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Original article

Bacteriological Profile and Antimicrobial Resistance in Ascitic Fluid of Patients with Community Acquired and Nosocomial Spontaneous Bacterial Peritonitis

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Abstract:

Background: Spontaneous bacterial peritonitis is the most frequent infection complicating liver cirrhosis. Recent changes in bacterial ecology and emerging antibiotic resistance have resulted in failure to respond to empirical therapy with 3rd generation cephalosporin in 33%-75% of cases and such failure is associated with reduced survival. **Aim of the work**: To identify the causative bacteria of community acquired and nosocomial SBP and their antimicrobial resistance patterns in an attempt to perform a local bacteriological surveillance to optimize empirical treatment. **Patients and methods**: Three hundred patients with ascites due to liver cirrhosis were enrolled in this study. All patients were subjected to history taking, clinical examination, ascitic fluid analysis, culture and ultrasonography. SBP was diagnosed by ascitic PNL ≥250/mm^3. **Results:** One hundred and eighty-five patients (61.7%) were diagnosed as SBP. Community acquired SBP (83.8%) was more common than nosocomial SBP (16.2%). One hundred and forty patients (75.7%) had culture positive, and 45 patients (24.3%) had culture negative SBP. Gram positive (G+) cocci (64.3%) were more common than Gram negative (G-) bacilli (35.7%). Among culture positive cases, 110 patients had community-acquired and 30 patients had nosocomial SBP. The overall cefotaxime resistance was 44.4%; being higher in nosocomial (100%) than community acquired group (37.5%). No resistance to ampicillin/salbactam, piperacillin/tazobactam, vancomycin, linezolid, meropenem or tigecyclin was identified. **Conclusion:** There is an emerging pattern towards G+ bacteria and 3rd generation cephalosporins resistance in the

causative bacteria of SBP especially nosocomial type while piperacillin/tazobactam, vancomycin, linezolid, meropenem or tigecycline still can be used in resistant cases.

Key words: Spontaneous bacterial peritonitis, community acquired, nosocomial, antibiotic resistance.

Abbreviations: SBP: Spontaneous bacterial peritonitis, PNL: Polymorphonuclear leukocytes, G+: Gram positive, G–: Gram negative.

Introduction:

Bacterial infections are major causes of morbidity and mortality in patients with liver cirrhosis. They account for 25%–46% of hospital admission due to acute decompensation events in these patients [1]. The most common infection that occurs (about 25-27% of the cases), and simultaneously the most severe one, is spontaneous bacterial peritonitis (SBP), followed by urinary infections (20-22%), pneumonia (15-19%) and bacteremia (12%) [2& 3]. Historically, gram-negative bacteria were the main causative agents of SBP, with *Escherichia coli* and *Klebsiella* spp. being the most frequently isolated organisms [4].

However, over the last few decades a major shift in the epidemiology of infectious bacteria in patients with cirrhosis occurred with an increasing prevalence of gram-positive, quinolone-resistant, and multidrug-resistant bacteria [5]. This may be attributed to the extensive use of quinolones for prophylaxis, the increasing use of invasive procedures, the rising prescription of broad-spectrum antibiotics and the broadening criteria for admission in intensive care units among health institutions [3 & 6]. Multidrug-resistant (MDR) organisms are predominantly found in nosocomial spontaneous bacterial peritonitis, being reported in about 20%–35% of the episodes [3].

However, about 4%–16% of community-acquired spontaneous bacterial peritonitis are also caused by MDR organisms [7 & 8]. The increasing prevalence of MDR bacterial infection has been associated with failure of empirical antibiotic therapy and poor prognosis [9] due to a higher mortality rate, an increased duration of in-hospital stays and higher healthcare related costs when compared to infections caused by susceptible strains [10]. Therefore, the latest practice guidelines recommended that distinguishing nosocomial from community-acquired cases was necessary for effective treatment of SBP [11 & 12]. This study was

done to identify the causative bacteria of community acquired and nosocomial SBP and their antimicrobial susceptibility patterns.

Patients and methods:

Study design: This cross-sectional study enrolled 300 consecutive patients with ascites due to liver cirrhosis who were admitted into Hepatology, Gastroenterology and Infectious Diseases Department in Benha University Hospital with clinical manifestations suggesting SBP during the period between April 2018 and February 2020. Ascitic fluid analysis including culture and sensitivity tests were done in the Clinical Microbiology lab of Clinical and Chemical Pathology Department in Benha University Hospital. The study was approved by the committee of ethics of scientific research of Benha Faculty of Medicine and written consents were obtained from the patients for participation in the study.

