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STUDY OF THE MICROBIOLOGICAL PROFILE OF SPONTANEOUS BACTERIAL PERITONITIS IN PATIENTS OF CIRRHOSIS OF LIVER WITH ASCITIS

General Medicine

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ABSTRACT

Background: Cirrhosis is a chronic disease of the liver in which diffuse destruction and regeneration of hepatic parenchymal cells occur, with diffuse increase in connective tissue, leading to disorganisation of the lobular architecture1. Spontaneous Bacterial Peritonitis is a frequent infectious complication in patients with cirrhosis and ascites. The most common gram negative bacteria isolated from SBP patients with liver cirrhosis are E coli and Klebsiella spp, while the most common gram positive bacteria are staphylococcus spp, streptococci spp and enterococci 2. Early antibiotic treatment of spontaneous bacterial peritonitis is critical. However, as the landscape of microbiological resistance is continuously changing in recent times, with an increasing number of multidrug-resistant organisms, the current management of SBP is more challenging. **Objective:** To find out the pathogens causing Spontaneous bacterial peritonitis and their antimicrobial susceptibility pattern. **Materials and Methods:** A Hospital based prospective observational study was carried out on 109 patients diagnosed with liver cirrhosis and ascites, admitted in the department of General Medicine. Those patients that fit the inclusion and exclusion criteria were chosen as participants and diagnostic abdominal paracentesis was done before the first dose of antibiotic and ascitic fluid was examined for cell count, neutrophil count, protein, gram stain, direct microscopy for fungus and bacterial culture and sensitivity. **Results:** The prevalence of SBP was 24.77%. E-Coli (38.48%) was the most common bacteria isolated followed by Klebsiella Aerogenes (15.38%), MRSA (15.38%), Acinetobacter Lwoffii (7.69%), Klebsiella Pneumoniae (7.69%), Enterobacter Cloacae (7.69%) and Staphylococcus Aureus (7.69%). Out of 10 gram negative bacteria which were isolated, 3 (23.07%) isolates were XDR (Extensively drug resistant) bacteria and 2(15.38%) isolates were MDR (Multi drug resistant) bacteria.

KEYWORDS

cirrhosis, ascites, SBP

INTRODUCTION

Cirrhosis is characterized by fibrosis and nodule formation of the liver, secondary to a chronic injury, which leads to alteration in the normal lobular architecture of the liver[3]. Cirrhosis is the 11th most common cause of death globally at present and combined with hepatocellular cancer it causes about 3.5% of deaths worldwide. Spontaneous bacterial peritonitis is the most frequent bacterial infection in cirrhosis patients[4]. It is defined as the infection of ascitic fluid in the absence of any intra-abdominal surgically correctable source of infection. It is estimated that the incidence of SBP reaches 3.5% at 1 year in outpatients with decompensated cirrhosis and varies between 7% and 30% in hospitalized patients with cirrhosis and ascites[4,5]. The diagnosis of this form is made in the presence of an elevated ascitic fluid polymorphonuclear leucocyte count $\geq$ 250 cells/mm^3 and an ascitic fluid culture positivity and without any evidence of surgically treatable external or intraabdominal source of infection[6]. Most of the cases show growth of a single organism[7]. The two variants of SBP include Culture negative nonneutrocytic ascites(CNNA) and Monobacterial Non Neutrocytic Bacterascites (MNB). In CNNA there is A PMN count of > 250 cells /mm^3 and a negative ascitic fluid culture in the absence of even a single dose of antibiotic[8]. MNB is diagnosed when the PMN counts are < 250 cells/mm^3 and the ascitic fluid shows culture positivity for a single organism with no evidence of surgically treatable intraabdominal source of infection[9].

Spontaneous infections of the ascitic fluid are mainly due to gut derived bacteria[10]. Gram negative aerobic rods such as E coli and Klebsiella pneumoniae are the causative organisms in majority of cases of SBP. The enteric nature of these organisms indicate the gut as their source[11]. These organisms cause SBP and MNB. Anaerobes account for only 1% of SBP [12]. SBP, MNB and CNNA are probably caused as a result of the colonization of susceptible ascitic fluid from spontaneous bacteremia or the weeping of bacteria laden lymph from the liver capsule as it forms ascitic fluid. Although direct transmural migration of bacteria from the gut into ascitic fluid has been postulated, the loss of gut mucosal integrity has also been documented. Bacteria translocate from the gut lumen across the submucosal lymphatics and are detected in mesenteric lymph nodes[13]. From the mesenteric lymph nodes the bacteria spread to spleen, liver or blood stream.

