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A Study on Clinical and Laboratory Features of Spontaneous Bacterial Peritonitis in Chronic Liver Disease

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Abstract

Objective: *To determine the clinical and laboratory features, bacterial profile and antibiotic sensitivity pattern of Spontaneous Bacterial Peritonitis (SBP) in Chronic Liver Disease (CLD) patients presenting at a tertiary care hospital of Goa medical college hospital*

Study Design: *Cross-sectional study. This study was done in department of medicine Goa medical college hospital, Panaji, Goa.*

Methodology: *CLD patients with ascites were recruited from Goa medical college hospital. Basic demographics, symptoms and clinical signs of patients were recorded. Patients with the history of antibiotic use within last 3 days or any intra-abdominal source of infection were excluded. Diagnostic paracentesis was done for ascitic fluid detailed report (D/R) and culture. Blood sample was collected for total leukocyte count, serum proteins and billirubin levels.*

Results: *Out of a total 100 CLD patients, 27 (27%) were diagnosed with SBP, Nine (33.7%) patients presented with classical SBP, 12 (44.4%) had culture negative neutrocytic ascites and 6 (22.2%) had bacterascites. Fever, abdominal tenderness and constipation were common in SBP patients. Ascitic fluid culture was positive in 15 (55.5%) patients. E. coli (63%) was the predominant pathogen followed by Enterococcus species (15%). Resistance was high against cephalosporins (78%) and fluoroquinolones (69.6%) and least against amikacin (13%) and meropenem (12%).*

Conclusion: *Ascitic fluid D/R and culture together can lead to the accurate diagnosis of SBP and can guide for the right antibiotic choice as resistance to commonly prescribed antibiotic is common in such patients.*

Keywords: *Chronic liver disease. Spontaneous bacterial peritonitis. Ascitic fluid. CNNA. Bacterascites. SAAG.*

INTRODUCTION

We know from the literature up to 50% of patients with cirrhosis develop ascites within 10 years of the diagnosis. [1, 2] Spontaneous Bacterial Peritonitis (SBP) is a common and most dreaded complication in such patients with liver disease and ascites. In patients with incidence of SBP ranges from 7% to 30% per annum [3]. Due to various advances in the diagnosis and treatment, there has been a significant decrease in the mortality associated with SBP from 90% to 20% since its first description.[4]

Clinical presentation of SBP is nonspecific and highly variable. Up to 10%- 30% of patients with SBP have been found to be completely asymptomatic [5, 6.] Common signs and symptoms are fever, diarrhea, gastro intestinal bleeding, abdominal pain/tenderness, vomiting, diarrhea, hepatic encephalopathy etc.[7, 8]

A classical case of SBP is diagnosed on the basis of neutrophil count greater than 240/cmm and a positive ascitic fluid culture. Other two types of SBP i.e. Culture Negative Neutrocytic Ascites (CNNA) and Bacterascites (BA), based on the ascitic fluid analysis (cell count and C/S) results. CNNA has a negative culture with a higher neutrophil count (i.e.> 240/cmm) while in Bacterascites, ascites fluid culture is positive but neutrophil count is < 240/cmm.[9]

Apart from the symptoms or ascitic fluid cell count, various biochemical tests like serum proteins, albumin, Serum Ascites Albumin Gradient (SAAG), ascitic fluid glucose and ascitic fluid proteins/albumin levels are also shown to predict or suggest the presence of SBP in cirrhotics.

Majority of the time bacterial translocation from the intestinal lumen is the preceding factor for the development of SBP. [9] Hence we see commonly gram negative aerobic bacteria from the family of enterobacteriaceae (60%) as the predominant cause of SBP. Non-enterococcal *Streptococcal* species predominantly *Streptococcus pneumoniae* (35%) are the second most frequent bacterial pathogens grown from ascitic fluid[10,11] but off late SBP episodes due to gram positive pathogens are being increasingly noticed .[12,13] These changes are thought to be due to indiscriminate use of antibiotics, increasing number of invasive procedures and hospitalization in intensive care units and suggest a need for the constant assessment of common bacterial pathogen and their culture and sensitivity to guide empirical treatment of SBP patients.

