderness, absence of bowel sounds and pre-hepatic coma manifestation as lack of concentration in decompensated liver disease increase the susceptibility of SBP. 2- Imaging: a- Chest x-ray, and b- Abdominal & Pelvic U/S Scanning of the abdomen and pelvis. 3- Laboratory investigations: a- Complete blood count (CBC), b- PT. Normal PT regarded as 12 second and International Normalized Ratio (INR) Normal INR<I, c- Liver functions tests (total plasma proteins, serum albumin, ALT, AST, total and direct serum bilirubin, &ALP), d- Kidney function test (serum creatinine, blood urea nitrogen).

Asiatic fluid analysis: 1- Cytological, bacteriological and biochemical examination of ascetic fluid, and 2- Examination of ascetic fluid for LAF (Warrell *et al*, 2003).

Results

The present study was conducted on 100 patients admitted to Al-Hussein and Sayed Galal hospitals the period from January 2015 to August 2015. They were 80 males (80%) and 20 females (20%) and their ages

ranged between 32-73years (mean 53.2±SD9.2). GI: 60 patients 45 males and 15 females, and GII: included 40 patients suffering from end stage liver disease without SBP 35 males and 5 females.

Table 1: Pattern of clinical manifestation among group

Parameter	GI	GII	T- test	P- value
No symptoms	10(16%)	26(65%)	14.08	<0.001*
Fever	29(48%)	4(10%)	8.83	0.003*
Abdominal pain	28(46%)	4(10%)	8.06	0.005*
Encephalopathy	26(43%)	4(10%)	6.63	0.008*
Jaundice	12(20%)	4(10%)	1.01	0.265
Splenomegaly	36(60%)	10(25%)	11.61	0.001*

Table 2: Comparison between cases and controls as regard liver function tests

Parameter	GI (mean ±SD)	G II (mean ± SD)	P- value
Serum albumin (g/dl)	2.41 ± 0.45	2.6 ± 0.4	0.93
Total bilirubin (mg/dl)	1.7 ±0.4	1.5 ±0.3	1.1
Direct bilirubin (mg/dl)	0.6 ±0.2	0.5 ±0.2	1.1
ALT (U/L)	30 ±19	40 ±10	0.98
AST (U/L)	50 ±7	49 ±10	0.96
Prothrombin concentration (%)	58 ±10%	57 ±12%	0.98

Table 3: Parameters among the studied groups

Parameter	GI (mean ±SD)	GII (mean ± SD)	P- value
Glucose (mg/dl)	101.5 ± 32.8	154.6 ± 51.3	<0.001*
Total protein (g/dl)	1.64 ± 0.54	2.41± 0.66	<0.001*
LDH (IU/L)	424.9 ± 154.8	106.1 ± 37.3	<0.001*
WBC count (/mm3)	4150.7 ± 1202.3	159.5 ± 72.4	<0.001*
(SAAG) (g/dl)	2.14 ± 0.36	2.3 ± 0.48	0.12

Table 4: Mean of Lactoferrin, LDH, leucocytic count, protein, albumin & glucose in ascetic fluid and sera of patients & controls.

Items	GI (mean ±SD)	Group II (mean ± SD)	P- value
Lactoferrin(ng/ml) Ascitic fluid	4040±1791	138±46.9	<0.001
LDH(IU/L)			
Ascitic fluid	424.9±154.8	106.1±37.3	0.002
Serum	562.6±126.2	481.6±136.8	0.148
A/S ratio	0.67±0.21	0.23±0.14	<0.001
Leucocytes(/mm3)			
TLC	4150.7±1202.3	159.5±72.4	<0.001
PMNs	3451.2±1148.2	33.2±13.9	<0.001
Total protein(g/dl)			
Ascitic fluid	1.64±0.54	2.41 ± 0.66	<0.001
Serum	6.11±1.03	6.64 ± 0.92	0.04
A/S ratio	0.27	0.43±0.21	0.009
Albumin(g/dl)			
Ascitic fluid	3.65±0.36	5.98 ±.65	0.002
Serum	2.41±0.45	2.6 ± 0.4	0.047
SAAG	2.14±0.36	2.3± 0.48	0.128
Glucose (mg/dl)			
Ascitic fluid	101.5±32.8	154.6±51.3	0.005
Serum	114.2 ±31.9	152.3±42.6	0.062
A/S ratio	0.9 ±0.29	1.1± 0.36	0.048

Table 5: Comparison between culture of ascetic fluid among case and control groups

Culture results:	G I	GII	P value
Positive results:	(30%)	0 (0%)	<0.001*
Negative results:	42 (70%)	40 (100%)	

Table 6: Mean of Lactoferrin, LDH, PMNs, total protein, albumin and glucose content in culture +ve and/ or -ve ascetic fluid of GI.

