Journal of the Egyptian Society of Parasitology, Vol. 53, No.1, April 2023
J. Egypt. Soc. Parasitol. (JESP), 53(1), 2023: 51 – 56
Online: 2090-2549

SPONTANEOUS BACTERIAL PERITONITIS PROFILE IN DECOMPENSATED CIRRHOTIC EGYPTIAN PATIENTS

By
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Abstract

Bacterial infections are common and life-threatening in cirrhotic patients with ascites. Among patients who survived the first episode of SBP, about 70% experienced a recurrence within a year. Bacterial causative agent(s) and response to treatment were evaluated in 104 decompensated cirrhotic patients with ascites who were presented to Tropical Medicine Department, Ain Shams University Hospitals from February 2019 to June 2022 were evaluated for incidence of SBP, bacterial causative agent(s) and response to treatment. They were divided into two groups: GA received Rifaximin (N=52) and GB received Norfloxacin (N=52), Diagnostic paracentesis was done as needed for ascitic fluid analysis and culture, clinical and bacteriological profile of SBP was recorded.

The results showed that the ascitic fluid infection in patients was 28.8% in both group, with symptoms of abdominal pain (100%) and fever (63.3%). Culture negative neutrocytic ascites (CNNA) was in 63.33%, Monomicrobial non neutrocytic bacterascites was in 33.3% and polymicrobial ones was in 3.33%. The isolated bacteria were *E. coli* and *Staph. coagulase* negative, of 30 % in each group.

Keywords: Patients, Ascites, Spontaneous bacterial peritonitis, Rifaximin, Norfloxacin.

Introduction

Ascites is a common complication in cirrhotic patients, up to 60% of them developed ascites within 10 years during the disease course (Ginès *et al,* 2010). Piano *et al.* (2019) in Italy reported that in hospitalized patients globally, a high prevalence of infection with multidrug-resistant (MDR) bacteria in cirrhotic patients. They added that differences in prevalence of MDR bacterial infections in worldwide indicate the need for different empirical antibiotic strategies in different continents and countries. Fernández *et al*. (2021) in Europe reported that delayed diagnosis and inappropriate empirical treatments are associated with poor prognosis & increased mortality. El-Amin *et al.* (2017) in Egypt reported infections among cirrhotic was 61%, ascitic fluid infection (AFI) was the most common infection in cirrhotic patients and accounted for 44.3% of infections. Hou and Sanyal (2009) in USA identified ascites as the pathologic accumulation of fluid in peritoneal cavity as a common manifestation of liver failure, being one of cardinal signs of portal hypertension. Fernández *et al.* (2007) in Spain reported that main factor for ascites development in a cirrhotic patient with is portal hypertension due to increased intrahepatic resistance to blood flow compounded by the splanchnic vasodilatation resulted of local vasodilators production. Ascitic fluid infection is classified into five types based on polymorph nuclear cell count, ascitic fluid culture results and clinical features: classic culture-positive SBP, culture-negative SBP (culture-negative neutrocytic ascites, (CNNA), monomicrobial & polymicrobial bacterascites, and secondary peritonitis (Runyon, 2009). Its diagnosis is by positive ascites culture and/or absolute neutrophil count within ascites fluid of ≥250 cells/mm^3 (Runyon, 2013). Gram-negative bacteria were the main causative agent of SBP, with *Escherichia coli* and *Klebsiella* spp. (Marciano *et al,* 2019). But, major changes were more prevalence of gram-positive, quinolone-resistant, & multidrug-resistant (MDR) bacteria (Alexopoulou *et al,* 2013). The common isolates were species of *Streptococcus*, *Enterococcus*

and *Staphlococcus* (Acevedo, 2015).

Common symptoms and signs have some association with SBP include fever, diarrhea, gastrointestinal bleeding, abdominal pain /tenderness, vomiting, diarrhea and hepatic encephalopathy (Caruntu and Banea, 2006). But, Nguyen *et al.* (2022) in Vietnam reported that clinical presentation of SBP was highly variable and non-specific, and significant number of SBP patients was even completely asymptomatic and thus the paracentesis diagnosis was recommended.

This study aimed to find SBP frequency or its variants in CLD patients association with different clinical pictures, and to identify bacteriological profile response to Rifaximin or Norfloxacin**.**

Materials and Methods

This prospective study included 104 patients with ascites admitted to Tropical Medicine Department, Ain Shams University Hospitals. They were with end stage liver disease and ascites and divided into 2 groups of 52 each. GA treated with Rifaximin® and GB treated with Norfloxacin®.

