Clinical, Laboratory and Bacterial Profile of Spontaneous Bacterial Peritonitis in Chronic Liver Disease Patients

Safia Bibi, Waquaruddin Ahmed, Ambreen Arif, Furqan Khan and Syed Ejaz Alam

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 Karachi.
Study Design: Cross-sectional study.
Place and Duration of Study: PMRC Centre for Gastroenterology and Hepatology and Jinnah Postgraduate Medical Centre, Karachi, from April 2010 to March 2012.
Methodology: CLD patients with ascites were recruited from PMRC Centre for Gastroenterology and Hepatology and Jinnah Postgraduate Medical Centre, Karachi. 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 leucocyte count, serum proteins and bilirubin levels.
Results: Out of a total 152 CLD patients, 38 (25%) were diagnosed with SBP. Eight (24.2%) patients presented with classical SBP, 20 (52.6%) had culture negative neutrocytic ascites and 10 (26%) had bacterascites. Fever, abdominal tenderness and constipation were common in SBP patients. Ascitic fluid culture was positive in 19 (50%) patients. E. coli (65%) 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.
Key Words: Chronic liver disease. Spontaneous bacterial peritonitis. Ascitic fluid. CNNA. Bacterascites. SAAG.
proposed 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 antibiogram 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 and association of different signs, symptoms or laboratory findings with SBP. Further, we also aimed to 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 from April 2010 to March 2012 at Pakistan Medical Research Council’s (PMRC) Research Centre for Gastroenterology and Hepatology in collaboration with medical units of Jinnah Postgraduate Medical Centre (JPMC), Karachi. Patients were recruited from outpatient Department of PMRC Research Centre and Medical Wards of JPMC. 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. 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 were excluded from the study.

Based on the inclusion and exclusion criteria, CLD patients with ascites were recruited for the study. A predesigned structured proforma was used to record patient’s demographics, symptoms and clinical signs. Paracentesis (only diagnostic tap) was performed using all standard precautions for all study participants. Total 15 - 20 cc ascitic fluid was collected from each patient for ascitic fluid detailed report and culture and sensitivity. Blood sample (5 - 8 cc) of patients was also collected to perform TLC, serum billirubin, serum total protein and serum albumin.

Eight to ten ml of ascitic fluid was inoculated in oxoid blood culture bottles (for aerobic and anaerobic culture) at the bed side using aseptic technique. While 3 cc sample was directly cultured on two blood agar plates (for aerobic and anaerobic bacteria), chocolate agar plate following centrifugation and incubated at 37°C. Direct culture plates were monitored daily for 48 hours for any growth. Blood culture bottles were incubated for 05 days at 37°C and monitored daily for any signs of positive culture (turbidity, gas production). Bottles showing any signs of positivity were sub-cultured on blood agar, chocolate agar and MacConkey’s agar.

CLSI (Clinical Laboratory Standards Institute) guidelines were followed for identification and sensitivity testing of all the isolates. Sensitivity testing was performed on Mueller Hinton agar using Kirby Bauer disk diffusion method. All negative bottles were sub-cultured on 5th day for confirmation of negative result.

All the results of laboratory investigations (biochemical as well as bacteriological) were also recorded in the proforma to facilitate data management and entry. The study was approved by ethical review committee of Jinnah Postgraduate Medical Centre, Karachi 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) version 16.0. 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 2 years, a total of 152 patients with CLD and ascites were enrolled. These included 62 (40.8%) males and 90 (59.2%) females. The mean age of participants was 46.45 ± 13.75 years, with a minimum age of 15 years and maximum age of 85 years. Majority i.e. 118 (77.6%) patients were hospitalized while 34 (22.4%) patients were enrolled from Outpatient Department (OPD).

Of the total 152, 38 (25%) patients had SBP with 8 (21%) having classical SBP, 20 (52.6%) having CNNA and 10 (26.3%) BA (Table I). Among 118 hospitalized patients 27 (22.8%) had SBP while out of 34 outpatients 11 (32.3%) patients were diagnosed with SBP. Viral markers were available for 117 (77%) patients, out of these 80 (68.4%) patients were HCV positive, 18 (15.4%) were HBV positive, 2 (1.8%) had co-infection of HBV and HCV while 17 (14.5%) patients were negative for both HBV and HCV. No significant association of HBV (p=0.054) or HCV (p=0.103) was observed with SBP.

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 a total 38 patients diagnosed with SBP, ascitic fluid culture was positive in 19 (50%) patients. Distribution of pathogens among these patients is reflected in the Figure 1. *E. coli* was the predominant pathogen that was isolated in 12 (63.2%) 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.