Parameter	Culture positive	Culture negative	P value
Lactoferrin(ng/ml), Ascitic fluid	3498.6	5700.8	0.18
LDH(IU/L), Ascitic fluid/Serumratio	0.59	0.71	0.058
Leucocytes(/mm ³), PMNs	4233.5	3115.9	0.46
Total protein(g/dl),Ascitic fluid/Serumratio	0.23	0.28	0.19
Albumin(g/dl), SAAG	2.1	2.16	0.62
Glucose, Ascitic fluid/Serumratio	1.02	0.85	0.22

Table 7: Correlation between lactoferrin and age, LDH, PMNs, total protein, SAAG & glucose content of GI.

Characteristics	Correlation coefficient	P- value
Lactoferrin Vs Age	0.067	0.643
Lactoferrin Vs LDH ascetic fluid/serum ratio	0.790	<0.001*
Lactoferrin Vs PMNs	0.567	<0.001*
Lactoferrin Vs total protein ascetic fluid/serum ratio	0.459	0.001*
Lactoferrin Vs SAAG	-0.397	0.004**
Lactoferrin Vs glucose ascetic fluid/serum ratio	-0.613	<0.001**

Table 8: Accuracy of Lactoferrin, LDH, PMNs, total protein, SAAG and glucose content in diagnosis of SBP.

Variants	Cut off	Sensitivity	Specificity	+ve Predictive	-ve Predictive
Lactoferrin(ng/ml), Ascitic fluid	≥260	100	100	100	100
LDH(IU/L) Ascitic fluid/Serumratio	≥0.45	100	100	100	100
Leucocytes(/mm ³) PMNs	≥1186	100	100	100	100
Total protein(g/dl), Ascitic fluid/Serumratio	≥0.35	20	50	50	20
Albumin(g/dl), SAAG	≥2.03	66	35	72	21
Glucose Ascitic fluid/Serumratio	≤0.93	44	50	69	26

Discussion

Generally, the ascites is a gastroenterological term for an accumulation of fluid in the peritoneal cavity that exceeds 25 mL. Causes of high SAAG ("transudate") are: a- Cirrhosis -81% (alcoholic in 65%, viral in 10%, cryptogenic in 6%), b- Heart failure-3%, c- Hepatic venous occlusion: Budd-Chiari syndrome or veno-occlusive disease, d- Constrictive pericarditis Kwashiorkor (childhood protein-energy malnutrition). Causes of low SAAG are: a-Cancer (metastasis and primary peritoneal carcinomatosis) -10%, b- Infection: Tuberculosis -2% or spontaneous bacterial peritonitis, c-m Pancreatitis -1%, d- Serositis, e- Nephrotic syndrome and f- Hereditary angioedema (Branco-Ferreira *et al*, 1998). Other rare causes: are: a- Meigs syndrome, b- Vasculitis, c- Hypothyroidism, d- Renal dialysis, e- Peritoneum mesothelioma, and f- Abdominal tuberculosis

SBP is a frequent and severe complication in patient with cirrhosis and ascites due to CLD with high mortality rate (20%-40%). SBP is probably related to several impaired

defense mechanisms, such as depressed reticuloendothelial system, phagocytic activity, leucocyte dysfunction, reduced serum complement and low bacterial activity of ascitic fluid (Singal *et al*, 2014).

Some patients with SBP have symptoms and signs clearly suggestive of peritoneal infection whereas others may be completely asymptomatic or there may be minor symptoms only. Therefore, diagnostic paracentesis is used commonly in cirrhotic patients with ascites to investigate the presence of SBP (Runyon *et al*, 2013). Also, SBP causes an inflammatory reaction resulting in an increased number of PMNs in ascitic fluid. It was reported that diagnosis of SBP is established when the ascitic fluid PMN count is greater than 250 cells/mm³ (Chi *et al*, 2015).

Lysis of the PMNs during transport to the laboratory, may occur which may lead to false negative results. As well manual measurement of the ascitic fluid PMN is operator dependant, makes quality control difficult, and can delay the diagnosis. In small clinics without a laboratory, a longer time is re-

quired, sometimes until the next day. On the other hand, automated cell counters provide a reliable, easier, quicker PMN count and reproducible results within a few minutes; they may also considerably simplify the diagnostic approach and clinical management of SBP (Parsi *et al*, 2008b).

