Clinical and Bacteriological Profile of Spontaneous Bacterial Peritonitis in Cirrhotic Patients

Piyush Harchand, Veenu Gupta, Gautam Ahluwalia, Rajoo S Chhina

ABSTRACT

Background and objectives: Spontaneous bacterial peritonitis (SBP) is a frequent complication in patients with chronic liver disease and ascites. This can develop slowly and insidiously or remain clinically unrecognized until the appearance of symptoms. The mortality rate after a single episode ranges from 20 to 40%, and early diagnosis is required for adequate treatment and prevention of new episodes. The aim was to study the clinicobacteriological profile of SBP and its variants in patients of cirrhosis.

Materials and methods: This prospective study was conducted on cirrhotic patients with ascites admitted in a tertiary care hospital. Basic demographics, symptoms, and clinical signs of patients were recorded. Diagnostic paracentesis was done for ascitic fluid cytology and culture. Identification and antimicrobial susceptibility of the isolates was done in VITEK system.

Results: Of a total of 113 cirrhotic patients, 58 (51.3%) were diagnosed with SBP. Culture-negative neutrocytic ascites (CNNA) was the commonest presentation. The most common symptoms were abdominal distension followed by fatigue, anorexia, and jaundice. Majority of patients belonged to Child-Pugh's Grade C. Of 58 cases of SBP, 22 were culture positive. Gram-negative isolates were predominant (77.3%). Escherichia coli was the commonest isolate. Gram-negative isolates were highly susceptible to colistin followed by tigecycline, amikacin, and carbapenems; 59% of the isolates were multidrug resistant (MDR) and 13.6% were extensively drug resistant (XDR).

Interpretation and conclusion: Prevalence of SBP in cirrhotic patients was 51.3% and Gram-negative isolates were predominant. Ascitic fluid culture and susceptibility testing can lead to accurate diagnosis of SBP and can guide for treatment as resistance to antibiotic is common.

Keywords: Bacterascites, Cirrhosis, Culture-negative neutrocytic ascites, Serum ascites albumin gradient, Spontaneous bacterial peritonitis.

INTRODUCTION

Cirrhosis is a chronic disease of the liver in which diffuse destruction and regeneration of hepatic parenchymal cells has occurred, with diffused increase in connective tissue leading to disorganization of the lobular architecture. The main causes of cirrhosis are alcoholic liver disease, hepatitis B, hepatitis C, nonalcoholic steatohepatitis, hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. The most common complications are gastrointestinal (GI) hemorrhage, ascites, bacterial infections, encephalopathy renal failure, hepatocellular carcinoma, and hepatic failure. The World Health Organization has estimated that cirrhosis is responsible for 1.1% of all deaths occurring worldwide.

Spontaneous bacterial peritonitis is a frequent and severe complication in such patients with liver disease and ascites. This can develop slowly and insidiously or remain clinically unrecognized until the appearance of symptoms like fever and abdominal pain. The incidence of SBP in cirrhotic patients varies between 7 and 30% per year. Early detection of SBP is extremely valuable for patients, since the mortality rate among untreated patients is around 50%.

Clinical presentation of SBP is highly variable and nonspecific. A significant proportion (approximately 10–30%) of patients with SBP may even be completely asymptomatic. Common symptoms and signs that are reported to have some association with SBP include fever, diarrhea, GI bleeding, abdominal pain/tenderness, vomiting, diarrhea, hepatic encephalopathy, etc.