Inclusion criteria: Adult patients with ascites due to liver cirrhosis (based on medical history, clinical examination, laboratory investigations and abdominal ultrasonographic features as (coarse echo-pattern, irregular outline and hepatic veins attenuation) [13], either asymptomatic or presented with symptoms or signs suggesting SBP as [11]: i) local symptoms and/or signs of peritonitis (abdominal pain, abdominal tenderness, vomiting, diarrhea or ileus). ii) Signs of systemic inflammation: fever, chills, tachycardia, tachypnoea or shock. iii) Hepatic encephalopathy. iv) Renal failure. v) GI bleeding.

Exclusion criteria: Patients with ascites not due to liver cirrhosis e.g. cardiac, renal and tuberculous, compensated liver cirrhosis, secondary peritonitis or bacterascites (PMNs <250 cells/mm^3 and positive ascitic fluid culture), patients who received antibiotic in the last 3 months prior to admission or prophylactic treatment for SBP, pregnant females or patients with extrahepatic malignancy.

Definitions:

- **Spontaneous bacterial peritonitis (SBP):** it was defined by the presence of ascitic fluid polymorphonuclear leukocytes (PMN) greater than or equal to 250 /mm^3. **Community-acquired SBP (CA-SBP)** was defined as an infection diagnosed within the first 48 h of admission to hospital, whereas a diagnosis made more than 48 h after hospitalization was defined as **nosocomial SBP (N-SBP)** [14, 15]**.**

Patients with ascitic fluid PMN <250 /mm^3 who developed any symptoms, signs, or laboratory abnormalities suggestive of infection after 48 hours of admission (e.g., abdominal pain or tenderness, fever, encephalopathy, hypotension, renal failure, acidosis, peripheral leukocytosis) were subjected to another diagnostic paracentesis for diagnosis of N-SBP [16].

- **Multidrug-resistant bacteria (MDR):** bacteria resistance to 3 or more of the principal antibiotic families, including β-lactams e.g. extended-spectrum β-lactamase (ESBL) producing *Escherichia coli* and methicillin resistant Staphylococcus aureus (MRSA) [17].

- **Child and MELD scores:** were used for assessment of severity of liver diseases [18].

Methods: All patients were subjected to **a) Full history taking:** specially symptoms suggesting SBP or any probable risk factors of SBP (e.g. recent paracentesis, GIT bleeding, comorbid medical conditions, the use of immunosuppressive therapy and the presence of hepatocellular carcinoma) and previous use of antimicrobial drugs in the last week prior to hospital admission. **b) Clinical examination:** Including hyper or hypothermia, tachycardia, tachypnea, abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus, chills, hepatic encephalopathy, shock, renal failure or gastrointestinal bleeding. **c) Laboratory investigations:** including the following:
Complete blood count, urine analysis, fasting blood sugar (mg/dl), Liver profile tests: Aspartate aminotransferase (AST) (IU/L), Alanine aminotransferase (IU/L), serum total and direct bilirubin (mg/dl), serum albumin (mg/dl), Prothrombin time (sec), INR., Kidney function tests: serum creatinine (mg/dl). **d) Pelvi-abdominal US examination. e) Ascitic fluid sample aspiration** for cytological, biochemical and bacteriological analysis as the following:

I) Diagnostic paracentesis: After the skin was disinfected with an iodine solution, a sample of 25ml of ascitic fluid was aspirated by inserting the needle in the right lower quadrant of the abdomen; 3 cm cephalad and 3 cm medial to the anterior superior iliac spine using sterile gloves. Ultrasound guidance was used in patients in whom percussion cannot locate the ascites or in whom a first paracentesis attempt does not yield fluid despite the presence of shifting dullness.

II) Cytological analysis: Approximately 2 ml of ascitic fluid was placed in an EDTA tube for estimation of the total cell count and PNL count using an automated cell counter model Sysmex XT-1800i [19].

III) Biochemical analysis: Ten ml of ascitic fluid was used for chemical analysis of ascitic fluid albumin and glucose.

IV) Bacteriological analysis:

- At the bedside 10 ml of ascitic fluid was inoculated in aerobic blood culture bottle **(BacT/ALERT®** FA Plus culture bottles REF-410851 by Biomérieux-International [20]. These bottles were placed in an automated **BacT/ALERT® 3D 60** culture system and incubated at 37°C and continuously monitored for growth for at least 5 days.
- Isolated bacteria were identified by appropriate biochemical reactions according to presumptive identification. Bacterial identification and antibiotic sensitivity testing were done by manual disk diffusion method and by an automated system (**VITEK® 2 COMPACT 15).**

Statistical analysis:

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United states). Numerical data was summarized as means and standard deviations or medians and ranges. Categorical data was summarized as numbers and percentages. Comparisons between CA-SBP and N-SBP were done using independent t-test or Mann Whitney U test for parametric and non-parametric numerical data respectively. Categorical data was compared using Chi-square or Fisher's exact test if appropriate. All P values were two sided. P values less than 0.05 were considered significant.