**DISCUSSION**

Spontaneous bacterial peritonitis is a frequent complication in patients with chronic liver disease and ascites. The incidence of SBP (including CNNA and BA) was found to be 24.3% in the patients. International data or reports document an incidence of 8 - 30% in CLD patients presenting with ascites, which suggests that this study results are in concordance with these reports. This study results also correlate well with a local study conducted in Lahore which reported an incidence of 8 - 30% in CLD patients presenting with ascites, which suggests that this study results are in concordance with these reports. But some of the local studies reported quite higher incidence i.e. 38%, 47.5% and 56%, which was probably because of the difference in patient recruitment criteria, as all these studies enrolled patients who had a strong suspicion of SBP. Regarding SBP variants, CNNA was the most common picture 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. But, local
studies have a slightly different pattern which show bacterascites to be the least common entity. 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.

The frequency of SBP in the present study was slightly higher in non-hospitalized patients but no significant difference (p > 0.05) was observed between the two groups. This reflects that though SBP is a complication but it did not contribute much to the severity of patient's condition in our patients, as SBP is often reported to be asymptomatic in patients with cirrhotic ascites. This might also be explained through the fact that main reasons which significantly associated with hospital admission in liver disease patients were found to be hepatic encephalopathy, jaundice or high grade fever which did not show any significant association with SBP in this study.

With reference to the clinical presentation of patients we could not find any significant association between any of the studied symptoms or clinical signs and SBP. These findings are consistent with local and international data as many of the studies suggest that the presentation of SBP is highly variable and non-specific with patients often being asymptomatic and hence diagnostic paracentesis to establish the diagnosis is recommended.

Regarding biochemical parameters, none of the test showed any significant association between any of the studied symptoms or clinical signs and SBP. The mean value of SAAG was > 1.1 g/dl in both SBP and non-SBP cases which confirms that etiology of ascites was portal hypertension in these patients. This finding is in concordance with an Indian study which suggests that SAAG levels are > 1.1 g/dl in all ascites due to portal hypertension irrespective of infection. SBP patients in this study had lower mean SAAG value (1.586 g/dl) as compared to non-SBP patients (1.833 g/dl). Similar results were reported by Agarwal from India and Thiele et al. from Southern Brazil, while Nouman et al. observed a lower mean SAAG value (1.2 g/dl) in non-SBP patients as compared to SBP patients (1.5 g/dl).

Ascitic fluid culture was positive in 50% of SBP cases. International literature suggests a culture positivity rate of 31 - 71%. Similar results were reported from Lahore (47.5%) and Abbottabad (50%) but some studies have reported much lower rates of culture positivity i.e. < 25%. This difference could be attributed to the different culture techniques as Pawar et al. has reported a significant association between the culture technique and culture positivity ratio. Use of culture bottles achieved relatively better culture positivity rates as compared to aforementioned local studies.

Gram negative bacilli were isolated from 85% of culture positive cases with *Escherichia coli* being the leading pathogen associated with SBP followed by *Enterococcus* species. These results are consistent with the findings observed by other recent local and international studies. The main reason for SBP as reported in literature is bacterial translocation from gut hence the commonly isolated pathogens are usually enteric gram negative rods followed by *Streptococcus* species. Some of the studies have also reported the predominance of Gram positive organisms but that is very rare and is often due to some prophylaxis or some previous intervention.

Third generation cephalosporins being relatively safe, well tolerated and broad spectrum are considered treatment of choice for SBP patients while Amoxicillin/ clavulanate, fluoroquinolones or Piperacillin/ tazobactam are recommended as alternative regimens. Only 31.3%, 21.4%, 7.1%, of Gram negative pathogens were sensitive to fluoroquinolone (ofloxacin), cephalosporins (Ceftriaxone or Cefixime), and amoxyccillin/clavulanic acid respectively in this study, which is quite alarming as these represent three out of the four antibiotics of choice for SBP. Antibiotic sensitivity rates were higher against piperacillin/ tazobactam, amikacin and meropenem. Among Gram positive pathogens also resistance to ceftaxone and ofloxacin was common in this study. Similar higher rates of resistance against cephalosporins and fluoroquinolones are reported from Lahore, Pakistan, but international data still suggests a higher sensitivity to these drugs. These differences in the local and international regarding sensitivity pattern could be due to the wide spread and indiscriminate use of cephalosporins and fluoroquinolones in Pakistan. The present data suggests that amikacin could be used as an effective alternate antibiotic in SBP patients, though higher rates of sensitivity have also been observed against meropenem but it is not usually recommended in cirrhotic patients as it might contribute to the development of hepatorenal syndrome in these patients. This emerging antibiotic resistance among the isolated pathogens is very alarming since it is driving us very fast towards the post antibiotic era. Appropriate measures to prevent spread of drug resistant strain and indiscriminate use of antibiotics must be instituted stringently to curtail antibiotic resistance.

**CONCLUSION**

Twenty five percent patients with CLD and ascites developed SBP. Diagnosis of SBP on the basis of clinical manifestations is difficult hence diagnostic paracentesis for D/R and C/S is important. Resistance against oral antibiotics like fluoroquinolones, amoxicillin-clavulanate,
cefixime is high which renders the management of such patients difficult as outpatients. Amikacin and meropenem may be considered as optimal treatment choices for SBP patients.

REFERENCES