Besides the clinical symptoms or the ascitic fluid cell count, different biochemical tests like serum proteins, albumin, serum ascites albumin gradient (SAAG), ascitic fluid proteins/albumin, and ascitic fluid glucose levels can also predict or suggest the presence of SBP in patients with cirrhosis.
Bacterial translocation from the intestinal lumen is mainly considered the preceding factor for the development of SBP. For this reason, Gram-negative aerobic bacteria from the family Enterobacteriaceae are reported as the predominant (60%) cause of SBP. The single most frequently detected organism in ascitic fluid from patients with liver cirrhosis and SBP is Escherichia coli. Moreover, the most common Gram-negative bacteria involved in SBP in patients with liver cirrhosis are E. coli and Klebsiella sp., while the most common Gram-positive bacteria are Streptococcus sp., Staphylococcus sp., and Enterococci. Recent reports indicated that a quarter of organisms isolated from patients with nosocomial SBP infections are resistant to multiple commonly used antibiotics. The changes in bacteriological spectrum, increasing number of invasive procedures, and hospitalization in intensive care units suggest a need for the constant assessment of common bacterial pathogens and their antibiogram to guide empirical treatment. This is particularly relevant in countries, such as India where prevalence of antimicrobial resistance is high.

The aim of this study was to describe the clinical presentation, microbiological and antimicrobial susceptibility profile of SBP, and its variants in patients with cirrhosis in a Tertiary Teaching Hospital in Punjab, India.

MATERIALS AND METHODS

This prospective observational study approved by the Institutional Ethical Review Committee was conducted on 113 cirrhotic patients with ascites admitted to Dayanand Medical College and Hospital Ludhiana, Punjab, India, over a period of 15 months (April 2014 to June 2015). Patients of age >20 years with cirrhosis and ascites diagnosed based on clinical examination, endoscopy, liver biopsy, or ultrasound were included in the study after taking written informed consent. Those having ascites due to etiology other than cirrhosis were excluded from the study. Demographic information, symptoms, and clinical signs of patients were recorded on predesigned structured pro forma. Cirrhotic patients were graded as Child A, B, and C based on Child–Pugh classification.

Diagnostic paracentesis was done for ascitic fluid cytology and culture. The ascitic fluid sample was inoculated in Plus Aerobic/F culture vial or FA Aerobic culture vial and was loaded in the BACTEC (Becton Dickinson, USA) or Bac-T/Alert (bioMérieux, USA) microbial detection system respectively. They were incubated till the bottle indicated positive by the system or for a maximum period of 7 days. Organisms’ identification and antimicrobial susceptibility of the isolates were done as described by Collee et al using VITEK system (bioMérieux). Other investigations performed included liver function test, renal function test, coagulation profile, and complete blood count. All the results of laboratory investigation were recorded in the pro forma. The patients were grouped as patients with SBP and those without SBP. Patients with SBP were characterized as follows:

- **Classic SBP**: Ascitic fluid polymorphonuclear (PMN) leukocytes count ≥250 per mm³ and positive ascitic fluid bacterial culture with single organism in the absence of a surgically treatable intraabdominal source of infection.
- **Culture-negative neutrocytic ascites**: Ascitic fluid PMN leukocytes count ≥250 per mm³ and negative ascitic fluid culture in the absence of antibiotic treatment within 30 days and intraabdominal source of infection.
- **Monomicrobial nonneutrocytic bacterascites (MNB)**: Ascitic fluid PMN leukocytes count <250 per mm³, ascitic fluid culture positive for single organism, and no intra-abdominal source of surgically treatable infection.

Bacterial isolates were characterized as MDR, XDR, or pan drug resistant (PDR): MDR bacteria had acquired nonsusceptibility to at least one agent in three or more antimicrobial categories; XDR were nonsusceptible to at least one agent in all but two or fewer antimicrobial categories; PDR bacteria were resistant to all approved antimicrobial agents.

Statistical analysis of the data was performed using unpaired Student’s t-test for independent variables and chi-square (χ²) test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 113 cirrhotic patients with ascites included 98 (86.7%) males and 15 (13.3%) females. Majority of the patients were in the age group of 41 to 50 years followed by patients between 51 and 60 years. The mean age was 49.72 ± 10.3 years. In the study group, the most common etiology of cirrhosis was alcohol intake (54.9%) followed by both alcohol and hepatitis C infection (15.9%; Table 1). Of 113 cirrhotic patients with ascites, 58 (51.3%) had SBP with 19 (32.8%) of them presenting with classical SBP, 36 (62%) with CNNA, and 3 (5.2%) with MNB. The most common clinical features in patients with SBP and those without SBP are depicted in Table 2. More number of patients with SBP presented with decreased urine output as compared with patients without SBP and this difference was statistically significant (p = 0.005). However, melena was significantly less (p = 0.039) among patients with SBP as compared with those without SBP.