In recent years, due to the widespread use of antibiotic prophylaxis and the increased frequency of hospitalization in patients with complications of cirrhosis, the involvement of Gram-positive cocci and multi-drug resistant bacteria as the causative agents of SBP is on the rise[14]. This is related to the lowering of the effectiveness of the first-line therapy used at present and worsening of the prognosis, increasing in-hospital mortality. The changes in bacteriological spectrum, increasing number of invasive procedures, and hospitalisation in intensive care units suggest a need for constant assessment of common bacterial pathogens and their antibiogram to guide empirical treatment. This is particularly relevant in countries like India where antibiotic resistance is high. Recent guidelines put forward by the British Society of Gastroenterology (BSG) had shown the importance of early diagnosis and prompt treatment, which reduced in-hospital mortality from 90% to 20%[15]. This scenario of increasing antibiotic resistance highlights the relevance and importance of conducting such a study to identify the causative organisms and their antimicrobial susceptibility patterns in patients of SBP in the local population which may help greatly in changing the course of the disease.

AIM AND OBJECTIVE

To find out the pathogens causing Spontaneous bacterial peritonitis and their antimicrobial susceptibility pattern.

Inclusion Criteria

1. Male and female patients >12 years of age with a written consent.
2. All patients who have been diagnosed as cirrhosis of liver with ascites associated with portal hypertension.

Exclusion Criteria

1. Ascites due to renal, cardiac, tubercular and malignant pathologies and secondary peritonitis.
2. Patients who have undergone paracentesis before the study in the last 3 months and patients who are on antibiotic therapy in the past one month.
3. Pregnant women.
4. Patients with other sources of infections in the body like urinary tract, respiratory tract infections and others.
5. Patient who had any abdominal surgery in the past or abdominal trauma.
6. Bleeding diathesis.

Study place: Assam medical college and hospital, Dibrugarh, Assam
Study duration: one year (1st June 2019 to 31st May 2020)
Study design: Hospital based prospective observational study
Study population: All decompensated cirrhosis patients with ascites above 12 years of age who were admitted in the wards of Department of Medicine in Assam Medical and Hospital.

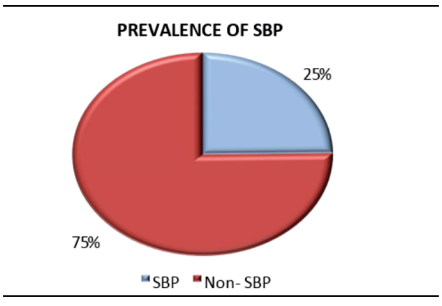
Sample size: considering 95% confidence interval with a margin of error of 10% and taking the findings of the study by Harchand P et al [18] as reference the sample size was considered to be 109 for this study.

Method of data collection: Data was collected from patients of cirrhosis with ascites admitted in AMCH after written informed consent. Patients were selected according to inclusion and exclusion criteria. For diagnosis of cirrhosis the Garcia – Tsao criteria[16] was used. By following proper aseptic technique 15 ml of ascitic fluid was removed and send for cell count, protein estimation, culture and sensitivity. For ascitic fluid culture and sensitivity about 10ml of ascitic fluid was inoculated in blood culture bottle (VersaTREK™ Redox™ Media_) at bedside using aseptic technique and sent to Microbiology. They were then incubated in the VersaTREK™ Automated Microbial Detection System (Thermo Scientific™) till the system indicated positive or for a maximum period of 5 days. All the negative bottles were subcultured on the 5th day for confirmation of negative result. The bottles which were indicated positive by the system were subcultured in Blood Agar and Mac Conkey's Agar media and incubated overnight at 37°C. Bacterial isolates were identified by their colony morphology, gram staining characteristics, motility tests and biochemical reactions as per standard protocol. Antibiotic susceptibility of the isolates was performed against 1st line and 2nd line antibiotics on Mueller Hinton Agar (MHA) by the Kirby Bauer disc diffusion method according to guidelines of CLSI[17]. The results were read and interpreted after 18-24 hours of incubation. The diameter of each zone was measured with a scale, recorded in mm and interpreted as sensitive or resistant, in accordance to CLSI guidelines.

