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Asymptomatic Spontaneous Bacterial Peritonitis in Adult Egyptian Patients with Decompensated Liver Cirrhosis: A Prospective Cohort Study

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Abstract: Spontaneous bacterial peritonitis (SBP) is an infection of the previously sterile ascitic fluid, without any apparent intra-abdominal source of infection. SBP is the most frequent bacterial infection in cirrhosis, accounting for 10-30% of all reported bacterial infections in hospitalized patients. We aimed to determine the frequency of SBP in asymptomatic cirrhotic patients with ascites and to assess the common causative Organisms responsible for the development of SBP and its variants in decompensated cirrhotic Egyptian Patients. We prospectively enrolled 720 cirrhotic patients who admitted to the Tropical Medicine Department, Al-Hussein University Hospitals, Al Azhar University, Cairo, Egypt over a period of six months from June 2014 to December 2014, only one hundred and sixty (160) adult decompensated cirrhotic patients with ascites and without symptoms suggestive of SBP were included in the study. Out of 160 cirrhotic patients with ascites, only 21(13%) patients fulfill criteria of having ascetic fluid infection including 3cases have SBP (PMNs count $\geq$ 250 cells/mm3 and positive ascetic fluid culture), 16 cases (76.1%) have Monomicrobial non neutrocyticbacterascites (MNB) (PMNs < 250 cells/mm3 and Positive ascetic fluid culture) and only 2 cases (9.5%) have Culture negative neutrocytic ascites (CNNA) (PMNs count $\geq$ 250 cells/mm3 and Negative ascetic fluid culture). Our study concluded that the prevalence of SBP in asymptomatic patients with liver cirrhosis and ascites is low and serum ESR level could be used as a predictor of SBP episode in the studied group of patients. Bacterial culture & sensitivity of ascetic fluid were predominantly resistant to Cefotaxime antibiotic therapy.

Keywords: MNB: Monomicrobial non neutrocyticbacterascites; **CNNA:** Culture negative neutrocytic ascites; **MELD:** Model of End-Stage Liver Disease; **AASLD:** American Association for the Study of Liver Diseases; **BT:** bacterial translocation.

1 Introduction

Spontaneous bacterial peritonitis (SBP) is an infection of the previously sterile ascitic fluid, without any apparent intra-abdominal source of infection [1]. SBP is the most frequent bacterial infection in cirrhosis, accounting for 10-30% of all reported bacterial infections in hospitalized patients [2].Seventy percent of Patients with cirrhosis, who have spontaneous bacterial peritonitis, are Child Pugh class C. In these patients, the development of spontaneous bacterial peritonitis is associated with a poor long-term prognosis [3].

The clinical detection of SBP requires a high index of suspicion because symptoms and signs of infection are subtle in most of patients. About 13% of patients are totally asymptomatic and a few studies evaluated the incidence of asymptomatic SBP in cirrhotic patients with ascites [4]. Fever and chills are clearly the most common manifestation of SBP. It occurs in as many as 80% of patients. Abdominal pain or discomfort is found in as many as 70% of patients. Alsoresistant ascites and Worsening of new-onset renal failure, paralytic ileus, hypotension and hypothermia are all reported [5].

SBP in patients with cirrhosis is considered to be the main consequence of bacterial translocation (BT), a process which is explained by the prescience of intestinal bacterial overgrowth, structural and functional alterations of the intestinal mucosal barrier and the deficiencies of the local immune response [6].

The American Association for the Study of Liver Diseases

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(AASLD) practice guidlines, 2012 recommends performing exploratory paracentesis in each patient with cirrhosis and ascites admitted to the hospital. To our knowledge this is the first study in Egypt that evaluates asymptomatic spontaneous bacterial peritonitis and its Common Causative Organisms in decompensated cirrhotic Egyptian Patients.

2 Patients and Methods

We conducted a prospective cohort study on asymptomatic SBP patients. The study was carried out in Tropical Medicine Department, Al-Hussein University Hospitals, Al Azhar University, Cairo, Egypt over a period of six months from June 2014 to December 2014. Out of seven hundred and twenty cirrhotic patients (720) were admitted to the hospital over this period, only one hundred and sixty (160) adult decompensated cirrhotic patients with ascites and without symptoms suggestive of SBP were included in the study.