In both patients with SBP and those without SBP, the majority of patients belonged to Child–Pugh’s Grade C (87.9% SBP; 83.6% w/o SBP) followed by Child–Pugh’s...
Grade B (12.1% SBP; 16.4% w/o SBP). None of the biochemical parameters showed any significant difference between patients with SBP and patients without SBP (Table 3).

Of 58 cases of SBP, 22 (37.9%) were culture positive, 19 had classical SBP, and 3 had MNB. Among the culture positive SBP, Gram-negative isolates were more common (77.3%) than Gram-positive isolates (22.7%). The most common isolate was *E. coli* (68.1%) followed by *Streptococcus agalactiae* (9.09%), *Enterococcus faecium* (9.09%), *Enterobacter* sp., *Klebsiella pneumoniae*, and *Streptococcus pneumoniae* (4.05% each). The Gram-negative isolates showed high susceptibility to colistin, tigecycline, amikacin, and carbapenems, while low susceptibility was seen toward cephalosporins and ampicillin (Graph 1).

All the Gram-positive isolates susceptible to penicillin, teicoplanin, vancomycin, linezolid showed less susceptibility to aminoglycosides (40%) and to fluoroquinolones, macrolides, and tetracyclines (20% each). Among the culture-positive isolates, MDR and XDR were seen in *E. coli* isolates. Of 15 *E. coli* isolates, 13 (86.6%) were MDR and 3 (20%) were XDR.

**DISCUSSION**

Spontaneous bacterial peritonitis is one of the most common bacterial infections in patients of cirrhosis with ascites. A delay in the diagnosis of SBP often leads to fatal outcome in patients with liver cirrhosis. In the current study, the majority of patients were males. The male to female ratio was 6.5:1, which was similar to that reported by Nadagouda et al,21 Paul et al,22 and Chawla et al.23 The male predominance in the current study may be because of higher frequency of alcoholic cirrhosis in the male subjects studied. The mean age of cirrhotic patients was found to be 49.7 ± 10.3 years. The findings were consistent with a study reported by Syed et al,24 where the mean age was 51.1 ± 11.7 years. The majority of patients had a history of alcoholism as underlying cause of cirrhosis, consistent with that reported by Nadagouda et al21 and Chawla et al.23 Most of the patients were in Child–Pugh’s Grade C (87.9% in SBP group and 83.6% in non-SBP group), similar...
to a study done in a tertiary care center in Southern India\textsuperscript{21} where 88.8\% patients of SBP were in Child–Pugh’s Grade C.

In the current study, 51.3\% of cirrhotic patients had SBP. Results similar to this study (56\%) were cited in a study done by Zaman et al\textsuperscript{25} whereas in a study by Bibi et al\textsuperscript{13} among patients with chronic liver disease at Karachi, 25\% were diagnosed with SBP. Various authors reported overall frequency of SBP as 38\%,\textsuperscript{26} 47.5\%,\textsuperscript{27} and 56\%\textsuperscript{28} in chronic liver disease patients.

Different presenting symptoms in patients with SBP were seen in the current study, out of which the most common was abdominal distension. Similar results have been reported by Paul et al\textsuperscript{22} In the current study, fatigue was the second most common presentation (96.5\%) and decreased urine output and melena were significantly related to SBP. However, this was not observed in earlier studies.\textsuperscript{21,22,25}

The mean SAAG in SBP and non-SBP group was 1.8 ± 0.3 and 1.9 ± 0.4 gm/dL respectively. There was no significant correlation between SAAG and SBP, whereas SBP patients had lower mean SAAG value as compared with non-SBP patients as reported in various studies,\textsuperscript{13,29} while Nouman et al\textsuperscript{30} observed a lower mean SAAG value (1.2 gm/dL) in non-SBP patients as compared with SBP patients (1.5 gm/dL).