Statistical analysis: Descriptive statistics were used for the baseline characteristics of the data. Quantitative variables were expressed as mean and standard deviation and qualitative variables presented as frequency and percentages. Association of categorical variables were assessed using chi-square test and if the cell values are less than 5 or zero, fishers exact test were used. For the comparison of continuous variables, Mann Whitney U test were used as the data doesn't follow normality. A p value less than 0.05 shows statistical significance. All data entered in Microsoft excel and analysed using SPSS version 20.00.

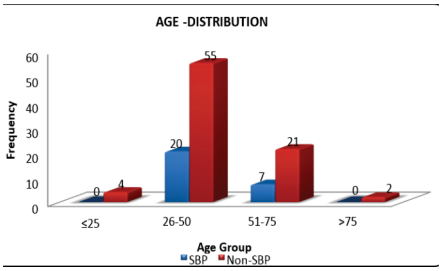
RESULTS

1) Out of the 109 patients of cirrhosis with ascites in our study, 27 (24.77%) patients were found to have SBP.



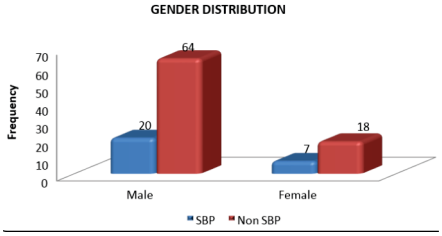
Graph 1: Prevalence Of Sbp In Study Population

2) Minimum age in our study population was 14 and maximum was 85. Majority (68.81%) of the study population belonged to the age group of 26 to 50 years.



Graph 2: Age Distribution Among Patients

3) Out of the 27 patients with SBP, 20 (74.1%) were males and 7 (25.9%) were females. Among the 82 patients without SBP, 64 (78%) were males and 18 (22%) were females.



Graph 3: Gender Distribution In The Study Population

4) Out of the 109 patients considered for this study, 27 patients had SBP. Of them, 10 cases (52%) were classic SBP, 3 cases (11%) were MNB, and 14 cases (52%) were CNNA. Among the 13 bacteria isolated, 3 (23.07%) were gram positive bacteria and 10 (76.93%) were gram negative bacteria.

Table 1: Distribution Of Bacteria Among Culture Positive Sbp

Bacteria	Frequency	Percentage
Gram Positive	3	23.07
Gram Negative	10	76.93
Total	13	100

5) Out of the 27 SBP cases, culture results were positive for 13 cases (48.15%). E-Coli (38.48%) was the most common bacteria isolated followed by Klebsiella Aerogenes (15.38%), MRSA (15.38%), Acinetobacter Lwoffii (7.69%), Klebsiella Pneumoniae (7.69%), Enterobacter Cloacae (7.69%) and Staphylococcus Aureus (7.69%).

Table 2: Bacterial Flora Observed In Culture Positive Sbp

Variable	Frequency	Percentage
Acinetobacter Lwoffii	1	7.69
E Coli	5	38.48
Klebsiella Aerogenes	2	15.38
Enterobacter Cloacae	1	7.69
Klebsiella Pneumoniae	1	7.69
Methicillin Resistant Staphylococcus Aureus	2	15.38
Staphylococcus Aureus	1	7.69
Total	13	100.00

6) Among the gram positive bacteria, all the three isolates were sensitive to Linezolid (100%; 3/3) and Cotrimoxazole (100% ;3/3). Azithromycin (100%;3/3) resistance was seen in all the three isolates followed by Ciprofloxacin(66.67%;2/3) and Erythromycin(66.67% ;2/3).

Table 3: Antimicrobial Susceptibility Pattern Of Gram Positive Bacteria

ANTIBIOTIC	MRSA (N=2)		Staphylococcus Aureus (N=1)		Total (%)	
	S	R	S	R	S (%)	R (%)
Azithromycin	0	2	0	1	0	100
Ciprofloxacin	1	1	0	1	33.33	66.67
Clindamycin	1	1	1	0	66.67	33.33
Cotrimoxazole	2	0	1	0	100	0
Tetracycline	1	1	1	0	66.67	33.33
Linezolid	2	0	1	0	100	0
Erythromycin	1	1	0	1	33.33	66.67

S-Sensitive, R-Resistant

8) In our study, culture was positive for 10 gram negative bacteria, in which maximum bacteria showed sensitivity to Meropenem 75% (6/8), Piperacillin Tazobactam 71.4% (5/7) and Amikacin 60% (6/10) followed by Cotrimoxazole 55.56% (5/9), Imipenem 55.56% (5/9) and Ciprofloxacin 50% (5/10). In second line antibiotics, Tigecycline 100% (5/5) and Minocycline 83.33% (5/6) showed maximum sensitivity. Maximum resistance was seen against Ampicillin 85.71% (6/7), Cefotaxime 85.71% (6/7) and Ceftazidime 75% (6/8) followed by Amoxyclav 62.5% (5/8), Levofloxacin 55.56% (5/9) and Ciprofloxacin 50% (5/10).

