ORIGINAL ARTICLE

COMPARATIVE STUDY OF CLINICAL AND BIOCHEMICAL PATTERN OF SPONTANEOUS BACTERIAL PERITONITIS (SBP) VERSUS NON SBP ASCITES IN CIRRHOTIC PATIENTS

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ABSTRACT

Objective: *To compare the clinical and biochemical pattern of spontaneous bacterial peritonitis (SBP) versus non-SBP ascites in cirrhotic patients.*

Material and Methods: *This case series was conducted at Medical C ward, Ayub Teaching Hospital, Abbottabad, Pakistan from 01-04-2008 to 31-03-2009 on 70 consecutive patients of liver cirrhosis. Relevant investigations were carried out to detect subacute bacterial peritonitis (SBP) and their clinical and demographic parameters were compared with non SBP cases.*

Results: *Out of 70 cirrhotic patients, SBP was found in 26 patients (37.14%). Out of 26 patients with SBP, 17 were male. Classic SBP was found in 10 patients (39%), culture negative neutrocytic ascites (CNNA) in 13 patients (50%) and bacterial ascites (BA) in 3 patients (11%). Abdominal tenderness was present in 80.77% of SBP and 50.09% of Non-SBP cases. Most of the patients in SBP group belonged to Grade 2 Hepatic encephalopathy, whereas Non-SBP patients were predominantly in Grade 1 encephalopathy. Biochemical and bacteriological markers provided significant difference between the two groups including mean serum bilirubin (SBP vs. Non-SBP group = 7.21 ± 5.1 mg/dl vs 2.18 ± 1.23mg/dl; p value=0.03) and ascitic fluid polymorphs (SBP vs. Non-SBP group = 1400±1200/cmm vs. 110±95/cmm; p=0.01).*

Conclusion: *SBP occurred in more than one third cases of cirrhosis liver. Abdominal Clinical features alone could not rule out the diagnosis of SBP. Biochemical and bacteriological tests were more suggestive of diagnosis. Further studies are suggested to validate the results of this study.*

Key Words: *Cirrhosis Liver, Ascites, Subacute Bacterial Peritonitis, Bacterial Ascites, Culture Negative* Neutrocytic Ascites.

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INTRODUCTION

Cirrhosis of the liver is the commonest outcome of the liver parenchymal disease due to variety of etiology. The cirrhosis of liver is reported to further complicate itself into liver failure, hepatocelluar carcinoma (HCC), and portal hypertension. Spontaneous bacterial peritonitis (SBP) is a frequent and a serious complication of end-stage liver disease worldwide.[1] Spontaneous bacterial peritonitis is defined as bacterial infection of the ascitic fluid without any intra abdominal surgical source of infection.[2] It is present at admission or developes during hospitalization in 8-25% of cirrhotic patients.[3] In decompensated cirrhosis with ascites it is commonly seen along with acute hepatic encephalopathy.[4] Distribution frequency of SBP in cirrhotic patients varies in different parts of world. Even though there has been improvement in mortality from SBP, the incidence of SBP is reported to be between 7-30% per annum in the western countries.[5-7]

Apart from that, a study conducted at Mahatama Ghandhi Institute of Medical Sciences India showed that SBP developed in 34.92% of patients while in Saudi Arabia 29.6% patients were diagnosed with SBP.[8,9] In a study conducted in Taiwan, the in-hospital incidence of SBP was 21.6%.[10] In Pakistan there has been a variable pattern of frequency of SBP. The maximum was reported at a center in Nawabshah, 64%[10], and the minimum being 32.9% at Rawalpindi General Hospital, Rawalpindi.[11] The study conducted at Aga Khan University Hospital Karachi showed a frequency of 33%.[12]

SBP may present in different shapes like *Bacterial Ascites (BA)*, *culture negative neutrocytic ascites (CNNA)*

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and *classic ascites (CA)*. These different variants vary in different studies. In Rawalpindi, BA & CNNA was found in 10% and 66.7% of patients with SBP respectively, while in Karachi, 11.12% and 44.44% respectively.[13]