Inclusion criteria: These were: 1- Patients who agreed to participate and gave informed written consent. 2- Male/female aged >18 years old. 3- All patients with liver cirrhosis and ascites, and 4- History or evidence of at least one previous SBP attack and clinically free at the time of inclusion.

Exclusion criteria: 1- Intra-abdominal infection (e.g. abdominal abscesses, cholecystitis or acute pancreatitis). 2- History of recent abdominal surgery. 3- Renal dysfunction. 4- Sepsis evidence and 5- Other comorbidities affecting patient life e.g. significant cardiac disease, pulmonary disease, portal vein thrombosis, HCC or other malignancies.

Patients were followed over 3 months for second SBP attack in both. SBP was suspected as newly developed abdominal pain, tenderness on palpation (with or without rebound tenderness), and fever, not responded to diuretics, hepatic encephalopathy or others necessitated hospitalization. The peritoneal fluid infection was confirmed by the PMNL in ascetic fluid ≥ 250/ml and/or positive culture. Ascitic fluid samples were collected before antimicrobial treatment for patients with suggestive SBP. Three samples of 10ml. each were taken under aseptic conditions and tested for total ascitic cell count and differential count, biochemical examination and microbiological culture on standard media for growth, which was identified type and antibiogram (Huang *et al*, 2014).

All patients were subjected to: 1- Full medical history & physical examination. Presence of fever, abdominal pain, rebound tenderness, absence of bowel sounds and pre-hepatic coma as lack of concentration in decompensated liver disease increased SBP susceptibility. 2- Imaging: pelvo-abdominal U/S. 3- Laboratory examinations for CBC, liver profile (albumin, total bilirubin, INR), renal function tests (Creat.), CRP, ascitic fluid, analysis for cell count, chemistry, culture and sensitivity.

Ethical consideration: The study was approved by Ain Shams University, Faculty of Medicine Research Ethical Committee with code FMASU MD 59/2019. A written consent was taken from each patient after explaining the study purpose. The study protocol complied with the ethical guidelines of Helsinki declaration (2008) as reflected in Institution's Human Research Committee.

Statistical analysis: Sample size was calculated based on an expected recurrence SBP rate of 70% among end stage liver disease patients, where 52 patients were in each group, analyzed by IBM SPSS software package version 20.0. Qualitative data were given as number and percent by minimum, maximum, median, range & mean ±SD, expressed using median with interquartile range (IQR). P value <0.05 was considered significant & < 0.01 was highly significant. Comparison groups was tested by Chi-square test and when > 20% of cells have expected count > 5 was tested by Fisher's exact test.

Results

HCV patients were males (60.6%) due to liver cirrhosis in 67.3% of them 56.7% were

CTP class C. Also, 48.1% were diabetic patients and 20.2% hypertensive.

There was significant difference between GA & GB in total bilirubin, higher INR in GA (P<0.05), with high difference in platelet count in GA (P <0.01). SBP in GA was 15 (28.8%) & 15 (28.8%) in GB. Ascitic infected fluid symptom was abdominal pain (100%) and fever (63.3%). Culture negative neutrocytic ascites was 63.33%, monomicrobial one 33.3%, polymicrobial one 3.33%. Isolated bacteria were *E. coli* and *St. coagulase* -ve, each in 30% of ascetic patients.

Details were given in tables (1, 2, 3 & 4).

Table 1: **C**omparison between groups as regarding basal demographic data, comorbidities and basal laboratory data:

Variations		GA (N= 52)	GB (N=52)	P-value	Significant
Age (years)		55.02 ± 9.35	56.15 ± 11.71	0.586	NS
Sex, *no. (%)*	Female	22 (42.3%)	19 (36.5%)	0.547	NS
	Male	30 (57.7%)	33 (63.5%)		
Etiology of chronic liver disease	HCV	35 (67.3%)	35 (67.3%)	0.993	NS
	AIH	4 (7.7%)	4 (7.7%)		
	HBV	2 (3.8%)	3 (5.8%)		
	unknown	10 (19.2%)	9 (17.3%)		
	Schistosomiasis	1 (1.9%)	1 (1.9%)		
Child-Pugh score, *no. (%)*	B	19 (36.5%)	26 (50.0%)	0.166	NS
	C	33 (63.5%)	26 (50.0%)		
History of clinically controlled comorbidities					
DM, *no. (%)*		25 (48.1%)	25 (48.1%)	1.000	NS
HTN, *n (%)*		10 (19.2%)	11 (21.2%)	0.807	NS
Baseline Lab. examinations					
S. Total bilirubin (mg/dl)		2.4 (1.55 – 4.1)	1.8 (1.3 – 3)	0.042	**S**
S. Albumin (g/dl)		2.51 ± 0.52	2.73 ± 0.64	0.052	NS
INR		1.72 ± 0.50	1.52 ± 0.45	0.035	**S**
S. Creatinine (mg/dl)		1.00 ± 0.23	0.95 ± 0.29	0.284	NS
WBCs/mm3		5.74 ± 2.82	5.60 ± 2.67	0.792	NS
Hemoglobin (gm /dl)		10.16 ± 1.73	10.95 ± 2.38	0.056	NS
Platelet/mm3		81 (55.5 – 109)	125.5 (69.5 – 157)	0.007	**HS**
CRP (<6 mg/l)	Median (IQR)	6.85 (1.9 – 13)	5 (1.45 – 14)	0.835	NS