In this study three XDR (Extensively drug resistant) bacteria(23.07%) and two MDR (multi drug resistant) bacteria (15.38%) were isolated. XDR bacteria included one each of Klebsiella aerogenes, E coli and Klebsiella pneumoniae. MDR bacteria included one each of E coli and Klebsiella aerogenes. XDR Klebsiella aerogenes was sensitive only to aminoglycosides (amikacin and tobramycin). XDR E coli was sensitive only to tigecycline with intermediate susceptibility to minocycline and doxycycline (tetracycline group). XDR Klebsiella pneumoniae was sensitive only to tetracyclines (tigecycline, doxycycline and minocycline).

Table 4: Antimicrobial Susceptibility Pattern Of Gram Negative Bacteria

ANTIBIOTIC	E Coli (N=5)		Klebsiella Pneumonia (N=1)		Klebsiella Aerogenes (N=2)		Enterobacter Cloacae (N=1)		Acinetobacter Lwoffii (N=1)		Total (%)	
	S	R	S	R	S	R	S	R	S	R	S(%)	R(%)
First Line Antimicrobials												
Amikacin	4	1	0	1	1	1	1	0	0	1	60	40
Amoxyclav	3	2	0	1	0	1	0	1	-	-	37.5	62.5
Ampicillin	1	4	0	1	-	-	0	1	-	-	14.28	85.71
Cotrimoxazole	3	2	0	1	1	1	1	0	-	-	55.56	44.44
Ciprofloxacin	3	2	0	1	0	2	1	0	1	0	50	50
Cefotaxime	1	4	0	1	-	-	0	1	-	-	14.28	85.71
Ceftazidime	1	4	0	1	-	-	1	0	0	1	25	75
Piperacillin Tazobactam	3	1	0	1	-	-	1	0	1	0	71.43	28.57
Levofloxacin	3	2	0	1	0	2	1	0	-	-	44.44	55.56
Imipenem	3	1	0	1	0	2	1	0	1	0	55.56	44.44
Meropenem	4	1	0	1	-	-	1	0	1	0	75	25
Second Line Antimicrobials												
Minocycline	1	0	1	0	1	1	1	0	1	0	83.33	16.67
Gentamicin	0	1	-	-	0	2	1	0	-	-	25	75
Tigecycline	2	0	1	0	1	0	1	0	-	-	100	0
Doxycycline	2	0	1	0	0	1	1	0	-	-	80	20
Tobramycin	0	1	-	-	1	0	0	1	0	1	25	75
Cefoperazone Sulbactam	1	0	0	1	1	0	1	0	-	-	75	25