Gram Negative anaerobic organisms are usually cultured from the ascitic fluid.[7] The microorganisms more commonly isolated from cases of SBP are: Escherichia coli (70%), Klebsiella species (10%), Proteus species (4%), Enterococcus faecalis (4%), Pseudomonas species (2%) and others (6%).[14] In Western countries, the frequency of isolation of gram negative bacteria is 40-50%[5,15,16] whereas at Jinnah Postgraduate Medical Center Karachi, E. Coli was identified as causative organism for SBP in 50% of the cases studied. SBP may present without any symptoms at all or may present with fever, abdominal pain or tenderness or any combination of these features. The frequency of clinical features varied in different studies. In Peshawar, common presentation of SBP was abdominal pain (78%) followed by abdominal tenderness (76%), fever (72%), jaundice (58%) and hepatic encephalopathy (48%).[17] Another local study showed that 80% of patients presented with abdominal pain, 77% with abdominal tenderness, 72% with fever, 65% with jaundice and 54% with hepatic encephalopathy.[18] Study from Nawabshah showed SBP presenting as Tenderness (87.5%), Jaundice (81%), abdominal pain (78%), hepatic encephalopathy (71%) and fever, (46.8%).[12] In studies conducted in the west, fever was present in 67.5-75% in patients with SBP, abdominal pain in 51.5% and abdominal tenderness in 53%. Approximately 50% of patients with SBP die during the same hospital admission[19], while 69% of patients have recurring infection within 1 year and this recurrence carries the same mortality.[20] Factors associated with an increased risk of SBP recurrence are a higher Child-Pugh class and a low protein concentration of ascitic fluid.[14]

This study was conducted to provide data regarding the clinical spectrum of SBP to help in developing a plan for prevention of this complication in cirrhotic patients in our setting.

MATERIAL AND METHODS

This was a descriptive study of 70 consecutive patients of liver cirrhosis with ascites who were aged 12 years and above, and was conducted in medical C unit of Ayub Teaching Hospital Abbottabad from 1st April 2008 to 31st March 2009. All patients were admitted and a detailed history was taken with special stress on history of jaundice and liver related symptoms in the past. Detailed examination of every patient was done with the physician looking for abdominal tenderness, abdominal wall rigidity, bowel sounds, ascites, jaundice, clubbing, leukonychia, palmar erythema, dupuyetren's contractures, spider nevi, pallor, gynecomastia, testicular atrophy in males, peripheral edema, caput medusae and splenomegaly.

The following investigations were done in all the patients.

- Complete blood count
- Blood urea
- X Ray Chest
- X Ray abdomen
- Abdominal ultrasound
- Liver function tests
- Serum proteins
- Hepatitis B surface antigen
- Hepatitis E antigen (Hepatitis B surface antigen positive only)
- Anti HCV antibodies
- Prothrombin time
- Asitic fluid R/E
- Culture and sensitivity of ascitic fluid (only relevant investigations which are reflected in the result are to be listed, others may be put in exclusion criteria or mentioned separately as routine investigations).

About 10 ml of ascitic fluid was taken in a disposable syringe for routine examination and was transferred in a culture bottle at bedside if the routine examination was suggestive of SBP.

Criteria for Diagnosis of SBP

The diagnosis of SBP was considered in the presence of > 500/cmm leucocytes[21] or presence of > 250 neutrophils in ascitic fluid.

Depending on cell count or culture of ascitic fluid SBP was classified into following variants:

1. *Bacter ascites* (BA). Defined as ascitic fluid leucocyte count <500/cmm or neutrophil <250/cmm with positive culture
2. *Culture negative neutrocytic ascites* (CNNA) defined as ascitic fluid leucocyte count >500/cmm or neutrophil count >250/cmm with negative culture
3. *Classic SBP* defined as ascitic TLC >500/cmm or neutrophil >250/cmm with positive ascitic fluid culture

Inclusion Criteria

All patients above 12 years of age, male and female, with proven liver cirrhosis and ascites were included. Diagnosis of cirrhosis was based on histopathology of liver biopsy. Ultrasound evidence of shrunken liver (<8cm) with increased echogenicity, ascites and

splenomegaly with presence of the stigmata of chronic liver disease were considered for the support of the diagnosis.

Exclusion Criteria

- Age less than 12 years
- History of use of antibiotics during past 10 days.
- Patient with secondary peritonitis e.g. gastrointestinal perforation, septicemia, intestinal obstruction, trauma and appendicitis.
- Patient in whom the diagnosis of liver cirrhosis was not established or liver biopsy was contraindicated or patient was not willing for biopsy. Following were considered contraindications of liver biopsy.
    - o Prothrombin time > 3 seconds beyond control
    - o Platelet count <90,000/cmm
    - o Moderate to severe ascites

All patients with SBP were given injection Cefotaxime 2g intravenous daily for 5 days followed by tablet Norfloxacin 400 mg PO OD for prophylaxis of secondary infections.