This study was conducted with the aim to find out the frequency of SBP or its variants in CLD patients. Also association of different symptoms, signs, or laboratory findings with SBP and identify the bacterial pathogens and their sensitivity pattern in order to find out the optimal antibiotic choice for such patients.

METHODOLOGY

It was a cross-sectional analytical study conducted in department of medicine Goa medical college hospital Bambolim Goa. Patients were recruited from outpatient Department of G M C and Medical Wards of GMC.

Patients diagnosed with chronic liver disease and also having ascites on the basis of clinical examination, liver biopsy or ultrasound were included in the study after taking written informed consent from patient or attendant.

Exclusion criteria - Those having ascites due to etiology other than liver disease, those who were already on antibiotics, those having some intra-abdominal source of infection like surgery, children under 15 years of age and those who did not consent to participate in the study.

A predesigned structured proforma was used to record patient's demographics, symptoms and clinical signs.

Diagnostic Paracentesis was performed using all standard precautions for all study participants. Total 15 - 20 cc ascitic fluid was collected from each patient for ascitic fluid report and culture and sensitivity. Blood sample (5 - 8 cc) of patients was also collected to measure TLC, serum billirubin, serum total protein and serum albumin.

All the results of laboratory investigations (biochemical as well as bacteriological) were also recorded in the proforma.

The study was approved by ethical review committee of G M C and informed consent was obtained from all participants or their attendants.

The data feeding and analysis was done on computer package SPSS (Statistical Package for Social Sciences). Frequency or percentages were calculated for categorical variables like gender, symptoms and clinical signs. Chi-square test was done to determine the association between SBP and categorical variables (like clinical symptoms and signs). Mean ± SD was calculated for continuous variables (e.g. age, ascitic fluid glucose, total proteins etc.) while student's t-test for independent variables was used to determine any significant difference between SBP and non-

SBP patients. In all statistical analysis only p-value < 0.05 was considered significant.

RESULTS

During 1.5 years, a total of 100 patients with CLD and ascites were enrolled. These included 40(40%) males and 60 (60%) females. The mean age of participants was 46.45 ± 13.75 years, with a minimum age of 18 years and maximum age of 85 years. Majority i.e. 75 (75%) patients were hospitalized while 25 (25%) patients were enrolled from Outpatient Department (OPD).

Of the total 100, 25 (25%) patients had SBP with 8 (32%) having classical SBP, 13 (52%) having CNNA and 4 (16%) BA (Table I). Among 75 hospitalized patients 18 (24%) had SBP while out of 25 outpatients 7 (28%) patients were diagnosed with SBP. Viral markers were available for 70 (70%) patients, out of these 51 (72.8%) patients were HCV positive, 8 (11.4%) were HBV positive, 2 (2.8%) had co-infection of HBV and HCV while 9 (12.8%) patients were negative for both HBV and HCV.

Regarding the clinical presentation of patients we could not find any significant association between any of the studied symptoms and SBP (Table II) in patients with SBP, similarly the study did not reveal any significant association of clinical signs including hepatic encephalopathy or abdominal tenderness with SBP (p > 0.05, Table II). Also none of the laboratory findings differed significantly between SBP and non-SBP patients (Table III).

Out of total 25 patients diagnosed with SBP, ascitic fluid culture was positive in 13 (52%) patients. Distribution of pathogens among these patients is reflected in the Figure 1. *E. coli* was the predominant pathogen that was isolated in 9 (69.2%) cases. Sensitivity pattern of Gram negative and Gram positive pathogens is depicted in Figures 2 and 3 respectively, which shows that sensitivity rates to commonly prescribed antibiotics like ofloxacin, ceftriaxone and amoxicillin/clavulanate were quite low but, most of the isolates were sensitive to amikacin, meropenem and piperacillin/tazobactam

Table I: Distribution of patients on the basis of ascitic fluid PMN cell count and culture.