S-Sensitive, R-Resistant

DISCUSSION

The prevalence of SBP in patients of cirrhosis of liver with ascites in this study was found to be 24.77% (27 out of 109). It is comparable to the study done by Paul et al[26] in Punjab and Bibi et al[19] in Karachi, Pakistan. In this study the maximum number of cases were in the age group 26 to 50 (68.81%) with a minimum age of 14 years and a maximum age of 85 years. These findings were similar to the ones found by Harchand et al[18] in their study in Punjab and Syed et al[20] in Nepal. In this study, majority of the cases were males (77%, 84 out of 109) as compared to females (22.94%, 25 out of 109). This is comparable to the study done by Sushanth et al[21] in Andhra Pradesh and Paul et al[41] in Punjab. Out of the total 109 cases of cirrhosis with ascites, 27 cases(24.77%) were diagnosed as SBP. It included 14 cases (51.85%) of Culture Negative Neutrocytic Ascites (CNNA), 10 cases (37.04%) of classical SBP and 3 cases (11.11%) of Monobacterial Non Neutrocytic Bacterascites (MNB). This is similar to the study done by by Harchand et al[18] in Punjab and Prasad et al[22] in Bihar on 55 SBP patients. In the present study gram negative bacteria were the main etiological agents (10/13;76.93%) isolated from ascitic fluid samples, this is similar to the study done by Harchand et al[18] where among the culture positive SBP, gram negative bacteria (77.3%) were common compared to gram positive bacteria (22.7%). Our result showed that Escherichia coli was the most common cause of culture-positive SBP. Bhardwaj et al[23] in their study also found Escherichia coli to be the most predominant bacteria followed by Klebsiella spp., Peptostreptococcus, and Staphylococcus aureus. Similar findings were also seen in the study done by Prasad et al[22] in Bihar in 2019 where Escherichia coli was the most common organism isolated (46.2%). The gram positive bacteria isolated in the ascitic fluid culture in our study were MRSA (2/3;15.38%) and methicillin sensitive Staphylococcus aureus (1/3;7.69%). Staphylococcus aureus (3/13;23.08%) was the second most common bacteria isolated after Escherichia Coli in the present study. Several studies had suggested an increase in the prevalence of SBP caused by gram positive bacteria. Rosalie et al[24] in their double cohort retrospective study showed an increase of Gram-positive bacterial isolates from 26% to 46% in a time period of 10 years from 2004 to 2014. Gram positive bacteria showed maximum sensitivity to Linezolid (100%) and Cotrimoxazole (100%) and maximum resistance to Azithromycin (100%) followed by Ciprofloxacin (66.67%) and Erythromycin (66.67%). In a study by Roy et al[25] , gram positive bacteria was found to be highly sensitive to linezolid (100%) and vancomycin (100%). Harchand et al[18] in their study also found all the Gram-positive isolates to be susceptible to penicillin, teicoplanin, vancomycin and linezolid. In the present study gram negative bacteria showed maximum sensitivity to Meropenem 75% (6/8), Piperacillin Tazobactam 71.4% (5/7) and Amikacin 60% (6/10) followed by Cotrimoxazole 55.56% (5/19), Imipenem 55.56% (5/9) and Ciprofloxacin 50% (5/10). In second line antibiotics, Tigecycline 100% (5/5) and Minocycline 83.33% (5/6) showed maximum sensitivity. Maximum resistance was seen against Ampicillin 85.71% (6/7), Cefotaxime 85.71% (6/7) and Ceftazidime 75% (6/8) followed by Amoxyclav 62.5% (5/8), Levofloxacin 55.56% (5/9) and Ciprofloxacin 50% (5/10).). In a previous study done by Harchand et al[18], the gram-negative bacteria isolated in their study showed high sensitivity to colistin, tigecycline, amikacin, and carbapenems, with low sensitivity toward cephalosporins and ampicillin.

In this study, three XDR (Extensively drug resistant) bacteria (23.07%) and two MDR (multi drug resistant) bacteria (15.38%) were isolated. XDR bacteria included one each of Klebsiella aerogenes, E coli and Klebsiella pneumoniae. MDR bacteria included one E coli and one Klebsiella aerogenes. XDR Klebsiella aerogenes was sensitive only to aminoglycosides (amikacin and tobramycin). XDR E coli was sensitive only to tigecycline with intermediate sensitivity to minocycline and doxycycline (tetracycline group). XDR Klebsiella pneumoniae was sensitive only to tetracyclines (tigecycline, doxycycline and minocycline). This pattern of increasing antibiotic resistance may be attributed to the rampant misuse of antibiotics. In a retrospective double cohort study done by Rosalie et al[24], it was found that the prevalence of multidrug resistant pathogens increased from 25% to 32% in a span of 10 years from 2004 to 2014. Thus various studies in different parts of the world has shown that the microbes isolated and their susceptibility pattern vary widely across geographical locations and with time. This highlights the importance of forming regional and local antibiotic policies in accordance with studies in the local population with timely revisions. The observations in the present study suggest that all ascitic fluid cultures are to be screened for the presence of MDR and XDR strains.

LIMITATIONS

Certain limitations of this study are the small study population and the number of bacterial isolates cultured were very less for formulating an empirical therapy.

CONCLUSION

Spontaneous Bacterial Peritonitis is one of the dreaded complications in patients of decompensated cirrhosis. Aggressive, appropriate and efficient interventions can sharply reduce the mortality and morbidity and improve the long term prognosis of these patients. All patients with suspected SBP should undergo diagnostic paracentesis before the first dose of antibiotic. In a suspected case of SBP, empirical antibiotics should be initiated at the earliest which should solely depend on the local antimicrobial susceptibility patterns rather than on international guidelines. With the alarming observation of XDR and MDR strains of

bacteria isolated in our study, as well as increased number of gram positive bacteria, it would be advisable to form local antimicrobial policies in accordance with studies in the local population with timely revisions and strict use regulations.

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