Results:

General characteristics and clinical presentation

One hundred and eighty-five patients (61.7%) were diagnosed as SBP and they were classified into 2 groups: Group (1): Community acquired SBP included (155 patients) and Group (2): Nosocomial SBP included (30 patients). Ascitic fluid culture revealed 140 patients (75.7%) with culture positive and 45 patients (24.3%) with culture negative SBP (neutrocytic ascites) (Fig.1).

The majority of SBP patients were males (62.2%), with mean age (60 ±6 years), 37.8% of patients were diabetic, 21.6% were hypertensive and 24.3% had HCC. The most common symptoms were abdominal pain (70.3%), hepatic encephalopathy (54.1%), fever (43.2%) and upper GI bleeding (43.2%) and most of patients had past history of esophageal varices and PPI therapy (73%) (Table 1 and Fig. 2). Most of patients in community acquired group were classified as Child C (87.1%) while all patients in nosocomial group were classified as Child C (100%) with statistically significant difference (p <0.037). Child and MELD scores were higher in nosocomial group than community acquired group with highly statistically significant difference (p <0.001) (Table 2).

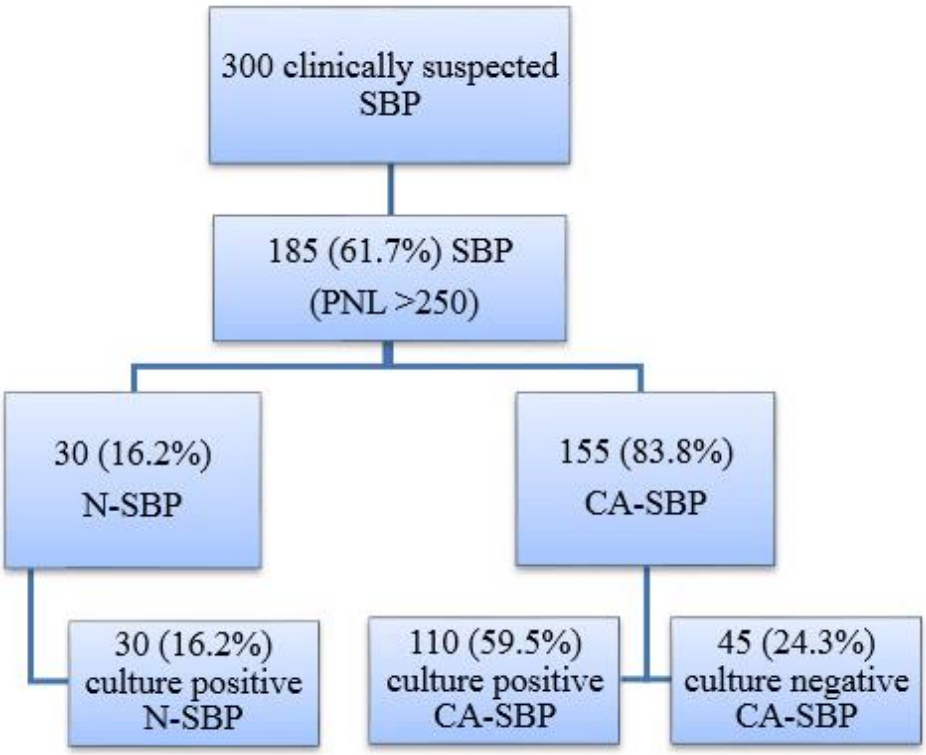

Fig. (1): Flow chart of enrolled patients according to ascitic fluid analysis and culture results.

Table (1): Comparison between community acquired and nosocomial SBP as regards baseline characteristics of SBP patients.