However, coulter counter findings of the neutrophil count have been shown to be inaccurate for relatively low levels of neutrophils in the ascitic fluid. Therefore, the manual PMN counting method is conventionally preferred. However, a recent study demonstrated that automated cell counts have sufficient sensitivity for diagnosing SBP, thus suggesting that this simple method may be used in place of traditional manual counting (Hirayuki *et al*, 2014).

PMNL counts in ascitic fluid were not always readily available. A delay in antibiotic therapy entails a high mortality rate. Therefore, considerable effort has been placed in developing a rapid and reliable test for diagnosis of SBP (Chi *et al*, 2015). Reagents strips for detection of leukocyte esterase have been used to test ascitic fluid and diagnose SBP. The sensitivity and specificity of this method have varied in different studies (Nousbaum *et al*, 2007).

Lactoferrin is an iron-binding protein found in human mucosal secretions as well as in the specific granules of PMNs and released on activation of the cells, and its presence in body fluids is proportional to the neutrophils (so no need for measurement of serum LAF). Therefore, measurement of ascitic fluid LAF could be clinically useful for detection of SBP in patients with cirrhosis. LAF also has been shown to be remarkably stable and resistant to degradation when left at room temperature for extended periods of time. This property makes this marker attractive for clinical use (Chi *et al*, 2015). The present study was conducted to evaluate the value of ascitic fluid LAF in diagnosis of SBP compared to other standard methods for diagnosis and to identify a clinically useful cut-off level that could be used for the future

development of a rapid bed-side test. The source LAF of is no need for measurement of serum lactoferrin.

As regard age & sex, in the present study, there was no statistically significant difference between the studied groups regarding the patient's age and gender. regard symptoms, in the present study, the most frequent presenting clinical features among the SBP group were fever in 29 (48%) patients, abdominal pain in 28 (46%) patients, hepatic encephalopathy in 26(43%) patients, splenomegaly in 36(60%) and jaundice in 12 (20%) patients. Asymptomatic patients constitute a relatively high percentage which they were 10(16%). Similar findings were reported (Caruntu and Benea, 2006) they found that fever is the most common manifestation of SBP and approximately 10% of the patients with SBP were symptomatic. Besides, Chi *et al*. (2015) estimated that most patients with SBP had symptoms and /or signs clearly suggestive of peritoneal infection, especially abdominal pain, fever and altered gastrointestinal motility. In contrary Wallerstedt *et al*. (2007) reported 8% of their 133 cirrhotic patients as being asymptomatic and abdominal pain and tenderness were more common in their patients with SBP.

As regard SAAG ratio: In the present study, there was no statistically significant difference between the studied groups regarding SAAG, as both included patients with ascites due to portal hypertension.

The serum-ascites albumin gradient indirectly measures portal pressure. The albumin concentration of ascitic fluid and serum must be obtained on the same day. The ascitic fluid value is subtracted from the serum value to obtain the gradient.

- If the difference is >1.1 g/dL, the patient has portal hypertension, with 97 percent accuracy, or If the difference is <1.1 g/dL, portal hypertension is not present.

The patients with a serum-ascites albumin gradient below 1.1 g/dl. (i.e.: without portal hypertension) rarely develop SBP. An ex-

ception may occur in patients with the nephrotic syndrome (Runyon *et al.*, 2004).

Regarding the ascetic fluid biochemical examination in the present study, the mean ascetic fluid glucose concentration was statistically significantly decreased in group I patients compared to control group which is statistically significantly increased. Lin *et al.* (2014) found that the concentration of glucose in the ascitic fluid, under normal conditions, is similar to that in the serum since glucose diffused readily across the membranes. However, ascitic glucose concentration decreases due to consumption by bacteria, white blood cells in the ascitic fluid in case of spontaneous bacterial peritonitis.

The mean ascetic fluid LDH concentration in the present study was statistically highly significantly elevated in (SBP) patients than control group. Runyon (2013) reported that lactate dehydrogenase (LDH) in ascitic fluid is released from PMNs that have lysed. The concentration is increased in SBP, and is even further elevated in secondary bacterial peritonitis. One study, for example, analyzed 22 patients whose ascitic fluid was examined before and then during an episode of SBP. The LDH concentration increased significantly during infection.

The mean ascetic fluid total protein concentration in the present study was statistically highly significantly decreased in SBP group than control group.