Of 58 cases of SBP, CNNA was the most common (62\%), followed by classical SBP (32.8\%) and MNB (5.2\%). The results were comparable with the studies done at Ayub Medical College, Abbottabad, Pakistan\textsuperscript{25} and Jinnah Postgraduate Medical Centre, Karachi, Pakistan\textsuperscript{13} in chronic liver disease patients with ascites where CNNA was the most common variant of SBP.

The relatively high incidence of CNNA may be because the patients were subjected to a very early ascitic tap, when the bacterial inoculum was still low, or possibly because of the difference in the proficiency of the culturing techniques between the different centers.

Ascitic fluid culture was positive in 37.9\% of SBP cases. Similar results were observed in various studies with culture positivity of 50\%\textsuperscript{13,31} and 47.5\%,\textsuperscript{27} but some studies have reported much lower rates of culture positivity, i.e., <25\%.\textsuperscript{28,32} This difference could be attributed to the different culture techniques. International literature suggests a culture positivity rate of 31 to 71\%.\textsuperscript{32}

In this study, Gram-negative organisms were found to be more common cause of SBP (77.3\%) similar to that reported by Bibi et al\textsuperscript{13} and Chawla et al.\textsuperscript{23} Among the Gram-negative isolates, \textit{E. coli} was the most common isolate. Similar results were cited in different studies conducted by Bibi et al\textsuperscript{13} Chawla et al,\textsuperscript{23} Syed et al,\textsuperscript{24} and Zaman et al.\textsuperscript{25} The main reason for SBP is bacterial translocation from gut.\textsuperscript{33} Hence the commonly isolated pathogens in SBP are usually enteric Gram-negative rods. 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.\textsuperscript{34}

The third-generation cephalosporins, being relatively safe, well-tolerated, and broad spectrum, are considered the treatment of choice for SBP patients, while amoxicillin/clavulanate, fluoroquinolones, or piperacillin/tazobactam are recommended as alternative regimens.\textsuperscript{19,35,36}
In our study, Gram-negative pathogens were susceptible to fluoroquinolones and cefepime (17.6%), amoxicillin/clavulanate (41.2%), and piperacillin/tazobactam (58.8%), whereas susceptibility of Gram-negative pathogens to fluoroquinolones (31.3%; 31.5%), cefepime (21.4%; 28.9%), and amoxicillin/clavulanate (7.1%; 20%) was reported in the literature respectively, by Bibi et al.\(^\text{13}\) and Chawla et al.\(^\text{23}\). Similar higher rates of resistance against cefepime and fluoroquinolones were also reported from Lahore, Pakistan,\(^\text{27}\) but international data still suggest a higher sensitivity to these drugs.\(^\text{37}\) These differences in the local and the international level regarding sensitivity pattern could be due to the widespread and indiscriminate use of cephalosporins and fluoroquinolones.

Gram-negative isolates were highly susceptible to colistin, tigecycline, amikacin, and carbapenems. This figure correlates well with that reported by Chawla et al,\(^\text{23}\) Banker et al,\(^\text{38}\) and Li et al,\(^\text{39}\) where carbapenems and amikacin showed good antibacterial activity against Gram-negative isolates. Gram-positive pathogens were 100% sensitive to vancomycin and linezolid, similar to reported by Chawla et al\(^\text{23}\) and showed high resistance to fluoroquinolones similar to that reported in the literature.\(^\text{13}\)

The present study suggests that amikacin could be used as an effective alternate antibiotic in SBP patients. Colistin and tigecycline are expensive antibiotics and add extra cost to the treatment, which has significant effect on economy at the individual and the society level.

The role of specimen culture and antibiotic sensitivity testing needs to be established in patient care protocol so that the antibiotic therapy can be tailored as per the culture and sensitivity testing report. Therefore all cirrhotic patients with ascites should undergo diagnostic paracentesis and ascitic fluid analysis for better selection of antibiotics to prevent antimicrobial resistance and for better outcome of cirrhotic patients.

REFERENCES