Variables	n (%)			P value
	Total n=185	Community acquired SBP (n = 155)	Nosocomial SBP (n = 30)	
Age (years): Mean ±SD	60 ± 6	60 ±7	60 ±5	0.814
Gender:				
- Males	115 (62.2%)	105 (67.7%)	10 (33.3%)	<0.001*
- Females	70 (37.8%)	50 (32.3%)	20 (66.7%)	
DM	70 (37.8%)	60 (38.7%)	10 (33.3%)	0.578
Hypertension	40 (21.6%)	40 (25.8%)	0 (0.0%)	0.002*
Smoking	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
History of Anti-HCV therapy	45 (24.3%)	40 (25.8%)	5 (16.7%)	0.286
Fever	80 (43.2%)	60 (38.7%)	20 (66.7%)	0.005*
Abdominal pain	130 (70.3%)	100 (64.5%)	30 (100.0%)	<0.001*
Vomiting	25 (13.5%)	20 (12.9%)	5 (16.7%)	0.581
Hepatic encephalopathy	100 (54.1%)	75 (48.4%)	25 (83.3%)	<0.001*
Diarrhea	5 (2.7%)	0 (0.0%)	5 (16.7%)	<0.001*
Upper GI bleeding	80 (43.2%)	70 (45.2%)	10 (33.3%)	0.231
Renal impairment	60 (32.4%)	45 (29.0%)	15 (50.0%)	0.025*
Septic shock	20 (10.8%)	15 (9.7%)	5 (16.7%)	0.259
HCC	45 (24.3%)	35 (22.6%)	10 (33.3%)	0.209
Previous paracentesis	60 (32.4%)	55 (35.5%)	5 (16.7%)	0.044*
Previous OV by endoscopy	135 (73.0%)	110 (71.0%)	25 (83.3%)	0.163
Previous PPI therapy	135 (73.0%)	115 (74.2%)	20 (66.7%)	0.395

Independent t test was used for age. Chi-square or Fisher's exact test was used.

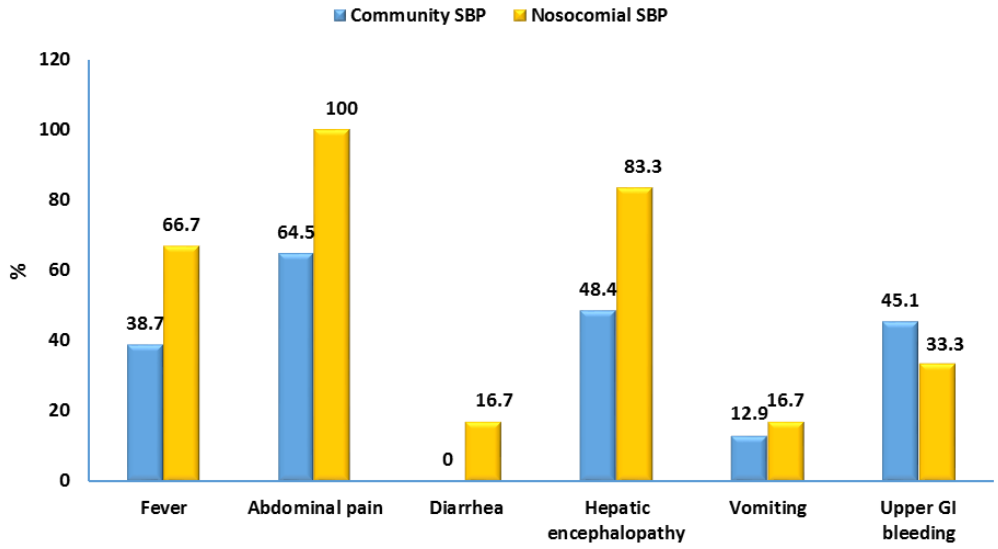

Fig. (2): Bar chart comparing present medical history of community acquired SBP patients with nosocomial SBP patients.

Table (2): Comparison between community acquired and nosocomial SBP groups as regards severity of liver diseases assessed by Child and MELD scores.

Variables		Community SBP (n = 155)	Nosocomial SBP (n = 30)	P value
Child score	Median (range)	12 (9 - 15)	15 (11 - 15)	<0.001*
Child class	B n (%)	20 (12.9%)	0 (0.0%)	0.037*
	C n (%)	135 (87.1%)	30 (100.0%)	
MELD score	Median (range)	20 (9 - 39)	23 (21 - 39)	<0.001*

Mann Whitney U test was used for numerical data. Chi-square test was used for categorical data.

Bacteriological profile

Gram positive cocci (64.3%) were more frequently isolated than Gram negative bacilli (35.7%) with predominant coagulase negative staphylococci (CoNS) (28.6%) and staph. aureus (25%) followed by E. coli (21.4%) while the least frequent was pseudomonas (3.6%). The most common bacteria in CA-SBP are CoNS and staph aureus (27.3%) while the most common bacteria in N-SBP are CoNS and E-coli (33.3%). Streptococci and Klebsiella pneumoniae were isolated in CA-SBP with statistically significant difference (p=0.032) while pseudomonas was isolated only in N-SBP with statistically significant difference (p<0.001). There was no statistically significant difference in the distribution of CoNS, Staph aureus and E-Coli between the two groups (table 3).