Patients data was analyzed on SPSS version 17 and p-value of < 0.05 was considered significant after application of statistical analysis.

RESULTS

Out of 70 cirrhotic patients, 42(60%) patients were male and 28 (40%) were female with males: female ratio of 1.5:1. SBP was found in 26 patients (37.14%). Out of these cases 17 (65.38%) were males and 9 (34.62%) were females. The different variants of SBP included:

- **Classic SBP**, found in 10 patients (39%),
- **CNNA**, found in 13 patients (50%),
- **BA**, was present in 3 patients (11%).

Clinical Presentation

This study noted that abdominal tenderness and pain were the leading clinical features in SBP (Table 1). Of all the clinical features identified, abdominal tenderness was present in 80.77 & of patients with SBP, and abdominal pain was present in 73.07%. Splenomegaly was present in 76.92% of patients with SBP. As compared to SBP these features were not that marked in non-SBP group, but still they were leading clinical features in that group, with abdominal tenderness present in 59.09%, splenomegaly in 54.54% and abdominal pain in 50% of the group. Palmar erythema was the next important clinical feature noted, 69.23% and 59.09% in SBP and non-SBP groups, respectively. Spider naevi were uncommon in both these groups, 30.76% and 22.72% respectively in SBP and non-SBP group respectively. It was further noted that some clinical features were noted more frequently in both these groups and that mere presence or absence of these factors could not alone rule in or rule out the diagnosis of SBP.

HEPATIC ENCEPHALOPATHY (Figures1-3)

After the patients were categorized into different grades of hepatic encephalopathy, it became apparent

CLINICAL PRESENTATION OF 70 PATIENTS OF LIVER CIRRHOSIS

Clinical Features	SBP n=26		Non-SBP n=44	
	Frequency	% age	Frequency	% age
Fever	18	69.2	22	50
Abdominal Tenderness	21	80.7	26	59.09
Abdominal Pain	19	73.07	22	50
Jaundice	14	53.84	13	29.54
Palmar Erythema	18	69.23	26	59.09
Splenomegaly	20	76.92	24	54.54
Spider Naevi	8	30.76	10	22.72
Dupuyetren's contracture	9	34.61	15	34.09
Gynecomastia	12	46.15	18	40.90
Testicular Atrophy	10	38.46	12	27.27

Table I

HEPATIC ENCEPHALOPATHY

Grade	SBP group n=26		Non-SBP group n=44		Total n=70	
	Frequency	%age	Frequency	%age	Frequency	%age
1	07	26.92%	27	61.36%	34	47.22%
2	11	42.30%	14	31.82%	25	34.72%
3	04	15.38%	03	06.81%	07	9.72%
4	04	15.38%	00	0.00%	04	5.55%

Table II

CHILD-PUGH'S GRADING OF PATIENTS

Grade	SBP group n=26		Non-SBP group n=44		Total n=70	
	Frequency	%age	Frequency	%age	Frequency	%age
A	01	3.85%	06	13.64%	07	9.72%
B	15	57.7%	26	31.82%	41	56.94%
C	10	38.46%	12	27.27%	22	30.56%

Table III

that most of the patients in SBP group (42.30%) belonged to Grade 2 hepatic encephalopathy while majority of non-SBP group (61.36%) belonged to Grade 1 hepatic encephalopathy (Table 2). Overall the status of patients according to CHILD-PUGH'S criteria is given in Table 3.

Biochemical Examination

The biochemical examination of all patients' studies yielded the following results. The mean Serum Bilirubin in SBP group was 7.21 ± 5.1 mg/dl. In Non SBP group it was 2.18 ± 1.23mg/dl (p value=0.03) which was significant. The mean serum ALT ± S.D, among SBP group was 150.12 ± 88.90 IU/L. The mean ALT ± S.D in non SBP group was 53 ± 38.42 IU/L.(p=0.02) showing a significant difference between these two groups.