Variable	PMN cell count	PMN cell count	
	> 240/cmm	< 240/cmm	Total
Culture positive	8(classical SBP)	4(Bacterascites)	25
Culture negative	13(CNNA)	75(Non SBP)	75
Total	21	79	100

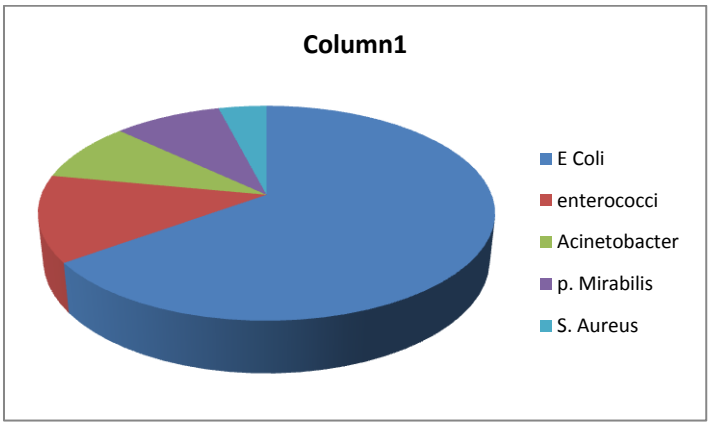
Table II: Association of different symptoms or clinical signs with SBP.

Symptoms/clinical signs	SBP(25)	Non SBP(75)
Fever	13(52%)	39(52%)
Abdominal pain	14(56%)	40(53.3%)
Nausea /vomiting	8(32%)	26(34.6%)
Diarrhea	3(4%)	7(9.3%)
Constipation	7(28%)	23(30.6%)
GI bleeding	5(20%)	14(18.6%)
Jaundice	11(44%)	35(46.6)
Hepatic encephalopathy	7(28%)	20(26.6)
Abdominal tenderness	13(52%)	39(52%)

Table III: Laboratory findings in SBP and non-SBP patients.

Laboratory tests	Non SBP		SBP		P value
Ascitic fluid	Mean	SD	Mean	SD	
Glucose	113	52.83	106.82	63.07	NS
Total proteins	1.827	1.29	1.86	1.06	NS
Albumin	0.881	0.56	0.94	0.54	NS
Blood					
WBC	9.88	9.21	11.07	7.59	NS
Total proteins	6.16	1.24	6.36	1.28	NS
Albumin	2.59	0.70	2.65	0.77	NS
Bilirubin	4.10	6.04	2.98	2.33	NS
SAAG(serum ascitic albumin gradient)	1.73	0.55	1.63	0.52	NS

Figure 1: Distribution of pathogens among SBP patients.



E coli -65
Enterococci- 13
Acinetobacter-9
Proteus mirabilis-9
Staph aureus -4

Table: IV Antibiotic sensitivity pattern of gram negative organisms.

Ampicillin	0%
Amoxiclav	8%
Cefixime	22%
Ceftriaxone	24%
Cotrimoxazole	28%
Ofloxoxin	32%
Gentamycin	40%
Chloramphenicol	50%
Tazobactam	70%
Amikacin	89%
Meropenem	90%

Table V: Antibiotic sensitivity pattern of gram positive organisms.

Tetracycline	25%
Penicillin	25%
Erythromycin	50%
Ceftriaxone	50%
Ofloxoxin	67%
Clindamycin	70%
Chloramphenicol	75%
Vancomycin	100%
Amikacin	100%
Ampicillin	100%
Amoxiclav	100%

DISCUSSION

Spontaneous bacterial peritonitis is a most common complication in patients with chronic liver disease and ascites. The incidence of SBP (including CNNA and BA) was found to be 25% in our cohort. International studies reports an incidence of 8 - 30% in CLD patients with ascites,[3, 14] which reciprocates that our results are in concordance with these reports.

Regarding SBP variants, CNNA was the most common followed by Bacterascites and classical SBP in descending order. Similar pattern of the distribution of different SBP variants has been reported by Evans *et al*.[15] But, some studies have a slightly different pattern which show Bacterascites to be the least common entity.[14, 16] Recent literature suggests bacterascites is not an uncommon phenomenon. The differences in frequency of different SBP variants within different populations may be due to more severity of disease in the cases as mentioned above apart from host factors like immunity and general health status of patients.