Considering antibiotic susceptibility of isolated bacteria, the overall highest antibiotic resistance was observed with ampicillin (100%) then oxacillin (penicillinase-stable penicillin) (72.2%) followed by trimethoprim/sulfamethoxazole (64%), cefotaxime (44.4%), levofloxacin (fluoroquinolone) (28%), ceftolozane/tazobactam (fifth-generation cephalosporin/ β-lactamase inhibitor) (16.7%), amikacin (14.3%), teicoplanin (12.5%) and imipenem (8.3%) (table 4).

When SBP episodes were classified into N-SBP and CA-SBP, resistance was more frequent in N-SBP and this was consistent with most of the studies on nosocomial and community acquired SBP considering resistance to levofloxacin (83.3% vs. 10.5%; p <0.001), ciprofloxacin (66.7% vs. 9.1%; p<0.001), oxacillin (100% vs. 66.7%; p <0.009), ceftolozane/tazobactam (50% vs. 0%; p=0.002), Gentamycin (50% vs. 17.6%; p =0.001), imipenem (33.3% vs. 0%; P = 0.001), cefotaxime (100% vs. 37.5%; p = 0.013) and cefoxitin (100% vs. 27.3%, p<0.001). Fortunately, no multi-drug resistant bacteria were detected in this study

(table 4) and no resistance to piperacillin/tazobactam, vancomycin, linezolid, meropenem or tigecycline was observed in both groups.

Table (3): Comparison between community acquired and nosocomial SBP groups as regards type of isolated bacteria in culture positive cases.

Isolated bacteria	n (%)		
	Community SBP (n = 110)	Nosocomial SBP (n = 30)	P value
Gram positive cocci	75 (68.2%)	15 (50.0%)	0.065
● CoNS	30 (27.3%)	10 (33.3%)	0.515
● Staph aureus	30 (27.3%)	5 (16.7%)	0.234
● Streptococci	15 (13.6%)	0 (0.0%)	0.032*
Gram positive bacilli	0 (0.0%)	0 (0.0%)	-
Gram negative bacilli	35 (31.8%)	15 (50.0%)	0.065
● E-Coli	20 (18.2%)	10 (33.3%)	0.073
●Klebsiella pneumoniae	15 (13.6%)	0 (0.0%)	0.032*
● Pseudomonas	0 (0.0%)	5 (16.7%)	<0.001*

Chi-square or Fisher's exact test was used.
N.B. Forty-five patients (29.0%) of community acquired group had culture negative SBP.

Table (4): Comparison between community acquired and nosocomial SBP groups as regards antibiotic susceptibility of isolated bacteria.

Antibiotic	Susceptibility	Community SBP (n = 110)	Nosocomial SBP (n = 30)	P value
Levofloxacin (LEV)	Resistant	10 (10.5)	25 (83.3)	<0.001*
	Sensitive	85 (89.5)	5 (16.7)	
Ciprofloxacin (CIP)	Resistant	5 (9.1)	10 (66.7)	<0.001*
	Sensitive	50 (90.9)	5 (33.3)	
Rifampicin (RF)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	55 (100.0)	10 (100.0)	
Clindamycin (DA)	Resistant	5 (7.7)	5 (33.3)	0.007*
	Sensitive	60 (92.3)	10 (66.7)	
Ampicillin-salbactam (SAM)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	25 (100.0)	0 (0.0)	
Tazobactam/piperacillin (TZP)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	20 (100.0)	10 (100.0)	
Vancomycin (VA)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	75 (100.0)	10 (100.0)	
Linezolid (LNZ)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	75 (100.0)	15 (100.0)	
Penicillin (P)	Resistant	95 (95.0)	20 (100.0)	0.588
	Sensitive	5 (5.0)	0 (0.0)	
Ampicillin (Amp)	Resistant	30 (100.0)	5 (100.0)	-
	Sensitive	0 (0.0)	0 (0.0)	
Oxacillin (OX)	Resistant	50 (66.7)	15 (100.0)	0.009*
	Sensitive	25 (33.3)	0 (0.0)	
Erythromycin (E)	Resistant	30 (50.0)	5 (100.0)	0.057
	Sensitive	30 (50.0)	0 (0.0)	
Sulfamethoxazole/ trimethoprim (SXT)	Resistant	65 (65.0)	15 (60.0)	0.641