The diagnosis of decompensated liver cirrhosis was based clinically on the presence of (jaundice, hepatic encephalopathy, edema and ascites), Biochemically on the presence of (hypoalbuminemia, Hypoprothrombinemia and Hyperbilirubinemia) and finely by Ultra-sonographic confirmation. . The severity of the liver disease was assessed in each patient according to the modified Child Pugh and Model of End-Stage Liver Disease (MELD) scores.

The aim of this study was to determine the frequency of SBP in asymptomatic cirrhotic patients with ascites and to assess the common causative Organisms responsible for the development of SBP and its variants in decompensated cirrhotic Egyptian Patients.

All patients were subjected to full medical history, carful clinical examination and routine laboratory tests including complete blood picture, liver and kidney function tests. Under a sterile technique, 30- 50 ml of ascitic fluid was aspirated, observed and divided into three parts. One part was inoculated into blood culture bottle and was sent for culture growth and other two portions were sent for cytological and biochemical analysis.

According to the International ascites club (2000) and EASL clinical practice guidelines (2010), the diagnosis of SBP was reached with a cutoff neutrophil count of 250 cells/mm3 in ascetic fluid.

All patients presented with clinical symptoms of infection, de novo or worsening hepatic encephalopathy, gastro-intestinal bleeding (within the last month), previous episode of SBP, treated recently with antibiotic or on Norfloxacin prophylaxis, non-cirrhotic ascities, nosocomial cases of SBP (developed during hospitalization in patients with normal ascitic fluid at the time of admission) or Patients who refuse to participate, all are excluded from the current study.

This study was approved by the Ethical Committee of Azhar University Hospitals, and a written informed consent was obtained from all enrolled participants. The participant consented form was recorded and kept with study documents and the ethics committee approved the consent procedure.

2.1 Statistical Analysis

The data were processed and analyzed using the statistical package for social sciences (SPSS) program. The expression of data in the form of mean, S.D. (standard deviation) for quantitative variables and description of qualitative variables by frequency and percent were used. Student t-test was used to make a Comparison between two groups' quantitative variables. Comparison of more than two groups' quantitative variables was carried out by one way ANOVA test. Chi-square test (Pearson chi-square) was used to compare between qualitative variables.

3 Results

From seven hundred and twenty (720) cirrhotic patients admitted to the hospital over a period of six months from June 2014 to December 2014, only one hundred and sixty (160) decompenated cirrhotic patients with ascites without symptoms suggesting SBP were included in the study. The number of male patients were 71 (44.4%) and females patients were 89 (55.6%) with a mean age of 52.8 years. Out of 71 male patients and 83 female patients included in this study, only 15 (21.1%) male patients and 6 (7, 2%) female patients respectively fulfill criteria for ascetic fluid infection. Age and sex distribution are shown in table 1. The study included 154 (96.3%) patients with Child C score and only 6 (3.7%) patients with Child B score. The mean MELD score was 20.1 (range 13-31) shown in table 2.

Table 1: Age & sex distribution among studied groups.

Age & sex distribution		Groups						T-Test or Chi-Square	
		Negative ascetic fluid infection			Positive ascetic fluid infection			T or X^2	P-value
Age (Year)	Range	23	-	81	35	-	61	0.411	0.682
	Mean ±SD	52.8	±	11.1	51.9	±	8.6		
Sex (Gender)	Male	n=56		40.29%	n=15		71.43%	7.167	0.007*
	Female	n=83		59.71%	n=6		28.57%		

Table 2: Comparison between ascetic fluid infection positive and negative cases according to Child class. And MELD Score.

Child Class and MELD scores		Groups						T-Test or Chi-Square	
		Negative ascetic fluid infection			Positive ascetic fluid infection			T or X^2	P-value
Child class.	B	n=4		2.88%	n=2		9.52%	1.695	0.193
	C	n=135		97.12%	n=19		90.48%		
MELD score	Range	13	-	29	13	-	31	-2.698	0.008*
	Mean ±SD	17.9	±	2.9	20.1	±	4.8		

Table 3: Shows Ascetic fluid culture results.