We found slightly higher frequency of SBP in non-hospitalized patients but it was statistically not significant ($p > 0.05$). This suggests that though SBP is a complication but it did not add much to the patients' symptoms as SBP is often described to be asymptomatic in patients with cirrhotis.[15]

We can explain this with the fact that most of the patients with liver disease get admitted to the hospital with hepatic encephalopathy, jaundice, or high fever, which didn't show any significance our study.

We could not find any significant association between clinical signs or symptoms and SBP. These findings are in accordance with other national and international data as many of them suggests highly variable presentation of SBP and with non-specific signs and symptoms. Since most of the patients are asymptomatic and hence diagnostic paracentesis to establish the diagnosis is recommended.[17]

When we compared the biochemical parameters, none of the test showed statistically significant difference between the two groups. The mean value of SAAG was > 1.1 g/dl in both non SBP and SBP cases which confirms that ascites was due to portal hypertension. This finding is in concordance study by Beg M which suggests that SAAG levels are > 1.1 g/dl in all ascites due to portal hypertension irrespective of infection.[18 19,] SBP patients in this study had lower mean SAAG value (1.633 g/dl) as compared to non-SBP patients (1.733 g/dl). Similar findings were reported by Agarwal and Thiele *et al*. [19, 20] while Nouman *et al*. observed a higher mean SAAG value (1.5 g/dl) in SBP patients as compared to non SBP patients (1.2 g/dl).[21]

In our study ascitic fluid culture was positive in 52% of SBP cases. International literature suggests a culture positivity rate of 31 - 71%.[14, 22] A study from Lahore showed similar results (47.5%) [16] but some studies have reported less than 25% rates of culture positivity.[14, 23] This

difference may be due to the different culture techniques as reported by Pawar *et al*. showing varied rate for different technique.[22] But after use of culture bottles, relatively better culture positivity rates obtained as compared to aforementioned local studies.

Gram negative bacilli were isolated from 87% of cases with *Escherichia coli* being most common pathogen associated with SBP followed by *Enteroccocus* species. These results are in accordance with other national and international studies.[16, 22 , 24] The main reason gram negative organism for SBP is due to bacterial transloc-ation from gut There are some studies which reported the predominance of Gram positive organisms, but that is very rare and is frequently due to some prophylaxis or some previous intervention.[21]

Third generation cephalosporins are broad spectrum, well tolerated and relatively safe treatment for SBP patients while Amoxicillin/ clavulanate, fluoroquinolones or Piperacillin/ tazobactam are recommended as alternative regimens.[2,4,8] Only 32%, 24%, 8%, of Gram negative bacilli were sensitive to ofloxacin, Ceftriaxone and amoxicillin/clavulanic acid respectively in our study, which is quite shocking as these are usual antibiotics of choice for SBP. Antibiotic sensitivity rates were higher against piperacillin/ tazobactam and amikacin.

Resistance of gram positive pathogens to ceftriaxone and ofloxacin was common in this study. Similar higher rates of resistance against these antibiotics are also reported from Lahore, Pakistan, unlike international data which suggests a higher sensitivity to these drugs.[24] These differences in the may be due to the wide spread and indiscriminate use of cephalosporins and fluoroquinolones in India. The present study suggests that amikacin could be the effective alternate antibiotic in SBP patients, nevertheless higher rates of sensitivity also seen against meropenem. But it is not usual recommendation because it known to contribute to development of hepatorenal syndrome. This emergence of antibiotic resistance is very alarming since it is driving us very fast towards the post antibiotic era. We should formulate appropriate measures to prevent spread of drug resistant strain and indiscriminate use of antibiotics to restrain antibiotic resistance.

CONCLUSION

SBP developed in 25% of patients with CLD and ascites. Diagnosis of SBP only on the basis of clinical manifestations is not easy hence diagnostic paracentesis for D/R and C/S is important. Due to development of resistance against oral antibiotics like fluoroquinolones, amoxicillin-clavulanate, cefixime, we find it difficult to manage such patients on outpatient basis. Amikacin and meropenem may be considered as optimal treatment choices for SBP patients.

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