	Sensitive	35 (35.0)	10 (40.0)	
Flucloxacillin (FL)	Resistant	20 (100.0)	0 (0.0)	-
	Sensitive	0 (0.0)	0 (0.0)	
Amikacin (AK)	Resistant	0 (0.0)	5 (33.3)	0.009
	Sensitive	20 (100.0)	10 (66.7)	
Kanamycin (K)	Resistant	10 (66.7)	5 (100.0)	0.266
	Sensitive	5 (33.3)	0 (0.0)	
Gentamycin (CN)	Resistant	15 (17.6)	15 (50.0)	0.001*
	Sensitive	70 (82.4)	15 (50.0)	
Azithromycin (AZM)	Resistant	20 (66.7)	0 (0.0)	-
	Sensitive	10 (33.3)	0 (0.0)	
Meropenem (MEM)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	40 (100.0)	10 (100.0)	
Imipenem (IPM)	Resistant	0 (0.0)	5 (33.3)	0.001*
	Sensitive	45 (100.0)	10 (66.7)	
Ertapenem (ERT)	Resistant	0 (0.0)	10(100.0)	<0.001*
	Sensitive	15 (100.0)	0 (0.0)	
Aztreonam (ATM)	Resistant	5 (100.0)	10 (100.0)	-
	Sensitive	0 (0.0)	0 (0.0)	
Ceftolozane/tazobactam (CT)	Resistant	0 (0.0)	5 (50.0)	0.002*
	Sensitive	20 (100.0)	5 (50.0)	
Cefuroxime (CXM)	Resistant	15 (50.0)	15 (100.0)	0.001*
	Sensitive	15 (50.0)	0 (0.0)	
Ceftriaxone (CRO)	Resistant	10 (50.0)	5 (100.0)	0.061
	Sensitive	10 (50.0)	0 (0.0)	
Cefoperazone (CFP)	Resistant	10 (50.0)	5 (50.0)	1
	Sensitive	10 (50.0)	5 (50.0)	
Cefotaxime (CTX)	Resistant	15 (37.5)	5 (100.0)	0.013
	Sensitive	25 (62.5)	0 (0.0)	
Cefoxitin (FOX)	Resistant	15 (27.3)	15 (100.0)	<0.001*
	Sensitive	40 (72.7)	0 (0.0)	
Tetracycline (TE)	Resistant	10 (25.0)	15 (100.0)	<0.001*
	Sensitive	30 (75.0)	0 (0.0)	
Tigecycline (TGC)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	5 (100.0)	15 (100.0)	
Cefadroxil (CFR)	Resistant	5 (100.0)	5 (100.0)	-
	Sensitive	0 (0.0)	0 (0.0)	
Ceftazidime (CAZ)	Resistant	10 (33.3)	0 (0.0)	0.292
	Sensitive	20 (66.7)	5 (100.0)	
Teicoplanin (TEC)	Resistant	0 (0.0)	5 (100.0)	<0.001*
	Sensitive	35 (100.0)	0 (0.0)	
Cefepime (FEP)	Resistant	10 (100.0)	0 (0.0)	-
	Sensitive	0 (0.0)	0 (0.0)	
Colistin (CS)	Resistant	0 (0.0)	0 (0.0)	-
	Sensitive	5 (100)	0 (0.0)	

Chi-square or Fisher's exact test was used.

Discussion:

The prevalence of SBP in this study was nearly similar to that reported by different local studies in Egypt as it was 57% in Kasr Alaini [27], 50% [28] and 76.7% [29] by two different studies in Mansoura, 56.1% in Zagazig [24] and 62% in Aswan [30]. While other Egyptian studies reported a lower prevalence of SBP as it was 13% in Al-Hussein University hospital [31], 31% in

Sohag [32], 44.3% in Assuit [33], 31% in Ain Shams [34], 19.6% in Menoufia [35], 35.5% in another study in Assuit [36] and 41.7% in Tanta [37]. The prevalence of SBP in the current study was higher than that reported in a global study on 1,302 patients from Asia, Europe and America which was 27% [10] and that reported in two different Indian studies as it was 38.09% [38] and 16.12% [39]. This difference may be attributed to the difference in samples' size, the mean age and the type of studied patients (whether inpatients or outpatients, symptomatic or asymptomatic), the wide use of PPI in the present study (73%) which may be a risk factor for SBP [40] in addition to poor immunity due to malnutrition of most patients with liver cirrhosis.

Furthermore, Benha University Hospital as a tertiary care hospital serving a large number of patients living in rural areas in and around Benha and so many patients are referred to it especially those with late presentation of decompensated liver cirrhosis may explain the high number of SBP prevalence in the present study.

Regarding classification of SBP patients according to site of acquisition of infection, community acquired SBP (83.8%) was more common than nosocomial SBP (16.2%) and this result is consistent with Kim and his colleagues [41] who reported in his study that 111 patients (85.4%) had CA-SBP and 19 patients (14.6%) had N-SBP and another study [9] which reported that 81.5% of patients had CA-SBP and 18.5% had N-SBP. Also, the current study was in agreement with that [42] which reported that 87% of patients had CA-SBP and 13% had N-SBP.