Results of ascetic fluid culture		Types of ascetic fluid infection						ANOVA or Chi-Square	
		SBP		MNB		CNNA		F or X^2	P-value
	Negative	0	0.00	0	0.00	n=2	100.%	20.222	0.003*
	Staph. aureus	n=3	100.00	n=4	25.00 %	0	0.00		
	E coli	0	0.00	n=10	62.50 %	0	0.00		
	Enterococci	0	0.00	n=2	12.50 %	0	0.00		

Table 4: Difference in liver function tests among ascetic fluid infection variants.

Liver function tests		Types of ascetic fluid infection									ANOVA or Chi-Square	
		SBP			MNB			CNNA			F or X^2	P-value
AST (IU/L)	Range	52	-	55	16	-	53	51	-	55	4.429	0.027*
	Mean ±SD	54.000	±	1.732	35.750	±	12.793	53.000	±	2.828		
ALT (IU/L)	Range	54	-	56	12	-	54	56	-	60	6.761	0.006*
	Mean ±SD	55.333	±	1.155	33.500	±	13.317	58.000	±	2.828		
T.BIL. (mg/dl)	Range	2.5	-	5.3	2.9	-	9.6	5.6	-	6.16	0.448	0.646
	Mean ±SD	4.367	±	1.617	5.388	±	2.049	5.880	±	0.396		
D.BIL. (mg/dl)	Range	2.1	-	5	0.9	-	6.7	4.8	-	5.28	0.357	0.705
	Mean ±SD	4.033	±	1.674	3.650	±	2.371	5.040	±	0.339		
S.ALB (g/dl)	Range	2.3	-	2.6	1.8	-	2.9	2.6	-	2.86	0.730	0.496
	Mean ±SD	2.400	±	0.173	2.388	±	0.408	2.730	±	0.184		
PT (seconds)	Range	14.6	-	14.9	14.5	-	25.5	16	-	17.6	0.845	0.446
	Mean ±SD	14.700	±	0.173	17.313	±	3.488	16.800	±	1.131		
PC (%)	Range	60	-	66	20	-	63	46	-	50.6	2.368	0.122
	Mean ±SD	64.000	±	3.464	44.375	±	15.637	48.300	±	3.253		
INR	Range	1.3	-	1.4	1.3	-	3.4	1.7	-	1.87	1.484	0.253
	Mean ±SD	1.300	±	0.075	2.050	±	0.768	1.785	±	0.120		

Interestingly, of the 160 cirrhotic patients with ascites, only 21(13%) patients fulfill criteria of having ascetic fluid infection. Of 21 patients, 3cases have SBP (PMNs count ≥ 250 cells/mm3 and positive ascetic fluid culture), 16 cases (76.1%) have Monomicrobial non neutrocyticbacterascites (MNB) (PMNs < 250 cells/mm3 and Positive ascetic fluid culture) and only 2 cases(9.5%) have Culture negative neutrocytic ascites (CNNA) (PMNs count ≥ 250 cells/mm3 and Negative ascetic fluid culture) as shown in figure 1.

The organisms grown from the ascetic fluid culture were as follows: E coli (n=10), Staph. Aureus (n=7) and Enterococci (n=2) with the results shown in table 3. Difference in liver function tests among ascetic fluid infection variants are illustrated in Table 4 without any statistical significant different among groups except elevated liver enzymes in SBP group. AlsoDifference in routine laboratory tests among ascetic fluid infection positive and negative patients were statistically insignificant except for elevated Erythrocyte Sedimentation Rate (ESR) among ascetic fluid infection positive patients