GRADES OF HEPATIC ENCEPHALOPATHY IN OVERALL STUDY POPULATION

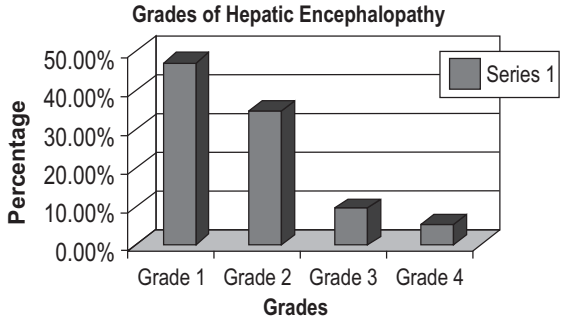

Fig. I

GRADES OF HEPATIC ENCEPHALOPATHY IN NON-SBP GROUP

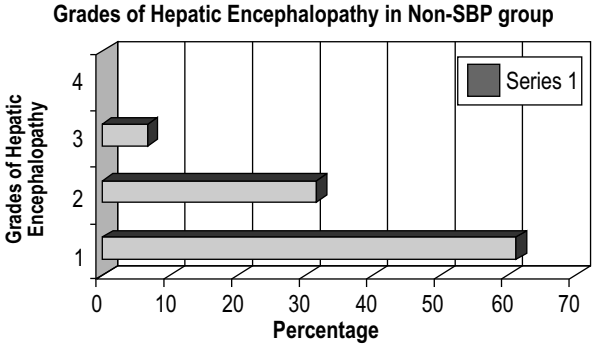

Fig. II

GRADES OF HEPATIC ENCEPHALOPATHY IN SBP GROUP

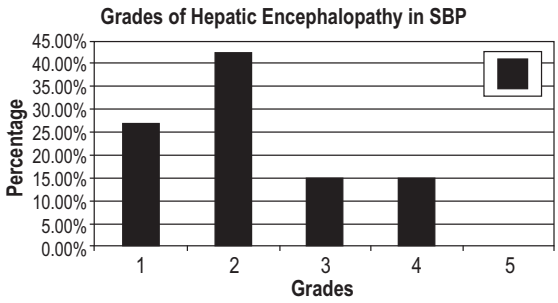

Fig. III

The mean serum albumin ± S.D in SBP group was 1.5 ± 0.32 g/dl and in Non SBP group it was 2.2 ±

0.60. (p= 0.002) showing a significant difference. The mean prolongation of Prothrombin time from control in SBP group was 7.31 ± 6.02 seconds. And mean prolongation of Prothrombin time from control in non SBP group was 3.20 ± 2.83 second. (p=0.03) which is significant. The mean BUN in SBP group was 65 ± 35 mg% and in non SBP group was 47.31±32 mg%. (p=0.07) which was not significant. The mean of total leukocyte count in asctic fluid of SBP was 1600±1400 / cmm and that of non SBP group was 240±145/cmm. (p = 0.002) showing significant difference. The mean count of Poly morphonuclear cells in ascitic fluid in SBP was 1400±1200 /cmm and that of non SBP group was 110±95/cmm. P=0.01 which was significant. The mean ascitic fluid albumin in SBP group was 1.35±0.72 g/dl. In non SBP group it was 2.23±1.3 g/dl. (p=0.02) which was significant. The mean ± S.D count of lymphocytes in SBP group was 310±210/cmm and that of non SBP group was 70±100/cmm (p=0.04) which was significant.

Viral Markers

Out of total 72 patients 45% patients tested positive for Hepatitis C virus. Another 30% (21) tested positive for HbsAg, Out of which 4 patients were Hbe positive. 15% patients tested positive for both Hepatitis C and HbsAg. 10% didn't test positive for any of viral markers.

Microorganisms

The frequency of microorganisms found in culture of ascitic fluid was in the following order:

E. coli	60%	(n=6/10)
Klebsiella	30%	(n=3/10)
Pneumoccous	10%	(n=1/10)

DISCUSSION

Spontaneous bacterial peritonitis is a common and potentially fatal complication of liver cirrhosis with ascites[1]. In this study 37.14% of patients hospitalized with cirrhosis had SBP This figure is close to figures reported by similar studies in Pakistan, 32.9% from Rawalpindi, 33% from AKU Karachi and 31.66% at MH Rawalpindi[10,11,22]. However, only one study from Nawabshah[12] had reported a very high prevalence of SBP of 64% and their results do not match with others and our study conducted in the region. Results similar to this study were cited in different studies from India[23], Saudi Arabia[8] and Africa[20]. The increased incidence of SBP in Pakistan as compared to west (7-30%) may be attributed to poor hygienic practices and prevalence of infectious diseases.