On the contrary, other studies reported a prevalence of N-SBP higher than CA-SBP such as that which reported that 55.8% vs 44.2% respectively and this difference may be a result of incorporation of multiple episodes for the same patient and bacterascites patients unlike the present study [21]. Whether N-SBP or CA-SBP was predominant, it was reported in the literature that the prevalence of N-SBP in most studies ranges from 14.6% to 69.3% [16].

Concerning the comorbid conditions of SBP patients, septic shock and hepatocellular carcinoma were prevalent in (10.8% and 24.3% of the patients respectively) and they were more common in N-SBP than CA-SBP. This was in agreement with Ding and his colleagues [43] who reported that septic shock was present in 7.5% and hepatocellular carcinoma was present in 28.7% of patients being more prevalent in

N-SBP than CA-SBP and Shi and his colleagues [44] who reported that 14.8 % of CA-SBP and 20.9% of N-SBP presented with septic shock. In the present study, diagnosis of esophageal varices in endoscopy was more common in N-SBP than CA-SBP in agreement with that study suggesting that further invasive interventions may contribute to N-SBP acquisition [42].

Most of the studied patients were classified as Child C (89.2%). Child and MELD scores were higher in N-SBP than CA-SBP with statistically significant difference. This was in agreement with that reported by several studies on SBP as the majority of patients were classified as Child C with a prevalence ranging from 71% to 87% [38, 45-47]. This can be explained in light of the fact that the most important risk factor for developing SBP is the advances in severity of liver disease [48]. On the other hand, some studies did not identify significant difference in Child scores and MELD scores among the different methods of acquisition of SBP [44 & 49].

According to results of ascitic fluid culture of SBP patients in the current study, 140 patients (75.7%) had culture positive SBP while 45 patients (24.3%) had culture negative neutrocytic ascites (CNNA) and this agreed the study [20] reporting that although the method of direct inoculation of ascitic fluid into blood culture bottles at the bedside increased the yield of bacteria up to 90%, cultures were still negative in approximately 30-50% of patients with an increased ascites PMN count.

On comparing culture positivity with SBP acquisition site, all patients with N-SBP had positive ascitic fluid culture while 71% of those with CA-SBP had positive culture with statistically significant difference (p-value = 0.001) and this was in agreement with an Indian study in which it was reported that 58% of CA-SBP and 100% of N-SBP were culture positive (p-value = 0.044) [50]. On the contrary, other studies reported lower percentages as 48% of N-SBP episodes were culture positive [47].

In the current study, positive cultures yielded Gram positive cocci (64.3%) more commonly than Gram negative bacilli (35.7%) with predominant coagulase negative staphylococci (CoNS) (28.6%), staphylococcus aureus (25%) followed by E. coli (21.4%) and this agreed with Egyptian studies as the study in Mansoura Specialized University Hospital which reported isolation of Gram positive cocci (48.8%) more commonly than Gram negative bacilli (12.2%) in SBP patients with predominant

staphylococcus spp., streptococcus spp. followed by Listeria monocytogenes then Klebsiella and E-coli [28] and the study in Al-Rajhy Liver Hospital, Assuit University [33] which found that the most common organisms in SBP were staphylococci [12/19 (63.2%)], followed by streptococci [3/19 (15.8%)]. An increasing incidence of SBP induced by Gram positive bacteria more than Gram negative bacteria in patients with decompensated liver cirrhosis had been observed in other studies worldwide (ranging from 29.3% to 62.5%) in accordance with the present study [49, 51-55].

Notably, there were some implications in the literature regarding the isolation of CoNS within ascitic fluid culture. Some authors had previously considered it as skin contaminant [41, 56], while others proposed guidelines to differentiate between contamination and significant infection in positive blood cultures of bacteraemic patients [57]. However, the absence of evidence-based recommendations to clarify the difference between contamination and significant positive ascitic cultures in up-to-date guidelines does not justify interpreting the isolation of CoNS as contamination [45, 58].

On the contrary, a study in Zagazig University Hospital in Egypt reported that *E-coli* was the most frequently isolated bacteria (56%), followed by *Klebsiella pneumoniae* 24% and *Staphylococcus aureus* 20% [24] and a study in Aswan University Hospital in Egypt also reported that positive cultures revealed gram-negative bacteria in 60% of SBP patients, predominantly *E-coli* (66.6%) and Klebsiella (33.3) gram-positive in 40% of patients, predominantly Staphylococcus aureus (60%) and streptococcus species (40%) [30]

The unusual trend to a high frequency of SBP caused by Gram-positive bacteria had been studied by various epidemiological investigators who explained the evidence behind this change by extensive use of quinolones in prophylaxis, the increasing number of invasive procedures, frequent admission of cirrhotic patients in intensive care units and rising empirical use of broad spectrum antibiotics[6, 58].