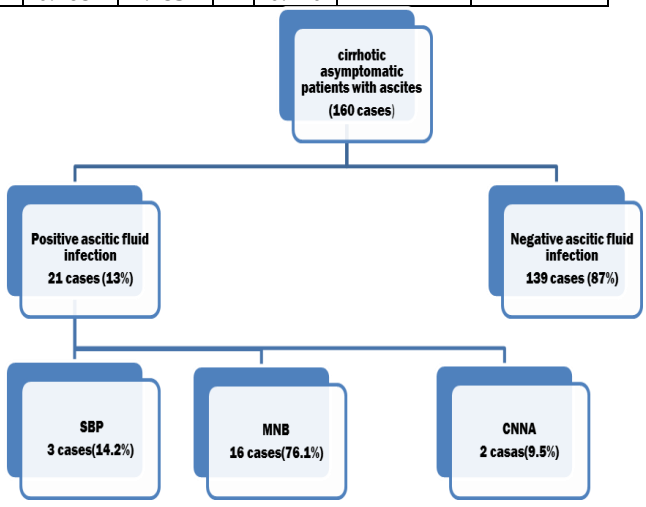

Figure 1: Results for ascetic fluid analysis.

group as shown in table 5.Physical and laboratory Characters of ascitic fluid analysis in SBP variants are shown in table 6.

Table 5: Difference in routine laboratory tests among ascetic fluid positive and negative patients.

Laboratory Tests		Groups						T-Test or Chi-Square	
		Negative ascetic fluid infection			Positive ascetic fluid infection			T or X^2	P-value
ESR	Range	5	-	110	15	-	107	-5.329	<0.001*
	Mean ±SD	37.295	±	18.487	64.571	±	37.416		
FBG (mg/dl)	Range	77	-	360	79	-	306	0.901	0.369
	Mean ±SD	133.683	±	71.464	119.386	±	63.806		
CREAT (mg/dl)	Range	0.3	-	1.4	0.6	-	1.3	1.503	0.135
	Mean ±SD	0.961	±	0.241	0.879	±	0.242		
HB ($x10^3$ g /dl)	Range	6.8	-	12.5	6.8	-	11.2	1.460	0.146
	Mean ±SD	9.315	±	1.103	8.937	±	1.127		
WBC ($x10^3$ /mm^3)	Range	3.2	-	10.3	3.9	-	10.7	-5.571	0.000
	Mean ±SD	6.257	±	1.946	8.900	±	2.508		
PLT ($x10^3$ /mm^3)	Range	39	-	200	46	-	111	0.575	0.566
	Mean ±SD	90.597	±	29.595	86.762	±	18.955		

Table 6: Physical and laboratory characters of ascitic fluid in SBP variants

Ascetic fluid analysis		Types of ascetic fluid infection									ANOVA or Chi-Square	
		SBP			MNB			CNNA			F or X^2	P-value
Appearance	Clear, yellow	0	0.00		n=4	25.00 %		0	0.00		10.687	0.030*
	Slightly turbid	n=3	100.00		n=4	25.00 %		n=2	100.0 %			
	Pale , yellow	0	0.00		n=8	50.00 %		0	0.00			
Albumin (g/dl)	Range	1.1	-	1.4	0.3	-	1.8	1.2	-	1.32	1.422	0.267
	Mean	1.25			0.838			1.260				
LDH (U/L)	Range	202	-	230	40	-	551	320	-	352	0.750	0.486
	Mean	216			203.500			336.000				
GLU. (mg/dl)	Range	91	-	114	58	-	224	110	-	121	0.652	0.533
	Mean	102.5			129.875			115.500				
Absolute Neutrophilic Count (Cells/mm^3)	Range	380	-	1230	10	-	150	290	-	305	10.738	0.001*
	Mean	995			83.1			297.500				

Table 7: Response to different types of antibiotic therapy.

Types of Antibiotics therapy	Number of cases Responded to antibiotics
Cefotaxime	3 cases
Cefoperazone-Levofloxacin	4 cases
Co-trimoxazole – Vancomycin	3 cases
Amoxycillinclavulinate – Imipenem	3 cases
Tazocin	2 cases
Vancomycin	2 cases
Ceftriaxone	2 cases

Although it is controversial whether antibiotic treatment in MNB cases is necessary because bacteria may be cleared naturally, all cases of positive ascetic fluid culture in our study were treated with antibiotics. Surprisingly, out of 19 patients with positive ascetic fluid culture, only 3 (15.8%) cases were Cefotaxime sensitive and16 cases (84.2%) were Cefotaxime resistant with response to other types of antibiotics including: Co-trimoxazole –Vancomycin (3 cases), Cefoperazone-Levofloxacin (4cases), Amoxycillinclavulinate –Imipenem (3 cases), Ceftriaxone (2 cases), Tazocin (2 cases) and finely Vancomycin (2cases) as shown in table 7.