SBP may present as bacter ascitis (BA), culture negative neutrocytic ascitis (CNNA) and classic Ascites (CA). In our study, BA was found to be 11%, CNNA 50% and CA was present in 39% of cases with SBP. In other studies conducted in region, BA was found in 11.12% and CNNA was found in 44.44% of patients with SBP at civil hospital Karachi[10]. And at MH Rawalpindi the frequency of BA and CNNA were 3.5% and 64.94% respectively[22]. Similar patterns of variants of SBP are also reported in studies from abroad.[2-5,8,9]

Thus BA is not an uncommon finding in cirrhotic patients with ascites. Further studies of large number of patients are needed to look into prevalence of BA in Cirrhosis with ascites. The difference in frequency could be attributed to host factors like immune and general health status, causative organisms, and small number of patients in these studies.

In our study 50% of patients with SBP had positive ascitic fluid culture. This figure is higher than reported by other local studies: 27.77% by Chowdary[24] and associates, 45% by Jafri[10], and 30% reported by Puri[23]. The microorganisms of SBP are usually of gut flora, mostly E. coli[5,23,25]. We found E coli in 60% of patients, Klebsiella in 30%, and pneumococci in 10% of cases of SBP. It is in full agreement with other studies done locally.[22,24,26] Similar results were seen in studies from india[9], Saudia Arabia[8] and Uruguay[20].

In contrast, a higher incidence of Gram positive organisms was seen in studies from spain[27] and Thailand[28]. The difference in frequency might be due to different number of patients in these studies. Cell *count* criteria in ascitic fluid appears to be a better method for the diagnosis of SBP, as it can provide an early diagnosis and hence early antibiotic therapy can be started so preventing serious complications.

In our study we found abdominal pain in 73.07% and abdominal tenderness in 83.77%. Other studies had shown pain in 80% and tenderness in 51.5% to 53.33% cases respectively[10,16,18]. However, it depends on the expertise of physician and the patient's description. In our study fever was present in 69.2% as compared to western studies where it was seen in 67 to 75% patients of SBP[25,28].

Infections anywhere in the body including SBP can precipitate hepatic encephalopathy *in cirrhotic patients* and it is therefore expected that clinical features of hepatic encephalopathy will be more in patients with SBP. The patients with jaundice in liver cirrhosis are more prone to various infections like SBP and SBP itself can cause deepening of jaundice [29]. Jaundice was observed in 53.84% in our study in SBP group, whereas this figure was 79% in a study conducted at Rawalpindi[11]. It is comparable with other studies.[2,5]

In our study we found statistically significant differences in serum bilirubin, ALT, neutrophils, Serum albumin, Prothrombin time, Ascitic fluid TLC neutrophils lymphocytes in ascitic fluid albumin between SBP and non SBP group. This is in full agreement in studies done locally[10-13] and abroad[8,9,20,28]. Hepatits B and C were major

underlying causes of cirrhosis in this study. Recently more prevelance of cirrhosis is shown among HCV positive patients. Different studies in Pakistan cite it in range of 18%, 37%, 62.5% and 65.5%[30-33]. This is in contrast to western data which reveals alcoholic cirrhosis as major cause in 60 to 70%[34]. This marked difference in etiology of cirrhosis is due to alcohol abstinence in our setting for social and religious reasons. Alcoholic abuse is quite common in western society but it is legally and religiously forbidden in Pakistan. On the other hand, high rate of *viral* infective etiology in Pakistan is due to lack of public awareness regarding hepatitis, use of disposable syringes and poor medical facilities. In our study the mortality in SBP patients was 35% and mortality in non SBP was 11.36%. mortality figures of SBP are close to those described by Jafri 36%[10] but much higher than mortality described by Khokhar which was 17%[24].

CONCLUSION

This study highlighted the significance of SBP as a major complication in cirrhotic patients in Hazara division and Northern areas of Pakistan. Males were affected more than females. This study compared the clinical profile of SBP with that of other developing countries and understandably the observed frequency of SBP was more than that of developed countries. We found that E.Coli were the commonest organism cultured in ascitic fluid as this organism is normally found in gut it may have translocated through the intestinal wall into the mesenteric lymph nodes and through systemic circulation to peritoneal cavity.

It is recommended that diagnostic tap of ascitic fluid should be routinely done in all patients with cirrhosis or chronic liver disease. In high risk patients of cirrhosis cost effective prophylactic antibiotic therapy should be started as soon as possible and a high index of suspicion should be maintained while dealing with patients of chronic liver disease and/or ascites.

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CONFLICT OF INTEREST

Authors declare no conflict of interest