Considering antibiotic susceptibility of isolated bacteria, the overall highest antibiotic resistance was observed with ampicillin, oxacillin, trimethoprim/sulfamethoxazole, cefotaxime, then levofloxacin in a descending order. The current percentages of resistance were

slightly different from other studies in which the highest antibiotic resistance was seen with levofloxacin 71% followed by ciprofloxacin 67.45%, co-trimaxozole 66% and ceftriaxone 64.52% as reported before [50] resistance rates were 28.6% to ciprofloxacin, 23.2% to gentamicin, 46.4% to ampicillin-sulbactam, 39.3% to trimethoprim-sulfamethoxazole, 28.6% to piperacillin-tazobactam, and 12.5% to carbapenems as observed [59].

No resistance to piperacillin/tazobactam, vancomycin, linezolid, meropenem or tigecycline was observed in the current study in both groups. This was consistent with a study by Friedrich and his colleagues [60] who reported that piperacillin/tazobactam was found to be a highly effective antibiotic in both N-SBP and CA-SBP (85.1% and 92.5%, respectively). Also, some researchers [49] reported in their study that no vancomycin-resistant bacteria were identified. This observation provides a support to their use in CA-SBP, Health care associated SBP and N-SBP according to latest EASL guidelines [11] and the variation in antibiotic susceptibility highlights the importance of national and regional antibiotic resistance data, to set the antibiotic policy or stewardship programs on antibiotic prescription.

Regarding cefotaxime, as a 3rd generation cephalosporin used to be the empirical therapy in SBP, some studies observed that patients with nosocomial SBP fail to respond to third-generation cephalosporins in up to 33%-75% of cases [61 & 62].

On the other hand, some studies reported lower resistance than the present study (13%–15%) [63] and others reported that the overall resistance to third-generation cephalosporins was 10% (being 3% in CA-SBP, 55% in N-SBP and 8% in HCA-SBP) [49]. Also, Ariza and his colleagues [14] in their study assessing SBP with blood and/or ascitic fluid culture, found an average global resistance to 3rd generation cephalosporins of 21.5% ,where 7.1% were observed in community-acquired infections, 21.1% in healthcare-associated infections, and 40.9% in nosocomial infections.

By contrast, many studies reported higher resistance to 3rd generation cephalosporin than the current study as the Egyptian study in Al-Hussein University Hospitals, Al-Azhar University [31] which was conducted on 160 asymptomatic SBP patients and revealed that it was (84.2%) and other studies reported that rate of cefotaxime resistance was 66.7% in N-SBP, being

significantly higher than non-nosocomial infections (34.6%) [59] but Piano and his colleagues [54] reported in their study that 81.3% of bacterial isolates were resistant to third generation cephalosporins with no significant difference between CA-SBP and N-SBP in the resistance to third generation cephalosporins (80% vs. 83.3%). This variation was probably as a result of different number of patients and the inclusion of bacterascites and asymptomatic patients in some studies in addition to the different geographical areas.

No multi-drug resistant bacteria were detected as a cause of SBP in the present study and this was in agreement with that observed in a study in a German university hospital [47] and a study in Switzerland [65]. The prevalence of infections caused by MDROs varies significantly between regions and even between institutions of a single region. This was demonstrated by a worldwide study reporting that the global prevalence of multidrug-resistant (MDR) bacteria was 34% (95% confidence interval 31%–37%) with the greatest prevalence in Asia (particularly in India being as high as 73%) and as low as 16% in the United States [66]. Another study performed in Europe also showed that MDRO rates was 34% in France [67]. Also, some studies showed an increased prevalence of infections caused by multi-resistant bacteria, especially in nosocomial episodes, up to 19% of all infections [25], others showed a prevalence of 44% [68].

Taking into account the site of acquisition of infection, it was reported in a systematic review on nosocomial spontaneous bacterial peritonitis that overall percentage of MDR bacteria ranges from 22% to 73% (from 36.8 to 50% for Gram-positive bacteria and from 30% to 66.6% for the Gram-negative bacteria) [52]. Although the results of the current may not be postulated in other health institutions, it is crucial have an insight into bacterial epidemiology of SBP in every hospital to improve patient safety, optimize use of antibiotics and avoid preventable risk factors of bacterial resistance.

Conclusion:

There is an increase in the rate of SBP caused by Gram-positive cocci more than Gram negative bacilli with predominant coagulase negative staphylococci (CoNS), staphylococcus aureus followed by E. coli. The causative bacteria of SBP and antibiotic resistance vary according to the site of acquisition of SBP. Antibiotic resistance was higher in N-SBP than CA-SBP and there in an emerging pattern towards 3rd

generation cephalosporins resistance and this should be considered when prescribing the empirical antibiotic of choice.

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