4 Discussion

SBP is a potentially life threatening complication in patients with cirrhosis and has typically been described in hospitalized patients [7]. The aim of this study was to determine the frequency of SBP in asymptomatic cirrhotic patients with ascites. And to assess the common causative Organisms responsible for the development of SBP and its variants in decompensated cirrhotic Egyptian Patients.

Hepatitis B and C viral infection were commonest causes of cirrhosis in our studied patients and higher frequency of

viral etiology is probably due to unawareness in general population regarding the way of spread of viruses and presence of multiple factors contributing to the wide spread of Hepatitis B and C viruses. Alcoholic cirrhosis is absent in our study because of religious restriction which is inconsistent with A study [8] that concluded 46.7% of cirrhotic patients are due alcoholism alone , 20% HCV and alcoholism, 20% hepatitis C alone, 6.7% hepatitis B alone and 2.2% HBV and alcoholism with the high prevalence of Alcoholic consumption in these areas.

The results of our study support that the prevalence of SBP in cirrhotic patients with ascites and with no obvious signs of infection is low. Only three out of 160 (1.87%) asymptomatic cirrhotic patients who were included in our study met classic criteria of SBP. concluded that the prevalence of SBP in asymptomatic patients with liver cirrhosis and ascites is low [9]. On the contrary, our study did not match with Khan *et al.,* 2014 [9] who found that 9.3% of cirrhotic patients were having asymptomatic SBP at their first clinical presentation.

Interestingly, MANY STUDIES could not find any case of asymptomatic SBP among cirrhotic patients and concluded that there is no need to carry out exploratory paracentesis in asymptomatic cirrhotic patients. His opinion was against the guidelines of American association for the study of liver diseases published in 2012 which recommend performing exploratory paracentesis on each patient with liver cirrhosis and ascites [10-13].

Our study revealed that serum inflammatory markers, such as erythrocyte sedimentation rate could help to predict an episode of SBP in asymptomatic individuals with ascites especially the difference observed in ESR level between ascetic fluid infection positive and negative sub- groups which appeared to be statistically significant.

Profiles of microorganisms isolated in 19 cases of ascetic fluid infection in our study included mainly 10 cases (47.62%) Gram- negative cocci (E. coli), 7 cases (33.33%) Gram- positive cocci (Staph. Aureus) and only two cases (9.52%) are Enterococci.

Out of 19 patients with positive ascetic fluid culture, only 3 (15.8%) cases were Cefotaxime sensitive and16 cases (84.2%) were Cefotaxime resistant with response to other types of antibiotics including: Co-trimoxazole – Vancomycin (3 cases), Cefoperazone-Levofloxacin (4cases), Amoxycillinclavulinate –Imipenem (3 cases), Ceftriaxone (2 cases), Tazocin (2 cases) and finely Vancomycin (2cases). which may be explained by the changing patterns of organisms causing SBP.

The limitation of our study is the small number of patients and also data were collected from only one hospital which may not reflect the true prevalence of asymptomatic SBP in Egyptian decompensated cirrhotic patients. Emerging microorganism resistance to third generation cephalosporin (Cefotaxime) is going to be a fact, so we recommend ascetic fluid culture and sensitivity in any decompensated cirrhotic patients and further studies on large number of patients are required to assess the problem.

In conclusion, the results of our study indicate that the prevalence of SBP in asymptomatic patients with liver cirrhosis and ascites is low and serum ESR level could be used as a predictor of SBP episode in the studied group of patients. Bacterial culture & sensitivity of ascetic fluid were predominantly resistant to Cefotaxime antibiotic which suggesting changes in the background of treatment lines and its epidemiological aspects. We would like to emphasize that our results should be interpreted with caution and may be applicable only to a selected population of patients and further studies are required to assess the problem.

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