This result agreed with Guarner and Soriano (2005) who concluded that low protein concentration in the ascetic fluid has been identified as a risk factor for SBP and these patients are candidates to receive long term prophylaxis to reduce the risk of infections and improve survival. Regarding ascetic fluid cultures in the present study, there is 18 patients (30%) were culture positive, and 42 patients (70%) were culture negative although they were clinically and laboratory diagnosed as SBP patients. This study also agreed with Khalifa *et al.* (2013) who reported that 70% of SBP patients had negative bacterial culture. So a positive bacterial cul-

ture is obtained in the minority of the patients with SBP and results are delayed for several days.

The present study showed that the majority of isolates were *E. coli* (66%). This result went with Park *et al.* (2003) who reported that Gram negative organisms accounted for over than 60% of cases of SBP with *E. coli* accounts for nearly half of all cases of SBP followed by *Klbsiella* species and other Gram negative bacteria. Almost 25% of cases are caused by Gram positive organisms, with Streptococcal species being the most common.

However Navasa (2008) noted that the rate of infection with Gram positive bacteria is markedly increased represented by Staphylococci group 23% and Streptococcus 9% and Pneumococcus isolates were 12% due to the invasive procedures, while the least isolated organisms were Pseudomonas species and Enterobacter species.

In the present study, there was a highly significant positive correlation between ascetic fluid LAF level and neutrophils in ascitic fluid in cases of SBP because LAF is one of the component of neutrophils and as neutrophil destruction usually occurs, this could explain the elevated LAF and positive correlation with WBCs. Also, in the present study there was positive correlation between ascetic fluid LAF and ascetic fluid LDH, as both LDH and LAF are released from disintegrating ascetic fluid neutrophils and their concentrations increase if the PMN count rises highly enough.

However, there was no correlation between LAF and other chemical parameters of ascetic fluid like glucose and protein, although all these parameters are very important keys for diagnosis of SBP and are the main laboratory parameters for diagnosis of SBP in the present study. Moreover all these chemical parameters showed a significantly statistically difference between cases and controls. This study showed that ascetic fluid LAF could discriminate between SBP and non-SBP samples. The highest com-

bined sensitivity and specificity of the ascitic fluid LAF to detect SBP was achieved at the level of 260ng/mL.

Parsi *et al.* (2008a) reported that the cut off value above 242ng/mL that had a sensitivity of 95.5% and specificity of 97% as well as there was a very significant difference between the LAF cases and controls in this study. In addition, the result of this study agreed with the report of Parsi *et al.* (2008b). This indicated that LAF in ascetic fluid proved a very useful marker for the diagnosis of SBP.

On the other hand, Abdel-Razik *et al.* (2015) stated that spontaneous bacterial peritonitis (SBP) was the important cause of mortality and morbidity in the Egyptian cirrhotic patients with ascites. Hassan and Abdel Rehim (2015) reported that despite intensive management, spontaneous bacterial peritonitis (SBP) was always associated with poor prognosis especially in the hospitalized patients. They concluded that the age, serum creatinine, bilirubin, and sodium were associated with SBP-related in-hospital mortality. The incorporation of these variables into CP and MELD significantly improves their predictive ability. iMELD followed by CrCTP provided useful prognostic information for critically ill patients with SBP.

As to the treatment, primary prevention of the spontaneous bacterial peritonitis (SBP) is an important strategy to reduce morbidity and mortality in the Egyptian cirrhotic patients with ascites. Elfert *et al.* (2016) found that Rifaximin was more effective than norfloxacin in the secondary prevention of SBP. The encephalopathy-related mortality and side effects were fewer in the rifaximin group. Salman *et al.* (2016) found that terlipressin and low-dose albumin plus terlipressin could be used as a therapeutic alternative to standard-dose albumin in high-risk SBP patients. Assem *et al.* (2016) reported that alternating norfloxacin- and rifaximin-based primary prophylaxis for SBP showed higher efficacy with the same safety profile when compared with monotherapy of norfloxacin.

Conclusion

Spontaneous bacterial peritonitis (SBP) is an acute bacterial infection of ascitic fluid. Generally, no source of the infecting agent is easily identifiable, but contamination of dialysate can cause the condition among those receiving peritoneal dialysis (PD).

The SBP occurs in both sexes in the children and adults and is a well-known and ominous complication in patients with cirrhosis. Of patients with cirrhosis who have spontaneous bacterial peritonitis, 70% were Child-Pugh class C, and the development of spontaneous bacterial peritonitis is associated with a poor long-term prognosis.

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