Table 2: Pattern of clinical manifestation of SBP among groups:

SBP		GA (N=15)	GB (N=15)	P value	Sig.
Abdominal pain		15 (100%)	15 (100%)	NA	NA
fever		9 (60%)	10 (66.7%)	0.704	NS
Lack of diuretics response		15 (100%)	15 (100%)	NA	NA
Response to SBP treatment	Improved	14 (93.3%)	15 (100%)	0.309	NS
	Deteriorated	1 (6.7%)	0 (0.0%)		
Time to favorable response In days	Mean ± SD	6.7 ± 1.73	6.9 ± 1.44	0.713	NS
	Range	4 – 11	5 – 10		

Table 3: Incidence of SBP and ascitic Fluid analysis among groups:

Variations		GA (N=15)	GB (N=15)	Total (N=30)	P value	Sig.
Incidence of SBP		15 (28.8%)	15 (28.8%)	30 (28.8%)	1.000	NS
Ascitic cell count	Median(IQR)	300 (125-800)	310 (88-550)		0.865	NS
	range	0 - 1870	25 - 4175			
Culture negative neutrocytic ascites (CNNA)		9 (60%)	10 (66.6%)	19 (63.33%)	0.48	NS
Monomicrobial non neutrocytic bacterascites		6 (40%)	4 (26.66%)	10 (33.3%)		
Polymicrobial non neutrocytic bacterascites		0 (0.0%)	1 (6.66%)	1 (3.33%)		

Table 4: Distribution of pathogens among SBP patients:

Culture positive SBP		GA (N=6)	GB (N=5)	Total (N=11)	P value	Sig.
organism	*E. coli* (GNB)	3 (50%)	0 (0.0%)	3 (30%)	0.05	NS
	Staph. Coagulase –ve(GPC)	3 (50%)	0 (0.0%)	3 (30%)		
	Acintobacter MDR (GNB)	0 (0.0%)	2 (40%)	2 (20%)		
	Staph.hemolyticus(GPC)	0 (0.0%)	1 (20%)	1 (10%)		
	Enterococci (GPC)	0 (0.0%)	1 (20%)	1 (10%)		
	Enterococci+klebsiella (GPC +GNB)	0 (0.0%)	1 (20%)	1 (10%)		

Discussion

SBP is a common severe complication in cirrhotic patients with ascites with high mortality rate, due to intestinal flora, increased intestinal permeability with consequent bacterial translocation, and systemic immune dysfunction (Bauer *et al,* 2001). Survivors of SBP attack have a poor prognosis as well as, after an initial diagnosis of SBP, one up to six-month and even one year mortality rates are 33%, 50% and 58% respectively (Khan *et al,* 2009). SBP was due to second leading cause of bacterial-related mortality in hospitalized patients up to 33% (Thuluvath *et al,* 2001). Fatal renal injury developed in 30-40% of SBP patients (Tandon and Garcia-Tsao, 2011). The rate of ascitic fluid infections caused by multidrug-resistant bacteria became very high with nosocomial SBP exhibited a greater resistance to antibiotics than those with community-acquired SBP (Alexopoulou *et al,* 2013).

In the current study, no SBP incidence difference was reported in both groups; 15 patients (28.8%) in each of GA and GB developed SBP (P =1). This agreed with Lutz *et al*. (2014), who reported a similar result with Rifaximin prophylaxis. Also, Marciano *et al.* (2019 reported that SBP incidence recurrednce in cirrhotic patients received secondary prophylaxis with norfloxacin was 28.53%.

In the present study, Rifaximin was nearly equal to Norfloxacin in preventing second attack of SBP. Elfert *et al.* (2016) showed that rifaximin was superior to norfloxacin, 3.88% of patients on rifaximin and 14.13% on norfloxacin developed SBP, with significant difference (P= 0.04). Lutz *et al.* (2014) declared the superiority of systemic antibiotics over rifaximin in SBP prophylaxis. They found a significantly lower SBP rate in patients treated with systemic antibiotic, than SBP rates in those without prophylactic treatment. They added that SBP occurred in patients (22%) without prophylaxis, 30% in Rifaximin group and none in those received systemic antibiotic prophylaxis. Systemically Absorbed antibiotics significantly reduced SBP occurrence compared to no prophylaxis (P= 0.04) and rifaximin (P= 0.02).

In the present study, the symptoms among all SBP patients were abdominal pain with increased amount of ascites and lack of diuretics response, fever was in 60% in GA & 66.7% in GB. This agreed with Victor *et al.* (1991), who reported that the main symptom was abdominal pain in 63% followed by fever in 40%. Al-Ghamdi *et al.* (2019) also in a retrospective study found that all cirrhotic patients had ascitic fluid infection and abdominal pain was in 81% and fever was in 33.5%, but 91.5% of them suffered from increased ascites. Goel *et al.* (2019) found that in 8/10 SBP patients suffered from abdominal pain and seven from fever.

In the present study, ascitic culture and sensitivity showed that 63.33% of patients had culture negative neutrocytic ascites (CNNA), 33.3% had monomicrobial bacterascites and 6.66% had polymicrobial non neutrocytic bacterascites. This agreed with Mostafa *et al.* (2011), they reported that > 50% of patients had negative ascitic culture and sensitivity, 35% of patients had bacterascites. Also, this agreed with Enomoto *et al.* (2014), who reported that < 50% of patients with infected ascites showed negative ascitic culture and sensitivity despite of high polymorph nuclear count. The high negative cultures frequency can be attributed to slow causative agent growth, its low number, use of antiseptic dressing before sampling or delay in its transportation. Culture negativity also may represent resolution phase of SBP where host defenses eliminated bacteria without treatment, but elevated neutrophil count was still present (Hoefs *et al,* 1982).

In the present study, the most frequently isolated bacteria were *E. coli* detected in 30% followed by *Staph. coagulase -ve* in 30% of them. *Acintobacter MDR* was isolated in 20% of patients while *Staph. hemolyticus* and *Enterococci* each of them was isolated in 10% of patients and 10% showed growth of both *Enterococci* and *Klebsiella* in the same culture.

In the present study, the most frequently isolated bacterial species in SBP ascitic fluid patients was *E. coli*. This agreed with Victor *et al*. (1991), they found that peritoneal fluid microbial isolates was *E. coli* (50%), followed by *Klebsiella pneumoniae* (11%). Such *et al.* (2005) reported that frequently isolates were *E. coli* (45%), *Klebsiella* spp. (11%), *Strept. pneumoniae* (8%) and other streptococci (12%), *Enterococcus* spp. (4%), *Staphl. aureus* (4%) & anaerobes (4%). This agreed with Koulaouzidis *et al.* (2007) and Shi *et al.* (2017), they reported that *E. coli* was the main isolate in SBP patients. Bacterial translocation from intestine into peritoneal lymphatic stations and abdominal cavity showed that intestinal bacterial overgrowth, & abnormal intestinal motility in portal hypertension patients (Salerno and La Mura, 2015). Norfloxacin was recommended as antimicrobial prophylactic agent for patients at risk of SBP (Angeli *et al,* 2018). Its efficacy decreased particularly in patients colonized with MDRO (Mücke *et al,* 2020). So, other broad spectrum antibiotics, such as ciprofloxacin, rifaximin, & sulfamethoxazole/trimethoprim were alternatively used (Wang *et al,* 2019).

Conclusion

Ascitic fluid infection is frequent among patients with chronic liver disease and cirrhosis, Almost 28.8% of them developed ascitic fluid infection. Abdominal pain was main presentation followed by fever. Culture negative neutrocytic ascites (CNNA) was more frequent than monomicrobial bacterascites and *E coli* was the main isolated organism. As to SBP treatment both antibiotics were more or less similar as prophylactic.

Authors' contribution: Hamdy designed the study, Mubarak, Al Balakosy, and Khedr developed methodology and helped in statistical analysis, Sebaweh collected data and wrote manuscript, Hassan performed ultrasonography for patients. All authors participated sufficiently in the work.

The study didn't receive any specific grant from any funding agency in public, commercial, or not-for-profit sectors.

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